Chiral Pyridine-Containing Ligands for Asymmetric Catalysis: Synthesis and Applications

Fredrik Rahm

Kungl Tekniska Högskolan
Stockholm 2003
Chiral Pyridine-Containing Ligands for Asymmetric Catalysis: Synthesis and Applications

Fredrik Rahm

KTH

Doctoral Thesis

Stockholm 2003

Kungl Tekniska Högskolan
Department of Chemistry
Organic Chemistry

This thesis deals with the design and syntheses of chiral, enantiopure pyridine-containing ligands and their applications in asymmetric catalysis.

Chiral pyridyl pyrrolidine ligands and pyridyl oxazoline ligands were synthesized and employed in the palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The influence of the steric properties of the ligands were investigated.

Ditopic ligands, containing crown ether units as structural elements, were synthesized and some of the ligands were used as ligands in the palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. A small rate enhancement was observed, compared with analogous ligands lacking the crown ether unit, when these ditopic ligands were used in dilute systems.

A modular approach was used to synthesize chiral enantiomerically pure pyridyl alcohols and C2-symmetric 2,2'-bipyridines, with the chirality originating from the chiral pool. Electronic and steric properties of the compounds were varied and they were used as ligands in the enantioselective addition of diethylzinc to benzaldehyde. The sense of asymmetric induction was found to be determined by the absolute configuration of the carbinol carbon atom. The electronic properties of the ligands had a minor influence on the levels of enantioselectivity induced by the ligands.

Chiral pyridyl phosphinite ligands and pyridyl phosphite ligands were synthesized from the pyridyl alcohols and evaluated as ligands in palladium-catalysed allylic alkylations. With the phosphinite ligands, the sense of chiral induction was found to be determined by the absolute configuration of the former carbinol carbon atom. A kinetic resolution of the racemic starting material was observed with one of the phosphite ligands. Moderate enantioselectivities were achieved.

Keywords: asymmetric catalysis, chiral ligand, chiral pool, oxazoline, crown ether, ditopic receptor, bipyridine, pyridyl alcohol, modular approach, \( P,N \)-ligand, diethylzinc, allylic alkylation.
# Table of Contents

Abstract  
Abbreviations  
List of Publications  

1. Asymmetric Synthesis ................................................................. 1  
   1.1 Introduction ........................................................................... 1  
   1.2 Ligand Design ................................................................. 2  

2. Chiral Enantiopure Pyridine-Containing Ligands ................... 5  
   2.1 Introduction ........................................................................... 5  
   2.2 2,2’-Bipyridines ............................................................. 5  
   2.3 Pyridyl Amines .............................................................. 9  
   2.4 Pyridyl Imines, Oxazolines, and Imidazolines .......... 12  
   2.5 Pyridyl Amides .......................................................... 20  
   2.6 Pyridyl Alcohols ............................................................ 22  
   2.7 Pyridyl Phosphines, Phosphinites, and Phosphites ....... 24  
   2.8 Aim of the Thesis ......................................................... 28  

3. Palladium-Catalysed Allylic Substitution ............................... 29  

4. Addition of Diethylzinc to Benzaldehyde .............................. 33  

5. Pyridine-Pyrrolidine Ligands ................................................. 37  
   5.1 Background ....................................................................... 37  
   5.2 Syntheses of Ligands ........................................................ 37  
   5.3 Results and Discussion .................................................... 38  

6. Pyridino-Oxazoline and Quinolino-Oxazoline Ligands: Influence of Steric Factors ......................................................... 39  
   6.1 Background ....................................................................... 39  
   6.2 Syntheses of Ligands ........................................................ 39  
   6.3 Results and Discussion .................................................... 40  

7. Chiral Ligands Containing Crown Ethers ................................ 43  
   7.1 Background ....................................................................... 43  
   7.2 Ligand Synthesis and Application in Allylic Alkylation .... 44  

8. Syntheses of Chiral Enantiopure Pyridyl Alcohols Starting from the Chiral Pool. Applications in Asymmetric Catalysis ......................... 47  
   8.1 Background ....................................................................... 47  
   8.2 Syntheses of Ligands ........................................................ 47  
      8.2.1 2-(1-Hydroxyalkyl)pyridines ....................................... 47  
      8.2.2 2-Bromo-6-(1-hydroxyalkyl)pyridines and 2,2’-Bipyridines .... 48  
      8.2.3 2-Bromo-6-(1-hydroxyalkyl)pyridines Derived From Neomenthyl Nitrile ......................................................... 50  
      8.2.4 6-Aryl-2-(1-hydroxyalkyl)pyridines ............................ 53  
   8.3 Determination of Absolute Configurations ....................... 53  
   8.4 Results and Discussion .................................................... 55
Abbreviations

BINOL 1,1’-bi(2-naphthol)
BSA N,O-bis(trimethylsilyl)acetamide
BSTFA N,O-bis(trimethylsilyl)trifluoroacetamide
COD cyclooctadiene
DAIB (–)-3-exo-(dimethylamino)isoborneol
DBNE (1S,2R)-(-)-2-(N,N-dibutylamino)-1-phenylpropan-1-ol
EDCI 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee enantiomeric excess
Eu(hfc)$_3$ tris[3-(heptafluoropropylhydroxymethylene)](+)-camphorato)europium
(–)-Icp$_2$-BCl (–)-B-chlorodiisopinocampheylborane
MTPA α-methoxy-α-trifluoromethylphenylacetic acid
n.r. no reaction
Si sinister, left, stereochemical descriptor for heterotopic faces
TBAF tetra-n-butylammonium fluoride
This thesis is based on the following papers, referred to in the text by their Roman numerals I-V:

I. **Application of (2′R,5′R)-2-[(2′,5′-Dimethylpyrrolidin-1-yl)-methyl]pyridine and (2′R,5′R)-2-[(2′,5′-Diphenylpyrrolidin-1-yl)-methyl]pyridine to the Palladium-Catalyzed Allylic Alkylation**
   Kenneth Wärnmark; Robert Stranne; Magnus Cernerud; Isabelle Terrien; Fredrik Rahm; Kerstin Nordström and Christina Moberg

II. **Palladium-Catalyzed Allylic Alkylation Using Pyridino-Oxazolines and Quinolino-Oxazolines as Ligands - Influence of Steric Factors**
   Ulf Bremberg; Fredrik Rahm and Christina Moberg

III. **Preparation of Chiral Enantiopure 2-(Hydroxyalkyl)pyridine Derivatives. Use of the Chiral Pool**
    Fredrik Rahm; Robert Stranne; Ulf Bremberg; Kerstin Nordström; Magnus Cernerud; Emmanuel Macedo and Christina Moberg

IV. **Pyridyl Phosphinites and Pyridyl Phosphites From Chiral Pyridyl Alcohols. A Modular Approach**
    Fredrik Rahm and Christina Moberg
    Manuscript

V. **Chiral Ditopic Receptors. Application to Palladium-Catalyzed Allylic Alkylation**
    Jean Bourguignon, Ulf Bremberg, Georges Dupas, Kristina Hallman, Lars Hagberg, Laurent Hortala, Vincent Levacher, Serghey Lutsenko, Emmanuel Macedo, Christina Moberg, Guy Quéguiner and Fredrik Rahm
    Submitted

Papers I and III were reproduced by permission of The Royal Society of Chemistry. Paper II was reproduced by permission of Elsevier Science.
1. Asymmetric Synthesis

1.1 Introduction

Over the last two decades, the increasing demand for enantiomerically pure substances, especially from the pharmaceutical industry, has encouraged the chemists to develop efficient synthetic methods for the production of single enantiomers of the compounds desired. Of all the pharmaceutical products sold world-wide in 2001, a value of $147 billion, or 36%, was due to single-enantiomer drugs.¹

In the quest for enantiomerically pure compounds, the synthetic chemist has three alternative paths to choose from: to start from a pure enantiomer of a natural product, to resolve a racemate into pure enantiomers or to use asymmetric synthesis.

Nature is the world-leading chemist in synthesizing chiral enantiopure substances and a vast variety of structures are available for the synthetic chemist to use. Low cost and high optical purity are two reasons for fishing in the chiral pool. However, several steps are often required for reaching the target molecule, resulting in low overall yields. Another disadvantage of this approach is that most natural products are readily available only in one enantiomeric form.

In a classical resolution, a chiral enantiopure resolving agent is used to transform a racemate into a mixture of diastereomers. After a conventional separation (for example crystallisation or chromatography), the resolving agent can be removed to yield the pure enantiomers. Kinetic resolution relies on a chiral nonracemic agent that reacts at a substantially higher rate with one enantiomer of a racemate than with the other. One drawback with both of these methods is that the maximum theoretical yield of the desired enantiomer is 50%. The use of dynamic kinetic resolution, in which the slow-reacting enantiomer is continuously racemised, can solve this problem. Chromatographic separation of a racemate on a chiral column or preferential crystallisation of one enantiomer may be attractive alternatives but, again, only 50% yield can be reached.

Asymmetric synthesis can be carried out either under substrate control using a chiral auxiliary, under reagent control using a chiral reagent, or by the use of a chiral catalyst. High diastereoselectivities and the possibility of conventional separations make the chiral auxiliary approach an attractive route to creating new stereogenic elements. Additional synthetic steps are, however, required for the attachment and final removal of the auxiliary. The need for a stoichiometric amount of an enantiopure substance can also cause problems, if the auxiliary is not easily removed and recycled after the synthetic sequence. High stereoselectivities can be reached with a chiral reagent as well, and there is no

need for additional synthetic steps. The problems connected with the use of stoichiometric amounts of an enantiopure substance remain, however. The reagent or auxiliary is often a derivative of the chiral pool, and again a problem can arise if the enantiomeric form desired is not available. A more sophisticated approach is to use a chiral catalyst, as only a catalytic amount of a chiral substance is required to yield a stoichiometric amount of a chiral product. A chiral catalyst can be either an enzyme, a catalytic antibody or an organometallic complex (an organic ligand coordinated to a metal ion), even though low molecular-weight organic catalysts are becoming increasingly employed. In contrast to enzymes and catalytic antibodies, organometallic catalysts are generally more tolerant to heating and various organic solvents. Another advantage of organometallic catalysts is that they can often be modified to catalyse transformations of several kinds. The same is true of catalytic antibodies, but the process of optimising the structure of a catalytic antibody is more complicated. One limitation of asymmetric catalysis is that it is hard to develop a catalyst that is not substrate specific. In many cases the catalyst has to be optimised for each new substrate, and a general catalyst can, at best, be developed for a limited substrate class. This thesis deals with organometallic complexes as chiral catalysts and the discussion will, therefore, be limited to this area hereafter.

The field of asymmetric catalysis has experienced exponential growth during the last decade, and several catalysts have become versatile everyday tools in asymmetric synthesis. Despite the increased understanding of the factors influencing for example enantioselectivity, the mechanisms behind most catalytic reactions are still not fully understood. The nature of the ligand has a profound influence on the properties of the catalyst, but the choice of solvent and counter-ion is often important as well. Furthermore, additives can sometimes modify the catalytic properties. In other words, extensive experimental work on finding successful combinations of these factors is required. Therefore, high-throughput screening technologies are being developed together with techniques for fast and simple analyses of yields and enantiomeric purities. In order to minimise the consumption of chemicals, methods allowing downsizing are also attracting increasing attention.

Efficient methods for the preparation of series of structurally modified ligands are also desirable. Preferably, a modular approach is employed, in which both steric and electronic properties of the ligand can easily be varied, starting from a common readily available structural unit.

1.2 Ligand Design

A successful ligand design is the key to an efficient catalyst. There are many aspects that have to be taken into account when a ligand for a certain metal-catalysed reaction is to be designed. In most metal-catalysed reactions, however,
the mechanism and/or the factors influencing the selectivity are not fully understood, which makes a totally rational design virtually impossible.

The ligand can be coordinated to a metal using one, two, or more bonds, making it a monodentate, bidentate, or polydentate ligand, respectively. Most ligands form a dative $\sigma$-bond to the Lewis-acidic metal using a lone electron pair of the most basic atom present, often a nitrogen or phosphorus atom, and are called $\sigma$-donors. Metals in low oxidation states have occupied high-lying d-orbitals which can be stabilised if the ligand possesses empty $\pi^*$ or $\sigma^*$ orbitals. This phenomenon is called $\pi$-backdonation and the ligand is referred to as a $\pi$-acceptor or a $\pi$-acid. The opposite situation arises if the ligand has filled orbitals that can interact with empty d-orbitals of the metal. One example is alkoxy ligands (RO) that can stabilise metals in relatively high oxidation states [for example Ti(IV) and Mn(V)] by interaction of the non-bonding oxygen lone pairs with the empty d-orbitals of the metal.\(^2\)

The electronic properties can easily be modified in tertiary phosphorus ligands. As the average electronegativity of the groups attached to phosphorus increases, the ligand becomes a poorer $\sigma$-donor but a better $\pi$-acceptor, the order of increasing $\pi$-acidity being PMe$_3$ < PAr$_3$ < P(OMe)$_3$ < P(OAr)$_3$ < PCl$_3$.\(^3\) Nitrogen ligands are normally good $\sigma$-donors and some ligands, for example 2,2'-bipyridine, phenanthroline, and terpyridine, also exhibit significant $\pi$-acidity. Metal complexes of these ligands are generally more stable than those of aliphatic amines. If the ligand contains a set of donor atoms with varying electronic properties, the difference in $trans$-influence has to be considered. $Trans$-influence is a thermodynamic property defined as the ability of a donor to weaken the bond $trans$ to itself (on the opposite side of the metal).\(^4\) This means that groups coordinated $trans$ to electronically different donor atoms exhibit different reactivities, as for example the terminal allylic positions in an $\pi$-allyl palladium complex with a $P,N$-ligand (Figure 1a).

The ligand also makes up the steric scaffold responsible for the transfer of chirality to the substrate. By proper steric (repulsive) influence of the ligand, the substrate(s) can be made to coordinate the metal in a specified fashion, facilitating enantioselection. An alternative is to introduce functionalities in the ligand capable of attractive interactions with the substrate or another participating reactant. In some instances it can be beneficial to use ligands with rotational symmetry and many successful ligands are for example $C_2$-symmetric. One reason to use such a ligand is that the number of possible complexes is reduced by a factor of two (Figure 1b). There is, however, no fundamental reason why ligands with rotational symmetry should be superior to $C_1$-symmetric ligands.

One important property of bidentate ligands is the bite angle (Figure 2a, $\beta_n$ shown in an arbitrary bidentate phosphorus ligand). Upon coordination to a metal ion, the preferences of both the ligand and the metal will determine the angle between the two coordination bonds. In square-planar and octahedral complexes the preferred $P - M - P$ angle is about $90^\circ$, whereas in tetrahedral complexes it is about $109^\circ$. A change in the bite angle can have a strong effect on the activity and/or the selectivity of the catalyst. Furthermore, bite angle and steric effects are often interrelated. By a change in the bite angle, sterically demanding groups on the ligand can be moved towards or away from the coordination site. The chelate ring size is also essential in this context (Figure 2b). A larger chelate ring will generally result in a larger bite angle. This can in turn affect the stability of the metal complex. A small metal ion is normally more stabilised by a five-membered chelate ring, whereas a six-membered chelate ring is better at stabilising a large metal ion.

Figure 1. Trans-influence (a) and symmetry (b).

Figure 2. Bite angle (a) and chelate ring size (b).


2. Chiral Enantiopure Pyridine-Containing Ligands

2.1 Introduction

Ligands containing nitrogen donors are known to be very useful in asymmetric metal catalysis. Compared with organophosphorus ligands, they are stable toward oxidation and are often easy to synthesize. Among the plethora of nitrogen ligands, those containing pyridine are of particular interest for several reasons. Pyridines are stable compounds with rich and well-known chemistry, and their electronic properties make them suitable as ligands for a large variety of metal ions. In addition, pyridine constitutes a rigid and well-defined platform, from which different ligands can be built. Some examples of pyridine-containing ligands that have been successfully applied in asymmetric catalysis are shown in Figure 3.

![Figure 3. Examples of pyridine-containing ligands used in asymmetric catalysis](image)

The following short summary is meant to give a brief overview of some families of pyridine-containing ligands that have been used in asymmetric catalysis. Chiral metal complexes not used in catalysis are not included. Excellent reviews already describe some types of ligands, and those further interested are referred to these. In this summary, ligands are divided into different families based on the basic pyridine-containing backbones, focusing on different synthetic strategies to attain the target ligands. The coordination modes of the ligands within a certain family can vary, making an unambiguous classification difficult.

2.2 2,2'-Bipyridines

2,2'-Bipyridines are excellent ligands for many metal ions and numerous complexes have been used successfully in asymmetric catalysis. In addition to

---

the two \( \sigma \)-donating nitrogen atoms, the fully conjugated \( \pi \)-system makes bipyridines good \( \pi \)-acceptors, resulting in remarkably stable metal complexes. There are several synthetic routes to bipyridines and depending on the structure of the target ligand, some are preferable to other routes. In the synthesis of \( C_2 \)-symmetric ligands the method of choice relies on nickel-mediated homocoupling of halopyridines already containing the chirality desired. In the first report of chiral nonracemic \( C_2 \)-symmetric 2,2\(^\prime\)-bipyridines, Bolm et al. used this approach to synthesize 7 from pyridyl alcohol 6 (Scheme 1), obtained by asymmetric reduction of the corresponding ketone using \((\text{--})\)-B-chlorodiisopinocamphylborane.\(^8\) Furthermore, 6 could be coupled with 2-pyridylzinc chloride in the presence of tetrakis(triphenylphosphine)palladium(0) to yield \( C_1 \)-symmetric bipyridine 8.

Scheme 1

Kwong and Lee synthesized a number of \( C_2 \)-symmetric bipyridines by the same method, but using optically active ketones from the chiral pool as the source of chirality (Scheme 2).\(^9\) Monolithiation of 2,6-dibromopyridine followed by reaction with \((\text{--})\)-menthone (10) and \((+\text{-})\)-camphor (11) yielded the bromopyridyl alcohols 12 and 13, respectively, as single diastereomers. Nickel-mediated homocoupling provided the corresponding bipyridines 14 and 15.

Scheme 2

---


Bipyridines containing one or two alcohol moieties have been used successfully in asymmetric additions of dialkylzinc reagents to prochiral aldehydes (Scheme 3). The addition of commercially available diethylzinc to benzaldehyde (16) has commonly been used to compare the ability of different catalysts to induce enantioselectivity. For a more detailed discussion on this reaction, see Chapter 4. The highest enantioselectivity was achieved with the $C_2$-symmetric camphor-based ligand 15, which favoured the formation of $(R)$-17 in 95% ee. The other ligands 7, 8 and 14 gave the same enantiomer in 92, 78 and 85% ee, respectively.

![Scheme 3](image)

**Scheme 3**

The introduction of a fused ring next to the pyridine moiety increases the rigidity of the steric scaffold, and in this manner makes the steric interaction between the ligand and the substrate coordinated to the metal more efficient. With this in mind, Katsuki and co-workers synthesized a series of bipyridines starting from 2-chloro-5,6,7,8-tetrahydroquinoline, 18 (Scheme 4). Deprotonation with LDA followed by reaction with various electrophiles yielded rac-19, which had to be resolved using chiral HPLC to provide enantiopure 20. Subsequent homocoupling yielded the bipyridines 21.

![Scheme 4](image)

**Scheme 4**

Many synthetic routes to $C_1$-symmetric 2,2'-bipyridines involve a condensation reaction between an $\alpha,\beta$-unsaturated carbonyl compound and a derivative of 2-acetylpyridine, in which the second pyridine ring is formed. In one report, (−)-pinocarvone 23 was condensed with 2-acetylpyridinepyridinium iodide 22, obtained by reaction of 2-acetylpyridine with iodine in pyridine, to yield $C_1$-symmetric bipyridine 24 (Scheme 5). Introduction of substituents to increase

the steric demand of the ligands was possible by deprotonation in the benzylic position followed by stereoselective attack of different electrophiles to yield bipyridines 25 as single diastereomers. This approach was recently extended to make the synthesis of C₂-symmetric bipyridines possible, thus avoiding the difficulties associated with the preparation of 2-halopyridines and the nickel-mediated homocoupling.

Scheme 5

Copper(I) complexes of many bipyridines have been used as catalysts in the asymmetric cyclopropanation of alkenes. In these studies, the cyclopropanation of styrene with tert-butyl diazoacetate (27a) has generally been employed as a model reaction to examine the activity and selectivity of various catalysts (Scheme 6). Early studies by Katsuki and co-workers showed that copper(I) complexes of C₂-symmetric 2,2'-bipyridines were efficient catalysts of this reaction. In the presence of trimethylsilyl-substituted bipyridine 21b (Scheme 4), the formation of both trans- and cis-28 proceeded with high enantioselectivities, 92 and 98% ee respectively, whereas the iso-propyl analogue 21a afforded the trans-isomer in 77% ee. The best result obtained with the C₁-symmetric ligands in Scheme 5 was accomplished with the benzyl-substituted ligand 25c, which provided trans- and cis-28 with 64 and 68% ee, respectively.

Scheme 6

Palladium complexes of several bipyridines have been evaluated as catalysts in allylic substitutions. Alkylation of rac-1,3-diphenyl-2-propenyl acetate (rac-29) with the nucleophile generated in situ from dimethyl malonate, BSA and KOAc

has normally been used to assess the performance of a new catalyst (Scheme 7). For a more detailed discussion on this topic, see Chapter 3. Only moderate enantioselectivities have generally been reported with 2,2'-bipyridines, but some ligands have been shown to induce higher levels of enantioselection. Palladium complexes of ent-25a-c (Scheme 5) were shown to be active catalysts in this reaction. Total conversions were reached, providing (R)-30 with 74, 79 and 89% ee, respectively.

![Scheme 7](image)

Complexes of bipyridines with rhodium(I) have been evaluated as catalysts in asymmetric hydrosilylation and transfer hydrogenation of ketones with varying success. Chiral enantiopure 2,2'-bipyridines have also attracted increasing attention as ligands in the asymmetric copper(I)-catalysed allylic oxidation of cycloalkenes.

### 2.3 Pyridyl Amines

The chiral pool contains a large variety of enantiopure amino derivatives that, either as such or after further functionalisations, can be used as ligands in asymmetric catalysis. Amine type ligands are generally chemically stable, but in contrast to their phosphorus counterparts not configurationally stable. This makes the use of stereogenic nitrogen atoms difficult. Bidentate ligands containing one pyridine donor and one amine donor have hitherto not found widespread applications in asymmetric catalysis, but some successful examples exist.

In the beginning of the 1990’s, Chelucci and co-workers reported the synthesis of several optically active pyridyl amine ligands starting from α-amino acids (Scheme 8). Cobalt(I)-catalysed co-cyclotrimerisation of nitrile 32, derived from L-proline (31), with acetylene gave 2-[(2S)-2-pyrrolidinyl]pyridine (3), after deprotection. Pyridyl amines 34 and 36 were synthesized using the same protocol, starting from L-valine (33) and L-isoleucine (35), respectively.

---

17 Trost, B. M.; Murphy, D. J. Organometallics 1985, 4, 1143.
These ligands have been shown to be highly efficient chiral inducers in the addition of diethylzinc to benzaldehyde (Scheme 3). When 3 was used as the ligand, (S)-17 was generated with nearly complete enantioselectivity. Ligands 34 and 36 provided the same enantiomer of the product with 91 and 98% ee, respectively. Compound 3 was also used as ligand in the palladium-catalysed allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate, resulting in the formation of the (R)-product of 64% ee.

Pyridyl aziridine 39 was synthesized starting from the chiral pyridyl imine 37, derived from picolinaldehyde and (S)-valinol. Stereoselective addition of iso-propylmagnesium chloride, followed by deprotection of the alcohol, gave pyridyl amine 38 in high yield and almost complete diastereoselectivity (Scheme 9). Quantitative ring closure to pyridyl aziridine 39 was then achieved with 1,1'-carbonyldiimidazole (CDI). Upon coordination of 39 to a metal ion the nitrogen atom becomes a stereogenic centre. Therefore, two complexes can form, depending on which face of the aziridine ring is turned towards the metal. When 39 was coordinated to palladium(II), however, selective (R)-coordination (40) occurred. This was explained by less steric interaction between the iso-propyl groups compared with the complex with S configuration on the aziridine nitrogen (41). The (R)-complex formed was used as a catalyst in the alkylation of rac-1,3-diphenyl-2-propenyl acetate with the preformed sodium salt of dimethyl malonate as nucleophile, resulting in 42% ee of (R)-30.

---

Scheme 9

One way of avoiding diastereomeric complexes due to lack of face-selective coordination of the amine moiety is to employ an intrinsically C₂-symmetric nitrogen-containing substituent. In this context, a series of ligands containing trans-2,5-methylpyrrolidine was synthesized (Scheme 10). Reduction of diketone 42 with baker’s yeast yielded (S,S)-2,5-hexanediol (43) of high enantiomeric purity, from which the C₂-symmetric pyrrolidine moiety was obtained. The stereogenic centres in pyridyl alcohols 46a and 46b were introduced through asymmetric reduction of ketone 45 using (+)- or (–)-B-chlorodiisopinocampheylborane, respectively.

Scheme 10

Ligands 47a and 47b were evaluated in palladium-catalysed allylic substitution of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The catalyst

derived from 47b demonstrated higher activity, as well as higher selectivity, giving 84% ee of the (R)-product in quantitative yield. When ligand 47a was used, the opposite enantiomer of the product was isolated in low yield and with low optical purity (13% yield, 27% ee).

The substituents in the 2- and 5-position of the pyrrolidine moiety can be varied, and other pyridine ligands containing the $C_2$-symmetric trans-2,5-disubstituted pyrrolidine moiety have been reported.

2.4 Pyridyl Imines, Oxazolines, and Imidazolines

Chiral pyridyl imines are readily available by Schiff base condensation of a pyridyl aldehyde or ketone, with a chiral amine. As mentioned above, chiral enantiopure amines are easily obtained from the chiral pool, making this route to chiral nitrogen-containing ligands attractive.

In an early study by Brunner et al., the Schiff bases obtained by condensation of picolinaldehyde (48a), 2-acetylpyridine (48b) and 2-benzoylpyridine (48c) with (S)-phenyl ethylamine (49) were used in the rhodium(I)-catalysed hydrosilylation of acetophenone (Scheme 11). An enantiomeric excess of 57% in favour of the (R)-product was reached when 50a was used as the ligand. Since then, a large number of pyridyl imines have been synthesized from a variety of chiral amines. Platinum(I) complexes of pyridyl imines have been used in hydrosilylations of ketones, and iridium(I) complexes have proven to be active catalysts in asymmetric transfer hydrogenations of ketones.

---

A modular approach was more recently used to optimise the structure of pyridyl peptide ligands used in copper-catalysed allylic substitutions (Scheme 12). Various catalytic systems were evaluated by varying the peptide part of the ligands as well as the substituents on the pyridine. The best result was achieved with a copper(I)-complex of ligand 53 in the ethylation of the allylic phosphonate 54, giving 55 in 83% yield and 90% ee.

Several ligands with the possibility of multidentate coordination have recently been reported. Pyridyl imine ligands with a pendant phosphine-containing arm have been used successfully in the enantioselective copper-catalysed conjugate addition of diethylzinc to enones. Schiff bases derived from the axially chiral amine 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN, 56) were synthesized and used in asymmetric catalysis (Scheme 13).

Scheme 11

Scheme 12


Brunner et al. used (S)-58 in the enantioselective ruthenium-catalysed transfer hydrogenation of acetophenone (Scheme 14), providing (S)-1-phenyl ethanol (61) in almost quantitative yield and with excellent enantiomeric excess (96% yield, 95% ee).  

![Scheme 13](image)

**Scheme 13**

The ruthenium(II)-complex of (R,R)-59 was shown to be an efficient catalyst in the cyclopropanation of styrene (Scheme 6). High trans: cis selectivity (90:10) as well as enantioselectivity (97 and 90% ee, respectively) were achieved when ethyl diazoacetate (27b) was used.

Oxazolines are very useful nitrogen donor moieties in organometallic chemistry, giving stable complexes with many metal ions. A large variety of oxazoline containing ligands, including pyridyl oxazolines (65), have been reported and several have been successfully applied in asymmetric catalysis. There are a number of methods of synthesizing chiral pyridyl oxazolines via the reaction of pyridyl nitriles (62) or picolinic acid derivatives (63) and optically active β-amino alcohols (64). The protocols most commonly used are shown in Scheme 15.

---

Scheme 15

The substitution pattern of the oxazoline ring can easily be varied by the use of different β-amino alcohols. The oxazoline ring also constitutes a rigid scaffold which can make the steric interaction between the ligand and the substrate coordinated to the metal ion more efficient than is possible with the pyridyl imine ligands discussed above.

The first chiral pyridyl oxazoline ligands were introduced by Brunner et al. in copper(II)-catalysed asymmetric monophenylation of meso-1,2-diols using a phenylbismuth reagent (Scheme 16).\(^{36}\) The best result was achieved with the (S)-valinol-based ligand 68, which gave 50% ee of the monophenyl ether 71.

Scheme 16

Rhodium(I) complexes of the pyridyl oxazolines 68 and 69 were found to catalyse the asymmetric hydrosilylation of acetophenone (Scheme 11), favouring the (R)-product with 62 and 83% ee, respectively.\(^{37}\) The enantioselectivity was increased to 89% when the diphenyl-substituted ligand 74 was used (Scheme 17).\(^{38}\) Introduction of the phenyl groups was achieved by using β-amino alcohol


73, synthesized from the amino acid ester 72 by addition of phenyl Grignard reagent.

![Scheme 17](image)

**Scheme 17**

Pyridyl oxazolines containing a chiral substituent in the 6-position of the pyridine ring were synthesized from the racemic pyridyl alcohol 75 in a four-step procedure (Scheme 18).\(^\text{39}\) Introduction of the oxazoline ring in the last step afforded a diastereomeric mixture, which was separated to yield optically pure 76 and 77. These pyridyl oxazoline ligands were shown to favour the formation of opposite enantiomers in the addition of diethylzinc to benzaldehyde. Ligand 76 gave \((S)\)-1-phenyl-1-propanol (17) in 71\% ee, whereas 77 gave the \((R)\)-isomer in 88\% ee.

![Scheme 18](image)

**Scheme 18**

Chiral pyridyl oxazolines have been used extensively as ligands in palladium-catalysed allylic substitution. The protocol described in Scheme 7 has generally been utilised to compare the performance of the various ligands. To increase the understanding of the factors influencing the activities and selectivities of the catalysts, series of ligands with varying steric\(^\text{40}\) and electronic properties\(^\text{41}\) have been synthesized. Some examples of reported ligands are presented in Figure 4 together with the enantioselectivity attained with the ligand in the catalytic reaction. These studies show that the introduction of a substituent in the 6-position of the pyridine ring can have a dramatic effect on the enantioselectivity of the catalyst. Electronic properties, on the other hand, have been shown primarily to affect the activity of the catalyst and only to a small extent the enantioselectivity.


Palladium catalysts derived from polymer-supported and dendritic pyridyl oxazoline ligands have also been used in allylic substitution. These catalysts are attractive for several reasons, especially since they can easily be recovered and reused.

Shortly after Brunner’s introduction of the pyridyl oxazolines in asymmetric catalysis, Nishiyama et al. published the synthesis of C₂-symmetric bis(pyridinooxazoline) ligands (pybox). Pybox ligands 1, 85, and 86 were prepared by the reaction of dipicolinic acid (84) with (S)-valinol, (S)-sec-leucinol, and (S)-tert-leucinol, respectively (Scheme 19). Rhodium(III) complexes of these ligands were prepared and used as catalysts in hydrosilylation of acetophenone (Scheme 11). Catalysts based on 1 and 85 gave the (S)-product with very high enantioselectivities, 94 and 91% ee, respectively, whereas pybox 86 provided an unselective rhodium catalyst. Interestingly, when the rhodium(I) complexes of the corresponding mono(pyridinooxazolines) 68 and 69 (Scheme 16) were used in the same reaction, formation of the (R)-product was favoured (60 and 91% ee, respectively).  

---

**Figure 4.** Ligands used in the palladium-catalysed allylic substitution of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. (Ligands 2 and 76-78 ref. 40a; 79 ref. 40a,b; 80-81 ref. 41a; 82-83 ref. 40b.)
The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.

Scheme 19

The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.

Scheme 19

The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.

Scheme 19

The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.

Scheme 19

The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.

Scheme 19

The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.

Scheme 19

The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.

Scheme 19

The pybox ligands have found widespread applications as ligands in asymmetric catalysis after the early reports by Nishiyama, and some have become commercially available. Recent reports on the use of pybox ligands include the ruthenium-catalysed asymmetric cyclopropanation of alkenes, the Lewis acid-catalysed enantioselective aldol addition, and the Lewis acid-catalysed enantioselective 1,3-dipolar cycloaddition.

Imidazolines are analogous to oxazolines regarding coordination mode and steric properties. Both heterocycles coordinate metal ions through the imine nitrogen atom and the five-membered rings provide virtually identical steric scaffolds (Figure 5). The main differences are found in the electronic properties. Imidazolines are somewhat more electron-rich, since nitrogen is less electronegative than oxygen. Moreover, the electronic properties can be changed by the introduction of various substituents (R') on nitrogen without the steric properties of the imidazolines being affected. In spite of these attractive features of the imidazoline moiety, very few metal complexes of this type of ligands have been reported. Some palladium complexes of chiral pyridyl imidazolines have recently been used in copolymerisation of carbon monoxide and styrene, but the applications in asymmetric catalysis have been scarce.
The synthesis of pyridyl imidazoline 88 from 2-pyridyl nitrile and (S,S)-1,2-diphenylethlenediamine (87, Scheme 20) was reported by Brunner and co-workers in 1989.\textsuperscript{50} Rhodium(I) and copper(II) complexes were prepared and used in the hydrosilylation of acetophenone, and in the monophenylation of meso-1,2-cyclopentanediol, respectively, but the yields and enantioselectivities were low.\textsuperscript{51}

Scheme 20

In a more recent study, the pyridyl imidazoline 88 was synthesized according to the procedure used by Brunner, and subsequently methylated to yield ligand 89 (Scheme 21).\textsuperscript{52} Ruthenium(II) complexes of ligands 88 and 89 were evaluated as Lewis acid catalysts in the enantioselective Diels-Alder reaction of methacrolein (90) with cyclopentadien (91). Both catalysts provided the product with a high \textit{exo}:\textit{endo} ratio (94:6), but with low optical purity (45 and 31\% ee of \textit{exo}-92, respectively). When a ruthenium(II) complex of pyridyl oxazoline 79 was used in the same reaction, the product was obtained in the same \textit{exo}:\textit{endo} ratio, but with higher optical purity (58\% ee).

Scheme 21

2.5 Pyridyl Amides

Chiral pyridyl amides are readily obtained by a condensation reaction of a suitable chiral amine (93) and a picolinic acid derivative (94, Scheme 22). Series of structurally modified pyridyl amides can conveniently be synthesized, since a large variety of chiral enantiopure amines are commercially available or easily prepared. The coordination chemistry of pyridyl amide ligands is rich and many metal ions are known to form stable complexes with this family of ligands.\(^{53}\) The pyridyl amide ligands represented by 95 can coordinate to a metal ion either as an \(N,N\)-donor or as an \(N,O\)-donor. The ligands can either act as neutral species or coordinate as anionic ligands after deprotonation of the amide functionality.

![Scheme 22](image)

Although a vast number of metal complexes of pyridyl amide ligands have been reported, their applications in asymmetric catalysis have been few. Bispyridyl amides derived from \(C_2\)-symmetric diamines have emerged as attractive ligands and some very successful applications have been published.

![Figure 6](image)

The \(C_2\)-symmetric bispyridyl amides 96 and 97 (Figure 6) were evaluated as ligands in the Lewis acid-catalysed ring opening of cyclohexene oxide with trimethylsilyl azide (Scheme 23).\(^{54}\) The best catalyst for this reaction was found to be the zirconium complex of ligand 96, which favoured the formation of the (1S,2S)-enantiomer of 99 in 71% ee.


In 1998, Trost and Hachiya used 97 as a ligand in the asymmetric molybdenum-catalysed alkylation of the allylic carbonate 100 (Scheme 24). Highly regioselective alkylations were achieved (101:102 49:1) and the chiral branched product 101 was obtained in 99% ee.

After this early report, the field of molybdenum-catalysed allylic alkylation has received a great deal of attention. A method that involves microwave-mediated acceleration under non-inert conditions was developed and used successfully in the reaction described in Scheme 24. Thus, a catalyst based on ligand 97 gave the branched product 101 in 98% ee after a reaction time of 7 minutes. The regioselectivity of the alkylation was slightly decreased (101:102 28:1). Differently substituted bispyridyl amide ligands were later synthesized and shown to induce even higher regioselectivities (up to 88:1) and enantioselectivities (>99% ee) after reaction times of 4-12 minutes.

Several structurally modified bispyridyl amide ligands have been synthesized and evaluated in the molybdenum-catalysed allylic alkylation in order to increase the understanding of the mechanism of this very useful reaction. Some applications to total syntheses of biologically active substances have recently

---

Scheme 23

In 1998, Trost and Hachiya used 97 as a ligand in the asymmetric molybdenum-catalysed alkylation of the allylic carbonate 100 (Scheme 24). Highly regioselective alkylations were achieved (101:102 49:1) and the chiral branched product 101 was obtained in 99% ee.

Scheme 24

After this early report, the field of molybdenum-catalysed allylic alkylation has received a great deal of attention. A method that involves microwave-mediated acceleration under non-inert conditions was developed and used successfully in the reaction described in Scheme 24. Thus, a catalyst based on ligand 97 gave the branched product 101 in 98% ee after a reaction time of 7 minutes. The regioselectivity of the alkylation was slightly decreased (101:102 28:1). Differently substituted bispyridyl amide ligands were later synthesized and shown to induce even higher regioselectivities (up to 88:1) and enantioselectivities (>99% ee) after reaction times of 4-12 minutes.

Several structurally modified bispyridyl amide ligands have been synthesized and evaluated in the molybdenum-catalysed allylic alkylation in order to increase the understanding of the mechanism of this very useful reaction. Some applications to total syntheses of biologically active substances have recently

---

57 Compared with reaction times of 3 hours in the original protocol, see ref. 55.
been reported. Molybdenum-catalysed allylic alkylations have also been performed with a solid supported bispyridyl amide ligand with excellent results.

Pyridyl amide ligands containing a phosphine moiety have been used with varying success in the copper-catalysed enantioselective conjugate addition of diethylzinc to enones.

2.6 Pyridyl Alcohols

Chiral pyridyl alcohols constitute a family of ligands that have been used extensively in asymmetric catalysis. They have been evaluated as ligands in asymmetric epoxidation of olefins, the nickel-catalysed enantioselective conjugate addition of diethylzinc to enones, and the enantioselective addition of diethylzinc to aldehydes (Scheme 3). The latter application has been, by far, the most comprehensively studied and a large number of pyridyl alcohol ligands have been shown to induce high to excellent levels of enantioselectivity. Some examples of reported ligands are shown in Figure 7 together with the enantioselectivity obtained in the catalytic reaction.

![Figure 7. Ligands used in the addition of diethylzinc to benzaldehyde. (Ligands 103, 6, and 104 ref. 65a, 105 ref. 65c, 106 ref. 65b, 107 ref. 9, 108 and 109 ref. 65e.)](image-url)

---

61 Belda, O.; Lundgren, S.; Moberg, C. Submitted for publication.
Large efforts have been devoted to finding efficient ways of synthesizing chiral pyridyl alcohols and a variety of successful methods have reported. Classical resolutions of racemic compounds as well as various kinetic resolution techniques have widely been employed. One example of an efficient dynamic kinetic resolution involving a ruthenium-catalysed isomerisation of the starting material was reported.

Several methods that involve asymmetric synthesis of chiral nonracemic pyridyl alcohols have been reported. Most of these include asymmetric reductions of the corresponding ketones. In a recent report, regio- and enantioselective functionalisation of 2-chloropyridine (110, Scheme 25) was achieved by deprotonation with the superbase BuLi-112 followed by the addition of benzaldehyde to yield chiral pyridyl alcohol 111 of moderate optical purity (58% ee). The absolute configuration of the major enantiomer formed was not reported.

![Scheme 25](image)

Some of the methods relying on asymmetric synthesis have shown somewhat poor results regarding the optical purity of the product desired. Therefore, separation of a scalemic mixture has often been required to provide the chiral pyridyl alcohol in an enantiomerically pure form.

The problems connected with the separation of scalemic (or racemic) mixtures can be avoided by the use of a diastereoselective synthesis starting from the chiral pool (vide supra). Some examples where chiral pyridyl alcohols have been synthesized from the chiral pool are shown in Scheme 26. Pyridyl alcohol 105 was obtained by a condensation reaction of (−)-pinocarvone (23) and the pyridinium bromide 113, followed by the diastereoselective introduction of the alcohol functionality. Compounds 108 and 109 were obtained as single diastereomers via the addition of the organometallic reagents 115 and 116, respectively, to the chiral ketone (−)-menthone (10). Cobalt-catalysed cocyclotrimerisation of acetylene with the chiral nitrile 118, derived from methyl (S)-lactate (117), yielded the optically pure pyridyl alcohol 119.

---

66 See Paper II
2.7 Pyridyl Phosphines, Phosphinites, and Phosphites

The electronic properties of a ligand are important to take into account when a catalyst is designed (vide supra). If the donor atoms of the ligand have different electronic properties, the difference in trans-influence may be used to achieve a more selective catalyst. A convenient way of introducing electronic dissymmetry is to use ligands containing different donor atoms. In this context, several phosphorus-nitrogen ligands (P,N-ligands) have been synthesized and used in asymmetric catalysis, in some cases with excellent results. Several chiral pyridine-containing P,N-ligands have been reported and some examples are discussed below.

Tridentate pyridyl diphosphine ligand 122 (Scheme 27) was synthesized in two steps from the diol 120, obtained by asymmetric reduction of the corresponding diketone using (–)-B-diisopinocampheylborane. Ligand 122 was evaluated in the ruthenium-catalysed asymmetric transfer hydrogenation of ketones and in asymmetric hydrogenations of imines with moderate results.

Scheme 26

Scheme 27

---

Katsuki and co-workers syntesised the pyridyl phosphines 126 (Scheme 28) from the chiral chloropyridines 123. Suzuki cross-coupling of the chloropyridines with \( o \)-hydroxyphenylboronic acid (124) gave the chiral pyridyl alcohols 125. The alcohol functionality was then used to introduce the phosphine moiety in a three-step procedure.

These \( P,N \)-ligands were used in the palladium-catalysed allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate as outlined in Scheme 7. The most efficient catalyst was based on ligand 126a and the (S)-enantiomer of the product was obtained in 97% ee. The enantioselectivity observed with ligand 126b was somewhat lower, 91% ee of the same enantiomer. Ligand 126a was also shown to be an efficient chiral inducer in the allylic alkylations of the cyclic substrates 2-cyclohexenyl pivalate (127) and 2-cycloheptenyl pivalate (128) with dimethyl malonate (Scheme 29). The alkylated products 129 and 130 were obtained in 87 and 94% ee, respectively.

Recently, a palladium complex of ligand 126a was used as the catalyst in asymmetric Baeyer-Villiger oxidations of cyclobutanones with good to excellent enantioselectivities. Palladium complexes of structurally similar pyridyl phosphines, derived from the chiral pool, have been used in the asymmetric allylic alkylation and in the asymmetric Heck addition. Efficient

---

catalysts based on pyridyl phosphine ligands with axial\textsuperscript{77} or planar\textsuperscript{78} chirality have also been reported.

Surprisingly few examples of chiral pyridyl phosphinite ligands have been reported, considering their straightforward syntheses from the corresponding chiral pyridyl alcohols. Pyridyl phosphinite ligands \textsuperscript{131} and \textsuperscript{133} were obtained by deprotonating the alcohol functionality followed by reaction with chlorodiphenylphosphine (Scheme 30).\textsuperscript{79} Rhodium complexes of these ligands were used in the asymmetric hydroformylation of olefins with varying success.

Scheme 30

A series of achiral pyridyl phosphinites were recently synthesized by van Leeuwen and co-workers and used to investigate the significance of the ligand bite angle \textit{(vide supra)} in palladium-catalysed allylic alkylations.\textsuperscript{80}

A few pyridyl phosphite ligands with axial chirality were reported by Faraone and co-worker.\textsuperscript{81} The chlorophosphite \textsuperscript{135} (Scheme 31), obtained from (S)-BINOL and phosphorus trichloride, was reacted with various 2-(1-hydroxyalkyl)pyridines \textsuperscript{134} to yield the chiral $P,N$-ligands \textsuperscript{136}. They were tested in the asymmetric palladium-catalysed allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 7). Ligand \textsuperscript{136a}, without a substituent in the 6-position of the pyridine ring, gave rise to a racemate in the catalytic reaction. When the 6-methyl-substituted ligand \textsuperscript{136b} was employed, the (S)-enantiomer of the product was formed, but with low optical purity (11\% ee). Increasing the steric hindrance of the pyridine moiety further (ligand \textsuperscript{136c}) gave a less selective catalyst, which afforded the same enantiomer in 7\% ee.

Scheme 31

One interesting $P,N$-ligand based on the 8-hydroxyquinoline scaffold was reported by Buono et al. in 1997.82 Ligand 140 (Scheme 32) was obtained by an exchange reaction between tri(dimethylamino)phosphine (137) and the chiral diamine 138, followed by addition of 8-hydroxyquinoline (139). Upon coordination to a metal ion, the phosphorus atom becomes a stereogenic centre and two diastereomeric complexes are possible. When ligand 140 was coordinated to palladium, however, only the complex with $R$ configuration at the phosphorus atom was formed.83 This ligand has been extensively used in asymmetric catalysis, and some examples include palladium-catalysed allylic alkylations82,84 and aminations,85 the copper-catalysed Diels-Alder reaction,86 and the copper-catalysed addition of diethylzinc to enones.84b,87

Scheme 32

---

2.8 Aim of the Thesis

This thesis deals with the syntheses of chiral, enantiopure pyridine-containing ligands and their applications in asymmetric catalysis. The syntheses of several families of ligands based on the pyridine backbone are described (Figure 8). The purpose of the study was to investigate the influence of the steric properties of the ligands employed in the palladium-catalysed allylic substitution. The applications of pyridyl pyrrolidine ligands and pyridyl oxazoline ligands to the catalytic reaction are presented in this context. Another goal was to demonstrate the utility of the chiral pool when synthesizing chiral enantiopure ligands. Thus, a series of chiral pyridyl alcohols were prepared from cheap, readily available natural products. The synthetic approach made the variation of steric and electronic properties of the pyridyl alcohols possible. The evaluation of these compounds as ligands in the enantioselective addition of diethylzinc to benzaldehyde is presented. Further functionalisations of the pyridyl alcohols into pyridyl phosphinites and pyridyl phosphites gave access to chiral $P,N$-ligands. Applications to palladium-catalysed allylic substitutions are discussed.

Figure 8. Various families of pyridine-containing ligands prepared.
3. Palladium-Catalysed Allylic Substitution

The palladium-catalysed allylic substitution (Scheme 33) is a powerful reaction, since a new stereogenic centre and a carbon-carbon or a carbon-heteroatom bond are formed at the same time. The reaction can be performed under mild conditions and a variety of substrates and nucleophiles can be used. Since the first report of an asymmetric palladium-catalysed allylic substitution by Trost and Siege in 1977,\textsuperscript{88} this reaction has developed into a versatile tool in asymmetric synthesis.

\[ \text{Scheme 33} \]

The reaction mechanism of the allylic substitution is well-known, at least when stabilised carbon or heteroatom nucleophiles are used (Figure 9).\textsuperscript{89} Association of an allylic substrate \textsuperscript{141}, typically an acetate or a carbonate, to palladium(0) followed by an oxidative addition generates the cationic \( \pi \)-allyl palladium(II) complex \textsuperscript{143}. The electrophilic palladium ion activates the allylic carbon atoms of the substrate for nucleophilic attack. Addition of the nucleophile gives the unstable palladium(0) olefin complex \textsuperscript{144}, which releases the product \textsuperscript{145} to regenerate the catalyst. The reaction proceeds, in principle, with net retention of configuration, since both the oxidative addition step and the nucleophilic addition occur with inversion of configuration at the reacting allylic carbon atom. However, the picture is more complicated, and several factors affect the stereochemical outcome of the reaction.

\[ X + \text{Nu}^- \xrightarrow{\text{Catalyst}} \text{Nu}^- + X \]


Figure 9. Catalytic cycle of the palladium-catalysed allylic alkylation.

Since the π-allyl complex plays a central role in the catalytic cycle, it is important to understand that it exists in a state of dynamic equilibrium. The ligands can dissociate, reassociate and change their geometry within the timescale of a catalytic cycle. There are at least two processes to take into account, syn-anti isomerisation and apparent allyl rotation. In the former process, also known as π-σ-π isomerisation, a syn-syn complex (Scheme 34) can be transformed into a syn-anti complex through a change in hapticity followed by rotation around the carbon-carbon bond and subsequent reformation of the π-allyl coordination. The isomerisation can proceed one step further and generate the corresponding anti-anti complex. When the substituents on the allyl group are large, as in the case of 1,3-diphenylallyl substrates, the syn-syn isomer is usually the predominant species in solution, but the equilibrium can be shifted to favour the syn-anti or the anti-anti isomer, for example, by the use of sterically demanding ligands.

Scheme 34

The apparent allyl rotation (Scheme 35) makes the two allylic termini switch positions with each other and in the process, the central carbon atom moves to the opposite side of the coordination plane. If the two ligands L and L’ are different, as in a C1-symmetric bidentate ligand, the apparent allyl rotation gives
rise to a diastereomeric complex. On the other hand, if L and L’ are identical, as in a $C_2$-symmetric bidentate ligand, this process generates two identical structures.

![Scheme 35](image)

The mechanism of apparent allyl rotation has been much debated. One suggestion involves a process similar to the syn-anti isomerisation (vide supra) with a rotation around the palladium-carbon bond in the $\eta^1$ intermediate.$^{90}$ Dissociation of one ligand, followed by rotation and reassociation, is another possibility.$^{91}$ A process in which a pentacoordinated allyl complex undergoes pseudorotation has also been suggested.$^{92}$

Depending on the choice of substrate, the enantiodiscriminating step can be either the oxidative addition or the nucleophilic attack.$^{90}$ The chiral information of a symmetrically substituted allylic substrate is lost upon oxidative addition, and the same meso allyl moiety is generated from both enantiomers of the substrate. If the catalyst is chiral, the allylic termini become diastereotopic and the enantioselectivity is determined by the regiochemistry of the nucleophilic attack. The ligand can affect the regioselectivity by steric or electronic effects, or by a combination of both. Electronic differences of the allylic termini can be induced by steric repulsion of the ligand, making one carbon-palladium bond longer (Figure 10). Nucleophilic attack is favoured at the allylic carbon atom with the longest carbon-palladium bond. Another way is to use a ligand with a set of electronically different donor atoms (Figure 1a), for example a $P,N$-ligand. Nucleophilic attack will preferentially occur at the allylic terminus trans to the phosphorus donor atom.

![Figure 10](image)

**Figure 10.** Electronic differences of the allylic carbon atoms, caused by steric repulsion of the ligand.

When a $C_2$-symmetric ligand is used, only one $\pi$-allyl complex has to be considered (the syn-anti, and anti-anti isomers are disregarded) and the task of

---


predicting the regioselectivity of the nucleophilic attack becomes more straightforward. If the transition state is early, it resembles the π-allyl palladium complex, and the nucleophile will attack the most electrophilic allylic carbon atom (path a, Scheme 36). On the other hand, if the reaction proceeds via a late transition state, the steric interactions in the produced olefin palladium complex have to be taken into account. In the addition step, the allyl group will rotate relative to the coordination plane, in order to make the palladium-olefin interaction possible. Nucleophilic attack that leads to the less sterically hindered complex will thus be favoured (path a, Scheme 36). However, in most cases it is not clear whether the transition state is early or late and both models should, therefore, be considered.

Scheme 36

4. Addition of Diethylzinc to Benzaldehyde

The catalytic asymmetric alkylation of a prochiral aldehyde using an organometallic reagent is one of the most useful methods to synthesize chiral secondary alcohols. A stereogenic centre is generated in the reaction and, at the same time, a new carbon-carbon bond is formed. This is one advantage of the enantioselective alkylation of aldehydes compared with the enantioselective reduction of ketones, in which the carbon skeleton is left unchanged throughout the reaction.

Early enantioselective alkylations of aldehydes were achieved with alkyllithiums and dialkylmagnesium reagents. However, a stoichiometric amount (sometimes more) of the chiral ligand was needed due to the high tendency of these organometallic reagents to add to the aldehyde, even at low temperatures.

The first catalytic enantioselective alkylation of benzaldehyde by the use of diethylzinc (Scheme 3) was reported by Oguni and Omi in 1984. They showed that a catalytic amount of optically active β-amino alcohols promoted the reaction. When (S)-leucinol was employed, (R)-1-phenyl-1-propanol was formed in 49% ee. The advantage of using diethylzinc instead of other organometallic reagents (vide supra) was that it did not add to the aldehyde in the absence of the chiral inducer. Consequently, the nonselective background reaction was no longer a problem.

Shortly after the successful application of (S)-leucinol as a ligand in the catalytic enantioselective alkylation of benzaldehyde, Noyori and co-workers showed that the β-amino alcohol DAIB (146, Figure 11) promoted the addition of diethylzinc to aromatic aldehydes with high levels of enantioselectivity (up to 99% ee). It was also shown that an equimolar mixture of diethylzinc and DIAB was unable to alkylate benzaldehyde, and that an excess of diethylzinc relative to DIAB was necessary for the reaction to take place, indicating the presence of a binuclear zinc complex in the catalytic cycle. Furthermore, a positive nonlinear effect was detected in the reactions employing DIAB as the ligand. When DIAB with an optical purity of 15% ee was used, (S)-1-phenyl-1-propanol was produced in 95% ee. Soai et al. used the β-amino alcohol DBNE (147, Figure 11) obtained from norephedrine, in the enantioselective alkylation of aliphatic aldehydes with excellent levels of enantioselectivity. Since these early reports of highly...

---

---
enantioselective alkylations of aldehydes a large number of successful ligands have been reported,\(^{100}\) and some examples are shown in Figure 11.

![Figure 11. Examples of ligands used in the enantioselective alkylation of aldehydes.](image)

Uncoordinated dialkylzinc reagents adopt a linear geometry around the central zinc atom, which makes the zinc-carbon bonds non-polar. As a consequence, the nucleophilicity of monomeric dialkylzincs is low and they do not react with aldehydes in hydrocarbon solvents. The reaction of a \(\beta\)-amino alcohol with a dialkylzinc compound generates an alkylzinc alkoxide 150 (Scheme 37), which is unable to act as an alkylating agent (\textit{vide supra}). Instead, this tricoordinate zinc complex acts as a bifunctional catalyst. The Lewis acidic zinc atom coordinates benzaldehyde \textit{via} an oxygen nonbonding orbital, which activates the carbonyl functionality for nucleophilic attack. Moreover, the Lewis basic oxygen atom in 150 coordinates another dialkylzinc to form the binuclear complex 151. This coordination distorts the geometry of the zinc reagent into a bent structure and the zinc-carbon bonds are elongated, resulting in increased nucleophilicity.

![Scheme 37](image)

The bornane backbone of 150 provides a clear distinction between the two diastereomeric faces of the five-membered zinc alkoxide ring. The two geminal methyl groups block the \textit{exo} face of the catalyst and the coordination of benzaldehyde is directed to the \textit{endo} face. Theoretical studies on the mechanism and on the origin of enantioselection, indicate that the alkyl transfer occurs \textit{via} a transition state of \textit{anti} trans geometry (152),\(^{101}\) \textit{i.e.} the five-membered zinc alkoxide ring and the terminal four-membered ring are oriented in an \textit{anti} fashion.


and the oxygen atom of the aldehyde uses its electron pair *trans* to the phenyl ring in the coordination to the zinc atom in the five-membered ring. The alkyl group is, consequently, transferred to the *Si* face of the aldehyde and the secondary product alkoxide is formed. The product is released from the catalyst as a zinc alkoxide and is further stabilised by the formation of dimers and, finally, tetramers.
5. Pyridine-Pyrrolidine Ligands

5.1 Background

Our interest in nitrogen-containing ligands for asymmetric catalysis led us to investigating trans-2,5-disubstituted pyrrolidines (153) as a structural element of such ligands (Figure 12). Several pyridyl oxazolines had previously been described by us and we wanted to compare the ability of the pyrrolidine moiety to induce enantioselectivity with that of the oxazoline. Pyridyl oxazoline 79 had been shown to induce moderate enantioselectivities (50% ee) in the palladium-catalysed allylic substitution of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 7). The easily available pyridyl pyrrolidines 154 and 155 were considered suitable candidates for such a comparison.

Figure 12

5.2 Syntheses of Ligands

The ligands were synthesized according to the procedure shown in Scheme 38. Diols 43 and 157 were obtained from the corresponding diketones by asymmetric reduction with baker’s yeast and (-)-B-chlorodiisopinocampheylborane, respectively. Mesylation of the alcohols and subsequent ring-closure with 2-(aminomethyl)pyridine (158) yielded the ligands desired.

Scheme 38
5.3 Results and Discussion

Ligands 154 and 155 were evaluated as ligands in the catalysis outlined in Scheme 7, and the results are shown in Table 1.

**Table 1.** Palladium-catalysed allylic substitution of rac-1,3-diphenyl-2-propenyl acetate in the presence of ligands 154, 155, and 79.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Ee (%)</th>
<th>Abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>154</td>
<td>18</td>
<td>S</td>
</tr>
<tr>
<td>155</td>
<td>64</td>
<td>R</td>
</tr>
<tr>
<td>79c</td>
<td>50</td>
<td>R</td>
</tr>
</tbody>
</table>

* The catalysts were generated in situ from 2 mol% bis[(π-allyl)palladium chloride] and 6 mol% ligand. The reactions were carried out in CH₂Cl₂ at rt.
* Determined by 'H NMR using Eu(hfc)₃ as chiral shift reagent.
* Results previously published, see ref. 40a.

The pyridine and pyrrolidine rings of ligands 154 and 155 have similar electronic properties, which means that the abilities of the ligands to induce enantioselectivity are based mainly on steric properties. Two diastereomeric π-allyl complexes can form as intermediates when a C₁-symmetric ligand is used in the alkylation of a symmetrically substituted allyl acetate (only the syn-syn complexes are considered, *vide supra*). The product is generally formed from the most stable isomer.⁹ In an earlier study by our group, it was assumed that complex 159, derived from ligand 79, is favoured over its diastereomer and that nucleophilic attack occurs on the allyl terminus *trans* to the oxazoline ring (Figure 13).⁴⁰ Based on this model, it seems reasonable to imagine that complex 160 is more stable than its diastereomer 161, because of the severe steric interaction of the two phenyl rings in the latter. The formation of the (R)-product can, therefore, be explained by nucleophilic attack on the allylic terminus *trans* to the pyrrolidine ring. These results indicate that a *trans*-2,5-distubstituted pyrrolidine moiety is more efficient in inducing enantioselectivity than an oxazoline, when they contain substituents of the same size.

**Figure 13.** Intermediate π-allyl complexes of ligands 79 and 155.
6. Pyridino-Oxazoline and Quinolino-Oxazoline Ligands: Influence of Steric Factors

6.1 Background

Several pyridyl oxazolines had previously been reported to induce varying levels of enantioselectivity in the palladium-catalysed allylic substitution of rac-1,3-diphenyl-2-propenyl acetate with malonate. Variation of the substituent in the 6-position of the pyridine ring had been shown strongly to influence the enantioselectivity (Figure 4). In an earlier study by our group, hydroxymethyl- and methoxymethyl-substituted ligands (2 and 76-78) had been synthesized and evaluated in the catalytic reaction.48

In order to increase the understanding of the factors that influence the enantioselectivity of the reaction, we decided to synthesize some novel pyridyl oxazolines and quinolyl oxazolines and evaluate them as ligands in the catalytic reaction.

6.2 Syntheses of Ligands

The quinolinyl oxazoline ligands 164 and 165 were synthesized from (R)-phenylglycinol and the 2-cyanoquinolines 162 and 163, respectively (Scheme 39). Copper chloride was chosen as the catalyst since the standard method (Scheme 15), which relies on zinc chloride as the catalyst, turned out to be unsuccessful in the reaction involving nitrile 163. The syntheses of ligands 167 and 169 started from 2-(hydroxymethyl)pyridine (134a). Introduction of the cyano group in the 6-position of the pyridine ring was followed by formation of the desired oxazoline 167 by the procedure described above. All attempts to methylate the hydroxy group, using either sodium hydride and methyl iodide in THF or sodium hydroxide and methyl iodide in DMSO, provided ligand 169 in low yields. We decided instead to carry out the O-methylation one step earlier in the synthesis. Thus, hydroxymethyl pyridine 166 was O-methylated under standard conditions to yield methoxymethyl pyridine 168. Formation of the oxazoline was achieved in a two-step procedure via the imidate, as described in Scheme 15. In the synthesis of 169 this protocol was found to be superior to the copper-catalysed process.
Scheme 39

We were also interested in the 7-hydroxyquinolinyl oxazoline 171 (Scheme 40), which we envisaged could be obtained from the corresponding nitrile 170. Zinc-catalysed formation of the oxazoline ring gave a mixture of two oxazoline-containing species that seemed to be in dynamic equilibrium. These species were assumed to be the quinolinyl oxazoline desired (171) and the corresponding tautomer 172. Due to problems appearing during attempts to isolate compound 171 in a pure form, the synthesis of this ligand was not pursued.

Scheme 40

6.3 Results and Discussion

The ligands were subjected to the catalytic reaction outlined in Scheme 7, and the results are presented in Table 2.
Table 2. Palladium-catalysed allylic substitution of rac-1,3-diphenyl-2-propenyl acetate in the presence of ligands 164, 165, 167, and 169.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
<th>Abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>164</td>
<td>99</td>
<td>73</td>
<td>R</td>
</tr>
<tr>
<td>165</td>
<td>n.r.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>167</td>
<td>93</td>
<td>88</td>
<td>R</td>
</tr>
<tr>
<td>169</td>
<td>99</td>
<td>82</td>
<td>R</td>
</tr>
</tbody>
</table>

*a The catalysts were generated in situ from 2 mol% bis[(π-allyl)palladium chloride] and 6 mol% ligand. The reactions were carried out in CH₂Cl₂ at rt.*

*b Isolated yields

*c Determined by HPLC using a chiral column (Daicel Chiralcel OD-H)

The steric influence exerted by ligand 164 is comparable to that of 6-methyl-substituted ligand 82 (Figure 4) and the enantioselectivities obtained with these ligands are almost identical (73 and 74% ee, respectively), whereas the use of ligand 165, with a hydroxy group in the plane of the quinoline ring, is detrimental to the catalysis. Interestingly, a ligand containing a 1-hydroxymethyl substituent in the 6-position of the pyridine ring (167) provides a more selective catalyst than does a ligand containing a 1-methoxymethyl substituent (169) in the same position (88 and 82% ee, respectively).

It is known that pyridines with a 1-hydroxyalkyl substituent in the 2-position of the pyridine ring adopt a conformation, in which the carbon-oxygen bond is in the plane of the pyridine ring, with the oxygen atom syn to the nitrogen atom. This conformation is favoured due to a hydrogen bond between the hydroxy proton and the pyridine nitrogen atom (Figure 14a). Pyridines with a 1-methoxyalkyl substituent in the 2-position adopt a different conformation, still with the carbon-oxygen bond in the plane of the pyridine ring, but with the oxygen atom anti to the nitrogen atom. This conformation is the most stable one mainly as a result of the repulsion of the electron pairs in the syn conformation (Figure 14b), but also due to a stabilising interaction of the nitrogen lone pair with the C-O antibonding σ-orbital (Figure 14c).

Figure 14. Intramolecular hydrogen bond (a), electron pair repulsion (b) and stabilising orbital interaction (c).

---

Palladium complexes of 6-(1-hydroxymethyl)pyridinooxazolines (Figure 15a) and 6-(1-methoxymethyl)pyridinooxazolines (Figure 15b) have further been studied in our group. The conformations of the ligands in the different complexes were deduced by X-ray crystallography, DFT-calculations and NMR experiments. It was shown that the ether ligand adopts a conformation similar to that in the free ligand, that is with the methoxy group turned away from the palladium ion. The situation was less clear with the alcohol ligand. It was shown that this ligand undergoes a conformational change when going from palladium(II) to palladium(0). The ligand adopts an anti planar structure in the palladium(II) complex, whereas in the palladium(0) complex, the hydroxy group is turned slightly towards palladium, forming an axial hydrogen bond to the metal ion. With this in mind, it is possible to rationalise the results obtained with these ligands in the catalytic reaction.

![Figure 15. Conformations of ligands containing a 1-hydroxyalkyl substituent (a) and a 1-methoxyalkyl substituent (b).](image)

Variations of the R- and R’-group on the hydroxyalkyl substituent had little influence on the enantioselectivities observed with the ligands [88% ee with 167 (R1=R2=H), 90% ee with 76 (R1=–Bu, R2=H) and 95% ee with 77 (R1=H, R2=–Bu), Figure 15]. With the hydroxy group in an axial position to palladium, the R-groups are located far from the allyl group and it is thus resonable that they do not have a major influence on the stereochemical outcome of the reaction.

Methoxyalkyl substituents, on the other hand, had a remarkable effect on the enantioselectivities attained with the ligands [82% ee with 169 (R1=R2=H), >99% ee with 2 (R1=–Bu, R2=H) and 15% ee with 78 (R1=H, R2=–Bu), Figure 15]. The preferred conformation of the methoxyalkyl group places the steric bulk in close vicinity to the allyl group, making the steric interaction very efficient.

This study shows that the substituent in the 6-position of the pyridine ring has a large influence on the enantioselectivity obtained with the ligand. Furthermore, the conformational preference of the ligand can be used to bring sterically demanding groups in close vicinity to the substrate and thus induce high levels of enantioselectivity.

7. Chiral Ligands Containing Crown Ethers

7.1 Background

Multiple interactions with a substrate are often found in enzyme-catalysed reactions. Organometallic catalysts based on ligands that are capable of coordinating a metal ion and, at the same time, being involved in a second interaction with the reacting substrate are attracting current interest. The secondary interactions can be of various types, for example hydrogen bonding, π-π-stacking or electrostatic interaction, and can result in increased selectivity as well as activity of a catalyst in favourable cases. Secondary interactions may also be used to bind a specific substrate to the catalyst and in that way selectively transform one substrate in a mixture of potential substrates (Figure 16a). Another function can be to induce regioselectivity in a reaction on a substrate containing several reactive functional groups. Some examples have been published, where the ligand interacts with an incoming nucleophile in palladium-catalysed allylic substitutions (Figure 16b). This approach is particularly attractive when a prochiral nucleophile is used, since the new stereogenic centre is created far from the basic ligand scaffold.

Figure 16. Selective substrate binding (a) and secondary interaction with a nucleophile (b), exemplified by ditopic ligands containing crown ethers.

We wanted to investigate the possibility to increase the reactivity and selectivity in the palladium-catalysed allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate by the use of ligands capable of secondary interactions with the nucleophile. The strategy was to synthesize ligands containing crown ether units as structural details, capable of binding the counterion of the nucleophile and thus making the secondary interaction possible. Several chiral ditopic ligands meeting these demands were synthesized and some were evaluated as ligands in the catalytic reaction.

7.2 Ligand Synthesis and Application in Allylic Alkylation

Esterification of the pyridyl oxazoline 167 with 4-carboxybenzo-18-crown-6 (173) using EDCI yielded the ligand 174 (Scheme 41). This ligand was evaluated in the allylation reaction with the preformed sodium salt of dimethyl malonate as the nucleophile and allylpalladium chloride dimer as the metal source. A variety of reaction conditions were tested, under which the nucleophile counter ion was assumed to be trapped by the crown ether. All results obtained with ligand 174 were compared with those obtained with ligand 175 (Figure 17) under the same reaction conditions, with the purpose of detecting differences in the reactivity and/or selectivity of the two systems.

Scheme 41

When the reactions were performed in THF at low concentrations (0.1 M), a small difference in reactivity was seen, the catalyst based on ligand 174 being 2.5 times more active than that based on ligand 175. No difference in reactivity could be detected at higher concentrations. These observations can be explained by the fact that the concentration of the nucleophile is quite high under these conditions, considering that the nucleophile salt is present in excess. In addition, the reactivity of the nucleophile is enhanced by the ability of THF to solvate the counter ion.

The sodium salt of the nucleophile was no longer completely soluble when the solvent was changed to dichloromethane. Under these conditions the crown ether solubilised a part of the nucleophile salt, thus making the nucleophile available for the reaction. To make the comparison of the two ligands more fair, benzo-18-
crown-6 was added to the reaction mixture, when ligand 175 was employed (1:1 ligand:crown ether). At low concentration (0.024 M), the catalyst based on ligand 174 was found to be twice as reactive as that based on ligand 175. Both catalysts favoured the formation of the (R)-product but the enantioselectivity was slightly higher in the reactions with the combination of ligand 175 and benzo-18-crown-6 than in those employing ligand 174 (75 and 67% ee, respectively).

In order to keep the concentration of the nucleophile low, we wanted to generate the nucleophile in situ and in close proximity of the reaction site. A method used earlier by Ito and co-workers was tested.\(^{106}\) Potassium fluoride was used as the base in a solid-liquid two-phase system with benzene as the solvent. The basicity of the fluoride ion is greatly increased when the potassium counter ion is bound to the crown ether. In this way the nucleophile can only be generated by potassium fluoride that has previously been complexed to the crown ether, hence in direct connection with the reaction site when a ditopic ligand is used. When the ligands were evaluated under these conditions, a two-fold excess of potassium fluoride was used in benzene. Benzo-18-crown-6 was added in the reactions involving ligand 175. When dimethyl malonate was used as the nucleophile precursor, no reaction occurred. The diester was probably not acidic enough to be deprotonated by the fluoride ion. The nucleophile precursor was, therefore, replaced by acetyl-acetone, which should be more easily deprotonated. When this method was used, the product was indeed formed but the reaction rates of the two catalytic systems were too low to allow a reliable comparison.

The \(C_2\)-symmetric bisoxazoline ligand 176 was synthesized from the corresponding bisoxazoline diol\(^ {107}\) and compared with its phenyl ester analogue 177 (Figure 18) in the allylation reaction described above. The reactions were performed in dichloromethane and the nucleophile was generated in situ from dimethyl malonate, BSA, and KOAc in order to keep the concentration of the nucleophile low. Benzo-18-crown-6 was added to the reactions using 177 as the ligand. No differences in reaction rates could be observed.

Figure 18

8. Syntheses of Chiral Enantiopure Pyridyl Alcohols Starting from the Chiral Pool. Applications in Asymmetric Catalysis\textsuperscript{III,IV}

8.1 Background

Chiral enantiopure 2-(1-hydroxyalkyl)pyridines had earlier been studied by our group. The two diastereomeric pyridyl alcohols \textit{181} and \textit{182} (Scheme 42) were synthesized in a two-step procedure from the nitrile \textit{179}, derived from (–)-menthol.\textsuperscript{108} Addition of 2-lithiopyridine (\textit{178}) to the nitrile, followed by aqueous work-up gave the pyridyl ketone \textit{180}, which was reduced to the diastereomeric alcohols in a ratio of 83:17.

\begin{center}
\begin{tikzpicture}
  \node (n1) at (0,0) {\textit{179}}; 
  \node (c1) at (1,0) {\textit{180}}; 
  \node (c2) at (2,0) {\textit{181}}; 
  \node (c3) at (3,0) {\textit{182}}; 
  \node (c4) at (4,0) {\textit{183}}; 
  \draw (n1) -- (c1) node [midway, above] {41\%}; 
  \draw (c1) -- (c2) node [midway, above] {74\%}; 
  \draw (c2) -- (c3) node [midway, above] {16\%}; 
  \draw (c3) -- (c4) node [midway, above] {41\%}; 
\end{tikzpicture}
\end{center}

\textbf{Scheme 42}

Due to the many applications of enantiopure 2-(1-hydroxyalkyl)pyridines as ligands in asymmetric catalysis (\textit{vide supra}) we wanted to extend the scope of this synthetic approach. The aim was to demonstrate the utility of the chiral pool when synthesizing series of enantiopure pyridyl alcohols and $C_2$-symmetric 2,2'-bipyridines.

8.2 Syntheses of Ligands

8.2.1 2-(1-Hydroxyalkyl)pyridines

We chose D-mannitol, L-lactic acid, L-mandelic acid, and (–)-menthol as starting materials in the syntheses of chiral enantiopure 2-(1-hydroxyalkyl)pyridines. The diastereomeric pyridyl alcohols \textit{184} and \textit{185} (Scheme 43) were obtained in one step by the reaction of 2-lithiopyridine (\textit{178}) with the aldehyde \textit{183}, synthesized from D-mannitol.\textsuperscript{109}

Scheme 43

The methyl ester 186 (Scheme 44) was obtained from esterification of L-lactic acid with methanol, followed by O-methylation. Addition of 2-lithiopyridine (178) to the ester gave the pyridyl ketone 187, which was reduced in situ to yield a mixture of the alcohols 188 and 189. Unfortunately, the epimeric alcohols had to be transformed into the corresponding silyl ethers to make chromatographic separation possible. The need for additional steps decreased the yields significantly. Subsequent deprotection yielded the pyridyl alcohols 188 and 189 in low overall yields, 13 and 4%, respectively.

Scheme 44

The pyridyl alcohol 192 (Scheme 45) was synthesized according to an analogous procedure, starting from the ester 190, obtained from L-mandelic acid. Reaction of 2-lithiopyridine (178) and 190 generated pyridyl ketone 191, which was reduced in situ at –78 °C to yield 192 as a single diastereomer.

Scheme 45

8.2.2 2-Bromo-6-(1-hydroxyalkyl)pyridines and 2,2'-Bipyridines

The same strategy was used to synthesize a number of pyridyl alcohols with a bromo substituent in the 2-position of the pyridine ring. These compounds were recognised as interesting synthons for the syntheses of various types of ligands, such as 2,2'-bipyridines and 2-aryl-substituted pyridyl alcohols. Thus, addition of 2-bromo-6-lithiopyridine (9), generated from 2,6-dibromopyridine (193, Scheme 46), to the aldehyde 183 gave the diastereomeric alcohols 194 and 195. Nickel-mediated homocoupling of the major isomer (194) gave the bipyridine
desired, but it was not possible to obtain a pure sample by the use of column chromatography. Therefore, 194 was first transformed into the corresponding tert-butyldimethylsilyl ether, which was then subjected to the nickel-mediated homocoupling, to give the bipyridine 196 in 51% yield over two steps. Desilylation provided the C₂-symmetric bipyridine 197 in quantitative yield.

Scheme 46
Addition of 2-bromo-6-lithiopyridine (9) to the ester 186 gave the pyridyl ketone 198 expected, in good yield (Scheme 47). Reduction of the ketone gave an epimeric mixture of pyridyl alcohols that had to be converted into the corresponding tert-butyldimethylsilyl ethers to make their separation by column chromatography possible. Thus, compounds 199 and 200 were isolated in 22 and 20% yield, respectively. Nickel-mediated homocoupling of the 2-bromopyridine derivative 199 and subsequent desilylation of compound 201 yielded the bipyridine 202.

Scheme 47
The 2-bromo-substituted pyridyl alcohol 203 (Scheme 48) was obtained as a single isomer by an analogous procedure, starting from the methyl ester 190.
Protection of the hydroxy group, followed by the nickel-mediated homocoupling and desilylation yielded the bipyridine \( 205 \) desired.

\[
\text{Scheme 48}
\]

8.2.3 2-Bromo-6-(1-hydroxyalkyl)pyridines Derived From Neomenthyl Nitrile

The syntheses of 2-bromo-substituted pyridyl alcohols derived from \((-\)-menthol proved not to be as straightforward as expected. When neomenthyl nitrile (179) was added to 2-bromo-6-lithiopyridine (9) in diethyl ether, no reaction was observed and the nitrile was recovered unchanged (Scheme 49).

\[
\text{Scheme 49}
\]

An increase in reactivity was accomplished by the use of a mixture of THF, hexane, and diethyl ether (1:1:2) as the solvent, but a complicated mixture of products was produced. This was probably due to unselective lithiation of 2,6-dibromopyridine to give several differently lithiated pyridine species.\(^\text{110}\) A reverse addition technique was employed to achieve clean monolithiation of 2,6-dibromopyridine in this solvent mixture. Thus, a solution of 2,6-dibromopyridine was added drop-wise to a solution of \( n \)-BuLi at \(-78^\circ C \) to generate 2-bromo-6-lithiopyridine (9) cleanly. In this solvent mixture, the addition of 2-bromo-6-lithiopyridine to neomenthyl nitrile (179), followed by aqueous work-up, yielded the pyridyl ketone \( 206 \) in 58% yield (Scheme 50). Reduction gave the diastereomeric alcohols \( 207 \) and \( 208 \) in 54 and 14% yield, respectively, after separation by column chromatography.

In the synthesis of the neomenthyl ketone 206, the epimeric menthyl ketone 209 (Figure 19) was formed to a small extent. The amount of the epimerised ketone formed was found to depend on the ratio of solvents in the solvent mixture used. When the reaction was performed in a 1:1:3 mixture of THF, hexane, and diethyl ether, 206 and 209 were formed in a ratio of 84:16 in 71% total yield. Unfortunately, separation by column chromatography was troublesome and only the neomenthyl ketone 206 was isolated in a pure form (58%, vide supra). Interestingly, when the solvent mixture was changed to 1:1:2 (THF:hexane:diethyl ether) the formation of the equatorial isomer 209 was favoured (82:18), but the total yield was low (44%). Due to the additional problem of separation by column chromatography, the menthyl ketone 209 was not obtained in a pure form by this approach. Attempts were made to epimerise the neomenthyl ketone 206 into the menthyl ketone 209 by the use of potassium hydroxide in toluene with a catalytic amount of 18-crown-6. After 22 hours of heating at reflux, a mixture of 206 and 209 was obtained in a 67:33 ratio. Once more, separation by column chromatography did not provide the pure menthyl ketone 209.

Figure 19

We decided to investigate the possibility of epimerising neomenthyl nitrile (179) before the addition of 2-bromo-6-lithiopyridine. We assumed that menthyl nitrile (210, Scheme 51), with the cyano group in an equatorial position, would be more reactive than 179 with the cyano group in an axial position. Furthermore, reaction of menthyl nitrile with 2-bromo-6-lithiopyridine was assumed to preferably yield the menthyl ketone 209.
Attempts to epimerise neomenthyl nitrile (179) into menthyl nitrile (210) had previously been made in our group. A variety of bases (\textit{n}-BuLi, lithium diisobutylaluminium and sodium methoxide) were used but the starting material was recovered unchanged in all cases. The synthesis of 179 by alternative routes also failed.

Encouraged by the partial epimerisation of the neomenthyl ketone 206 in toluene at reflux (\textit{vide supra}), we subjected neomenthyl nitrile (179) to the same reaction conditions. After heating at reflux for 22 hours, a 50:50 mixture of 179 and the epimerised menthyl nitrile (210) was obtained. When the reaction was carried out in butanol, with 30 mol\% of potassium tert-butoxide as base at 180 °C under microwave irradiation, a 54:46 mixture of 179 and 210 was obtained in 11 minutes. Due to the problem of removing the solvent from the rather volatile nitrile mixture (a considerable amount of the nitrile mixture was evaporated under high vacuum) several of solvents and bases were evaluated for the reaction heated by microwave irradiation. The best result was achieved in ethanol with 15 mol\% of sodium ethoxide as the base, yielding a 50:50 mixture of the nitriles after 20 minutes at 160 °C. Unfortunately, all attempts failed to separate the epimeric nitriles by distillation or by column chromatography. Pure menthyl nitrile (210)\textsuperscript{112} can be synthesized by an alternative procedure from the corresponding carboxylic acid, which can be obtained by the reaction of carbon dioxide with the Grignard reagent of (-)-menthyl chloride.\textsuperscript{113}

In order to generate the menthyl ketone 209, a 50:50 mixture of the epimeric nitriles was treated with 2-bromo-6-lithiopyridine in a 1:1:2 mixture of THF, hexane, and diethyl ether (Scheme 52). The menthyl ketone desired was obtained together with an unidentified by-product that could not be removed by column chromatography. Reduction of the ketone gave a 90:10 mixture of diastereomeric alcohols, 211 being the major isomer. A pure sample of the pyridyl alcohol 211 was obtained in 24% yield over two steps, after column chromatography. The minor diastereomer was unfortunately not isolated in a pure form.

---

\textsuperscript{113} Lebedev, M. Y. \textit{Personal Communication}
A series of sterically and electronically modified pyridyl alcohols were obtained by the introduction of various aryl groups in the 6-position of the pyridine ring. Thus, the 6-aryl-2-(1-hydroxyalkyl)pyridines 212-218 were synthesized via the Suzuki coupling of the 2-bromo-substituted pyridyl alcohols 203 and 207 with phenylboronic acid, o-methylphenylboronic acid, p-methoxyphenylboronic acid, and p-(trifluoromethyl)phenylboronic acid as outlined in Scheme 53. The reactions were carried out in a two-phase system of toluene, methanol, and water with tetrakis(triphenylphosphine)palladium and sodium carbonate and gave the 6-aryl-substituted pyridyl alcohols desired in 64-93% yield.

8.3 Determination of Absolute Configurations

The absolute configurations of the neomethyl alcohols 181 and 182 (Scheme 42) had previously been determined in our group by the use of NMR data of their Mosher ester derivatives. Diastereomeric esters were obtained by esterification of the major isomer of the alcohols with (R)- and (S)-MTPA. The esters were assumed to adopt the preferred conformation according to the model proposed by Mosher and Dale, with the trifluoromethyl group in the same plane as the carbonyl group, as well as the proton on the former carbinol carbon atom (Figure 20). In the ester derived from (R)-MTPA, an upfield shift of the signal assigned to

to the proton in the 2-position of the cyclohexane ring compared with the signal assigned to the same proton in the diastereomeric ester derived from (S)-MTPA, suggested that the major isomer should have \( R \) configuration at the carbinol carbon atom.

\[ \text{Figure 20. An ester derived from (R)-MTPA.} \]

However, Grayson and co-workers\(^\text{115}\) used an alternative synthetic route to obtain the pyridyl alcohols 181, 182 together with the two epimeric alcohols 219 and 220 (Figure 21), and determined their absolute configurations by X-ray crystallography. Their results showed that the absolute configurations of the carbinol carbon atoms in 181 and 182 were, in fact, opposite to those assigned by us. As a consequence, the 2-bromo-substituted pyridyl alcohols 207 and 208 were shown to have \( S \) and \( R \) configuration, respectively, at the carbinol centres, considering that 207 was obtained as the major isomer in the reduction of ketone 206. This assumption was corroborated by similarities of the NMR spectra of 181 and 182. By comparison of the NMR data of the menthyl epimer 211 with that of the pyridyl alcohols 219 and 220, pyridyl alcohol 211 was assumed to have \( R \) absolute configuration at the carbinol centre.

\[ \text{Figure 21} \]

Analogous determinations had also been made for the pyridyl alcohols derived from D-mannitol, L-lactic acid, and L-mandelic acid.\(^\text{116}\) The absolute configuration of pyridyl alcohol 192 was determined from NMR data of the corresponding Mosher ester. The presence of a NOE between the methoxy group in the Mosher acid part of the ester and the pyridine protons, and the absence of a NOE between the same methoxy group and the benzylic proton indicated this pyridyl alcohol to have \( S \) absolute configuration at the carbinol centre. Since our previous determinations had been proven wrong, we decided to confirm the absolute configuration of pyridyl alcohol 192 by the use of X-ray crystallography.\(^\text{116}\) It was shown that the absolute configuration was not in


\(^{116}\) The X-ray structure of pyridyl alcohol 192 was determined by Dr. Andreas Fischer, KTH Chemistry, Inorganic Chemistry, Stockholm, Sweden.
agreement with that assigned from the NMR experiments, and 192 was shown to have \( R \) configuration at the carbinol carbon atom.

Debromination of compound 203, via lithiation using \( n \)-BuLi followed by quenching with water, yielded 192 and was thus shown to have \( R \) configuration at the carbinol centre. A comparison of the NMR data of 188 and 189 with that of 192 and its diastereomer,\(^{117}\) suggested 188 to have \( R \) configuration at the carbinol centre. In analogy, silylated pyridyl alcohol 199 was assumed to have \( R \) configuration at the carbinol centre.

When pyridyl alcohol 194 was subjected to the nickel-mediated homocoupling (Scheme 46), some debromination occurred to yield 184. These alcohols were assumed to have \( S \) configuration at the carbinol centres. This assumption was based on the similarities of the NMR data of 184, 194, and their diastereomers, compared with the NMR data of the diastereomeric pairs of the alcohols derived from L-lactic acid and L-mandelic acid. Attempts were made to crystallise pyridyl alcohol 194 but no crystals suitable for X-ray crystallography were, unfortunately, obtained.

8.4 Results and Discussion

A number of the pyridyl alcohols and 2,2'-bipyridines described above were evaluated as chiral inducers for the addition of diethylzinc to benzaldehyde and the results are reported in Table 3. All reactions were carried out in toluene at 0 °C for 20 h. The reaction conditions were not optimised for each ligand since we were primarily interested in comparing the abilities of the various ligands to induce enantioselectivity.

\(^{117}\) When ketone 191 was reduced at room temperature, a diastereomeric mixture of alcohols was obtained in a ratio of 8:1, 192 being the major one.
Table 3. Addition of diethylzinc to benzaldehyde in the presence of chiral pyridyl alcohols and 2,2'-bipyridines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
<th>Abs. Config</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>181</td>
<td>94</td>
<td>64</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>182</td>
<td>96</td>
<td>64</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>207</td>
<td>84</td>
<td>69</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>208</td>
<td>88</td>
<td>56</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>211</td>
<td>94</td>
<td>28</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>216</td>
<td>80</td>
<td>79</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>217</td>
<td>96</td>
<td>79</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>218</td>
<td>84</td>
<td>82</td>
<td>S</td>
</tr>
<tr>
<td>9</td>
<td>192</td>
<td>94</td>
<td>67</td>
<td>S</td>
</tr>
<tr>
<td>10</td>
<td>203</td>
<td>77</td>
<td>54</td>
<td>S</td>
</tr>
<tr>
<td>11</td>
<td>212</td>
<td>93</td>
<td>67</td>
<td>S</td>
</tr>
<tr>
<td>12</td>
<td>213</td>
<td>74</td>
<td>61</td>
<td>S</td>
</tr>
<tr>
<td>13</td>
<td>214</td>
<td>85</td>
<td>66</td>
<td>S</td>
</tr>
<tr>
<td>14</td>
<td>215</td>
<td>83</td>
<td>70</td>
<td>S</td>
</tr>
<tr>
<td>15</td>
<td>202</td>
<td>88</td>
<td>47</td>
<td>S</td>
</tr>
<tr>
<td>16</td>
<td>205</td>
<td>90</td>
<td>83</td>
<td>S</td>
</tr>
</tbody>
</table>

* The reactions were carried out in toluene at 0 °C with 10 mol% ligand and 2.0 eq Et₂Zn (1.1 M in toluene). b GC-yields. c Determined by GC.

When the ligands derived from (-)-menthol were employed, the absolute configuration of the 1-phenyl-1-propanol (17, Scheme 3) formed was evidently determined by the absolute configuration of the carbinol centre of the ligand. Thus, pyridyl alcohols 181 and 182 favoured the formation of opposite enantiomers of the product but with the same selectivity (64% ee, entries 1-2). This observation is different to that made by Grayson and co-workers.\textsuperscript{118} The enantioselectivities attained with the 2-bromo-substituted pyridyl alcohols 207, 208 and 211 were strongly influenced by the relative configuration of the stereocentres of the ligands (69, 56 and 28% ee, respectively, entries 3-5). The steric scaffold of the menthyl ligand 211 was apparently less efficient at transferring the chirality than the scaffold of the corresponding neomenthyl ligand 208. The introduction of an aryl group in the 6-position of the pyridine ring had a positive effect on the enantioselectivities, and ligands 216, 217, and 218 gave the (R)-product in 79, 79 and 82% ee, respectively (entries 6-8).

The formation of the (S)-product was favoured, when the ligands derived from L-mandelic acid were subjected to the catalytic reaction. The enantioselectivity obtained with the 2-bromo-substituted ligand 203 was lower than that obtained with ligand 192 (54 and 67% ee, entries 10 and 9, respectively). Interestingly, the

\textsuperscript{118} The reactions were run in a 1:1 mixture of toluene and hexane and ligands 181 and 182 were reported to favour the formation of the (R)-product in 12 and 23% ee, respectively. See ref. 115.
selectivities induced by the 2-aryl-substituted ligands 212, 214, and 215 (67, 66 and 70% ee, entries 11, 13 and 14, respectively) were not markedly different from that induced by 192. The selectivity was, however, decreased to some extent when ligand 213, with a methyl group in the ortho position, was employed (61% ee, entry 12).

One interesting observation was that the electronic properties of the ligands had only a minor effect on the enantioselectivities observed. Thus, ligands containing a phenyl, a p-methoxyphenyl, or a p-(trifluoromethyl)phenyl group in the 6-position of the pyridine ring gave rise to roughly the same enantioselectivities (entries 6-8 and entries 11, 13 and 14). This is contrary to the results obtained with hydroxyalkylimidazoline ligands published by Casey and Smyth. In this study the electronic properties of the imidazoline ring was shown to strongly influence the levels of enantioselectivity obtained in the addition of diethylzinc to various aldehydes.

The bipyridines derived from lactic acid and mandelic acid, 202 and 205, were also evaluated as ligands in the addition reaction. The formation of (S)-1-phenyl-1-propanol was favoured in both cases, but the enantioselectivity obtained with the mandelic acid derived 205 was markedly higher (83% ee) than that obtained with the lactic acid derived 202 (47% ee). Interestingly, the bipyridine 205 acted as a more efficient chiral inducer than the 6-aryl-substituted ligands 212-215 (entries 16 and 11-14).

The sense of asymmetric induction for this series of ligands is in accordance with the enantioselectivity model proposed for β-aminoalcohols. The bulky R-group on the carbinol carbon atom directs the coordination of the aldehyde to the less sterically hindered face of the five-membered chelate ring (Figure 22). The aldehyde coordinates to the zinc atom in the five-membered chelate ring in an anti fashion (vide supra) and two competing transition structures can be drawn. The anti cis structure is higher in energy due to repulsive interactions between the ethyl groups in the four-membered ring, meaning that the (S)-product is preferentially formed via the anti trans structure.

Figure 22

9. Syntheses of Chiral Enantiopure \( P,N \)-Ligands. Applications in Asymmetric Catalysis

9.1 Background

We were interested in synthesizing some novel \( P,N \)-ligands starting from chiral enantiopure pyridyl alcohols and evaluate them as ligands in palladium-catalysed allylic alkylations. Methods for synthesizing series of structurally modified pyridyl alcohols had previously been developed in our group (vide supra) and the introduction of various phosphorus moieties by the use of the alcohol functionality present was envisaged.

9.2 Syntheses of Ligands

9.2.1 Pyridyl Phosphinites

The pyridyl phosphinite 221 was obtained from the pyridyl alcohol 192 by deprotonation using \( n \)-BuLi followed by reaction with chlorodiphenylphosphine (Scheme 54). Partial decomposition of the product was observed during purification by column chromatography and the phosphinite moiety was found to slowly oxidise upon standing. In situ protection of the labile phosphorus moiety using \( BH_3 \).SMe\(_3\) provided compound 222 in 77% yield. The easier purification and higher stability of the \( BH_3 \)-protected 222 compared with the unprotected 221, made us choose this approach in the synthesis of the 6-phenyl-substituted analogue 223.

![Scheme 54](image)

The diastereomeric neomenthyl ligands 224 and 225 (Scheme 55) were synthesized according to the same reaction sequence described above in 43 and 62% yield, respectively.
9.2.2 Pyridyl Phosphines

We were also interested in the pyridyl phosphine \( 228 \) (Scheme 56), which we envisaged could be obtained by a nucleophilic displacement of the tosylate group in compound \( 226 \) with lithium diphenylphosphide. However, no reaction was observed and the starting material was recovered unchanged. The leaving group was changed to mesylate and \( 227 \) was subjected to the same reaction. Once more, only starting material was recovered after the reaction.

The somewhat less sterically hindered mesylated pyridyl alcohol \( 229 \) (Scheme 56) was also used in the reaction. Yet again, only starting material was recovered, even when the reaction mixture was heated under microwave irradiation to 100 °C in a closed vessel. At 150 °C a complex mixture of unidentified products was obtained.

Due to these problems, the syntheses of pyridyl phosphines along this route were no longer pursued.

9.2.3 Pyridyl Phosphites

The pyridyl phosphite ligands \( 231 \) and \( 232 \) were synthesized as outlined in Scheme 57. The appropriate enantiomer of the chlorophosphite \( 135 \), obtained from BINOL and phosphorus trichloride, was reacted with the pyridyl alcohol \( 192 \) and triethylamine in toluene at low temperature, to yield the pyridyl phosphinites as moisture sensitive solids.
9.3 Results and Discussion

The $P,N$-ligands described above were used as ligands in the palladium-catalysed alkylation of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 58). Different methods to generate the catalysts were employed, depending on the nature of the ligand used. Attempts to generate the catalyst in situ by the use of allylpalladium chloride dimer were unsuccessful for the BH$_3$-protected ligands 222-225, which had to be deprotected with diethyl amine before use. The catalysts could also be generated in situ from the BH$_3$-protected ligands by the use of palladium acetate.\textsuperscript{120} The results of the catalytic reactions are presented in Table 4.

Table 4. Palladium-catalysed allylic substitution of rac-1,3-diphenyl-2-propenyl acetate with malonate in the presence of ligands 221-224 and 231-232.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Pd:L (% cat.)</th>
<th>Pd-source</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>Ee (%)</th>
<th>Abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>221</td>
<td>1:1.5 (4)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>4</td>
<td>100</td>
<td>46</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>222</td>
<td>1:1 (4)</td>
<td>Pd(OAc)₂</td>
<td>1.5</td>
<td>100</td>
<td>48</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>222</td>
<td>1:1 (2)</td>
<td>Pd(OAc)₂</td>
<td>17</td>
<td>100</td>
<td>48</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>222²</td>
<td>1:1 (4)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>8</td>
<td>100</td>
<td>48</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>222²</td>
<td>1:1.5 (4)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>8</td>
<td>100</td>
<td>47</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>223</td>
<td>1:1 (2)</td>
<td>Pd(OAc)₂</td>
<td>189</td>
<td>36</td>
<td>52</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>223³</td>
<td>1:1 (4)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>100</td>
<td>99</td>
<td>56</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>223³</td>
<td>1:1.5 (4)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>4</td>
<td>100</td>
<td>10</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>224</td>
<td>1:1 (2)</td>
<td>Pd(OAc)₂</td>
<td>4</td>
<td>95</td>
<td>44</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>224</td>
<td>1:1 (4)</td>
<td>Pd(OAc)₂</td>
<td>1</td>
<td>100</td>
<td>44</td>
<td>R</td>
</tr>
<tr>
<td>11</td>
<td>225</td>
<td>1:1 (2)</td>
<td>Pd(OAc)₂</td>
<td>16</td>
<td>95</td>
<td>50</td>
<td>S</td>
</tr>
<tr>
<td>12</td>
<td>231</td>
<td>1:1 (2)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>31</td>
<td>99</td>
<td>51</td>
<td>S</td>
</tr>
<tr>
<td>13</td>
<td>231</td>
<td>1:1 (4)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>21</td>
<td>99</td>
<td>51</td>
<td>S</td>
</tr>
<tr>
<td>14</td>
<td>232</td>
<td>1:1 (2)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>31</td>
<td>100</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>15</td>
<td>232</td>
<td>1:1 (4)</td>
<td>[(C₃H₅)PdCl]₂</td>
<td>21</td>
<td>100</td>
<td>5</td>
<td>S</td>
</tr>
</tbody>
</table>

² The catalysts were generated in situ from the amounts of the ligand and the palladium source indicated. The reactions were carried out in CH₂Cl₂ at rt. ³ Determined by HPLC. ⁴ Determined by HPLC using a chiral column (Daicel Chiralcel OD-H). ⁵ The ligand was deprotected with Et₂NH

All pyridyl phosphonite ligands derived from L-mandelic acid favoured the formation of the (R)-enantiomer of 30 (Scheme 58). Thus, the pyridyl phosphonite 221 afforded the product in 46% ee (entry 1). When the BH₃-protected analogue 222 was used together with palladium acetate, a highly active catalyst was generated. With a catalyst loading of 4%, full conversion was reached in less than 2 hours and the product was obtained in 48% ee (entry 2). Decreasing the catalyst loading to 2% resulted in the same enantioselectivity but the reaction time had to be prolonged to 17 hours for full conversion to be reached (entry 3). Deprotection of the phosphinite moiety followed by in situ generation of the catalyst by the use of allylpalladium chloride dimer, gave a less active catalyst but the enantioselectivity observed was maintained (48% ee, entry 4). The use of an excess of the ligand (Pd:ligand 1:1.5) did not affect the rate or the enantioselectivity of the reaction (entry 5).

The catalyst generated from the 6-phenyl-substituted ligand 223 and palladium acetate displayed a very low activity. Only 36% conversion was reached in 189 hours but the product was produced in somewhat higher optical purity (52% ee, entry 6) than when 222 and 223 were used. When the ligand (223) was deprotected prior to the catalytic reaction and the allylpalladium chloride dimer
was used as the metal source, full conversion was reached in 100 hours and the product was formed in 56% ee (entry 7). The use of an excess of the ligand (Pd:ligand 1:1.5) increased the reactivity dramatically but it was detrimental to the enantioselectivity observed (10% ee, entry 8).

It seems reasonable to assume that the aryl group in the 6-position of the pyridine ring makes the palladium complex formed rather crowded. This can account for the low activity observed for the catalyst based on ligand 223 (entries 6-7). Furthermore, when the ligand is present in excess, the possibility of monodentate coordination of two ligands through the phosphorus atoms to one palladium may generate a more active complex. In this coordination mode the transfer of chirality from the ligand to the substrate becomes much less efficient. This phenomenon can explain the dramatic increase in activity of the catalyst, and, at the same time, the drop in enantioselectivity of the reaction under these conditions (entry 8).

When the pyridyl phosphinites 224 and 225, derived from (-)-menthol, were used in the catalytic reaction, the absolute configuration of the product was determined by the absolute configuration of the benzylic carbon atom of the ligand. Thus, ligand 224 favoured the formation of the (R)-product in 44% ee (entries 9-10), whereas the diastereomeric ligand 225 favoured the opposite enantiomer of the product in 50% ee (entry 11).

The catalysts generated from the pyridyl phosphites 231 and 232, displayed the same activity in the reaction but gave the product with varying optical purity. Thus, ligand 231, derived from (S)-BINOL, favoured the formation of the (S)-product in 51% ee (entries 12-13), whereas ligand 232, derived from (R)-BINOL, gave rise to the same enantiomer of the product with very low optical purity (2-5% ee, entries 14-15). Interestingly, a kinetic resolution of the racemic substrate (rac-29) was observed with ligand 231. The optical purity of the substrate increased with increasing conversion (50% ee at 50% conversion and 76% ee at 93% conversion). On the other hand, a slight decrease in the optical purity of the product was observed with increasing conversion. At 50% conversion, the highest enantiomeric excess was observed (56%).

In the studies by Faraone and co-workers (vide supra), pyridyl phosphites 136, derived from (S)-BINOL, showed no or very low levels of chiral induction in the palladium-catalysed allylic alkylation discussed above. This was partly ascribed to the lack of rigidity of the six-membered chelate ring formed upon coordination to palladium. The presence of an additional substituent in the picolinic position of ligands 231 and 232 can be assumed to make the chelate rings of the palladium complexes of these ligands more rigid. The chelate rings should preferably adopt a conformation in which this substituent is situated in a pseudo-equatorial position (Figure 23a). If the chelate ring in the palladium
complex of ligand 231 adopts this conformation, the steric bulk of the ligand is positioned as showed in Figure 23b, and the ligand has thus Pr chirality. This is in agreement with the favoured formation of the (S)-enantiomer of the product in the catalytic reaction.

Figure 23

Upon an analogous inspection of the palladium complex of ligand 232, no clear conclusion about the location of the steric bulk can be made. The six-membered chelate ring is still slightly flexible, despite the presence of the pseudo-equatorial R-group (Figure 23a). Small conformational changes of the chelate ring leads to relocation of the steric bulk in the Pd-232 complex. Similar conformational changes in the corresponding complex of ligand 231 does not affect the position of the steric bulk to a great extent.

Pyridyl phosphites 231 and 232 were also evaluated as ligands in the palladium-catalysed allylic alkylation of 2-cyclohexenyl acetate (233) with dimethyl malonate according to Scheme 59. The results are shown in Table 5.

Table 5. Palladium-catalysed allylic substitution of rac-2-cyclohexenyl acetate with malonate in the presence of ligands 231 and 232.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Pd:L (%) cat.</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
<th>Abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>231</td>
<td>1:1</td>
<td>112</td>
<td>61</td>
<td>31</td>
<td>S</td>
</tr>
<tr>
<td>232</td>
<td>1:1</td>
<td>143</td>
<td>58</td>
<td>17</td>
<td>R</td>
</tr>
</tbody>
</table>

*a* The catalysts were generated in situ from 2 mol% bis[(π-allyl)palladium chloride] and 4 mol% ligand. The reactions were carried out in CH2Cl2 at rt.

*b* Isolated yields after column chromatography.

*c* Determined by 1H NMR using Eu(hfc)3 as chiral shift reagent. The absolute configuration was determined by comparing the optical rotation with a literature value.

The sense of asymmetric induction was seemingly determined by the absolute configuration of the axially chiral BINOL-moiety. In the reaction employing (S)-BINOL-based ligand 231, (S)-234 was obtained in 31% ee, while the diastereomeric ligand 232, derived from (R)-BINOL, favoured the formation of (R)-234 in 17% ee.

The favoured formation of the (S)-enantiomer of 234 with ligand 231 is in agreement with the Pr chirality of the ligand. Due to the low level of asymmetric induction obtained with ligand 232 it is hard to draw any conclusions regarding the stereochemical outcome of the catalytic reactions with this ligand. The flexibility of ligand 232 (vide supra) can make it susceptible to structural changes in the substrate coordinated to the palladium complex and, therefore, make it adopt different conformations depending on which substrate is used.
10. Concluding Remarks

Nitrogen ligands were synthesized and used in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with malonate. The steric properties of the ligands were shown to be important for the enantioselectivity observed in the catalytic reaction.

Crown ether-containing ligands were synthesized and some were used as ligands in the allylic alkylation reaction. A small rate enhancement was observed in dilute systems. It would be interesting to apply these ligands to reactions in which a secondary interaction with the substrate is possible, and in this way induce substrate selectivity.

The utility of the chiral pool as a source of chiral enantiopure starting materials was demonstrated. A modular approach was applied, in which a series of chiral pyridyl alcohols and $C_2$-symmetric 2,2'-bipyridines were synthesized from natural products.

The chiral pyridyl alcohols were shown to serve as useful synths for the preparation of chiral pyridyl phosphinite ligands and pyridyl phosphite ligands. Structural modifications of the ligands with the purpose to make their complexes with transition metal ions more rigid, could make these ligands interesting for further catalytic applications.
Acknowledgements

I would like to thank a number of people, who have made this work possible:

My supervisor Professor Christina Moberg for giving me the opportunity to work in her group and for all her inspiring enthusiasm.

All the present and former co-workers in group Ki, for the nice atmosphere in and outside the lab. I would especially like to thank Ulf Bremberg (for taking good care of me in the early days), Kristina Hallman (the best lab buddy senior), Christina Jönsson (for her never-ending energy and for being a good friend), Oscar Belda (for invaluable help with technical gadgets) and Stina Lundgren (the best lab buddy junior).

Anders Frölander, Christian Linde, Christina, Oscar and Åsa Sjöholm-Timén for helpful discussions and critical revision of this thesis. Erik Risberg for invaluable support with MS Word during the preparation of this thesis.

Åsa for encouragement in hard times, for company during awkward working hours and for being a good friend.

Erik for inspiring me with stories about expeditions and adventures and for being a good friend.

Christian for infinite support whenever needed and for straightening out my English. Timo Privalov for endless enthusiasm and keeping me company at odd working hours.

Ulla Jacobsson for valuable help in NMR matters, Jonas Hellberg and Krister Zetterberg for always taking time to share their knowledge in organic chemistry. Invgor Larsson, Lena Skowron, Jan Sidén and Henry Challis for help with all things mellan himmel och jord.

Sari Paavola, Ellen Santangelo, Åsa, Fredrik Allared and Dean Gillings for all good laughs at the end of the week.

All former and present co-workers at Organic Chemistry.

All my friends. Special thanks go to Jesper and Krister for great times under the surface and for all the adventures around the world. The trio in the People’s Republic of Hornstull for helping me to forget about work once in a while.

My family for support.

Finally I would like to express my deepest gratitude to Charlotte for support, understanding and love.