University of Évora

Instituto de Investigação e Formação Avançada

Homogeneous and Heterogeneous Asymmetric Catalysis with Bis(Oxazoline), Mono(Oxazoline) and Diphosphine Ligands

Dissertation for the Degree of European Doctor of Chemistry

Elisabete da Palma Carreiro

(B.Sc)

Professor Doutor Anthony Joseph Burke
Doutor Olaf Martin Walter

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Homogeneous and Heterogeneous Asymmetric Catalysis with Bis(Oxazoline), Mono(Oxazoline) and Diphosphine ligands

Abstract

The aim of this work was the study of mono(oxazolines), bis(oxazolines) and diphosphines in metal-catalyzed asymmetric reactions in the both homo- and heterogeneous phase.

A small library of seven mono(oxazoline) ligands, was synthesized and evaluated in a combinatorial homogeneous catalytic asymmetric cyclopropanation reaction (CACP). The kinetics, NMR spectroscopic and computational studies of the homo- and heterocomplexes revealed that the most stable in solution was the di-coordinated heterocomplex.

The synthesis of two *ortho*-substituted-Arylid-BOX ligands is described, which were evaluated in the CACP using Cu(I) and Ru(II) in organic solvents and biphasic media. The electrophilicity of the Arylid-BOX metallocarbenes was calculated using the Fukui Function. The Arylid-BOXs were immobilized on Montmorillonite K10 and on silica via non-covalent bonding and tested in the same reaction.

The synthesis of a polymer supported Arylid-BOX-derivative, and its application in the CACP with copper (I). Good yields, enantioselectivities and diastereoselectivities were obtained. Moreover, the polymer-bound catalyst could be easily and efficiently recycled.

Finally, the synthesis of supported PYRPHOS ligand on polyvinlyalcohol (PVA) and it's use in the catalytic asymmetric hydroformylation was studied.

Catálise Assimétrica Homogénea e Heterogénea com ligandos Bis(oxazolina), Mono(oxazolina) e Difosfinas

Resumo

Neste projecto de doutoramento teve-se como objectivo estudar ligandos mono-oxazolinas, bis-oxazolinas e difofinas em reacções catalíticas assimétricas nas fases homogéneas e heterogéneas.

Uma pequena biblioteca de sete mono-oxazolinas foi sintetizada e usada em ciclopropanações catalíticas assimétricas (CPCA) combinatórias. Os homo- e heterocomplexos formados com estes ligandos e cobre (I) foram alvo de estudos cinéticos, espectroscópia de RMN e computacionais, os quais indicaram que o heterocomplexo di-coordenado é o mais estável.

Arylid-BOXs com *orto* substituintes foram sintetizadas e usadas em CPCA usando Cu(I) e Ru(II) como pré-catalisadores e realizadas com solventes orgânicos e sistemas bifásicos. Estudos computacionais dos metalocarbenos das Arylid-BOX reforçaram o mecanismo concertado na CPCA. Os catalisadores Cu(I)-Arylid-BOX foram imobilizados em montmorilonite K10 e silica através ligações não-covalentes e testados em CPCA, os resultados revelaram bastante lixiviação do metal.

Um ligando derivado da Arylid-BOX foi ligado a uma resina polimérica, e usado em CPCA com Cu(I) e Cu(II). Os resultados revelaram-se semelhantes as CPCA na fase homogénea.

Por fim, o ligando PYRPHOS foi imobilizado no polímero polivinilalcool (PVA), e usado em hidroformilações catalíticas assimétricas catalisadas por Rh.

Abbreviations and symbols

a.u.	atomic units
acac	acetylacetonato
Ar	aryl
b	branched
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINAPHOS	(2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl)-(1,1′-binaphthalene-2,2′-diyl)phosphite
Bn	benzyl
BOX	bis(oxazoline)
BisP*	1,2-bis-(alkylmethylphosphino)ethane
CACP	catalytic asymmetric cyclopropanation
CAHF	catalytic asymmetric hydroformylation
CHIRAPHITE	1,3-Di-methyl-1,3-propanediyl]bis(oxy)]bis[4,8-bis(t-butyl)-2,10-dimethoxy- bibenzo[d,f][1,3,2]dioxaphosphepin
COD	cyclooctadieno
cs	chemoselectivity
d	doublet
δ	chemical shift
DAST	diethylaminosulfur trifluoride
DBF-BOX	2,2'-(4,6-dibenzofurandiyl)bis[4,5-dihydro-4-phenyloxazole]
DCM	dichlorometane
dd	double doublet
de	diasteromeric excess
DEGUPHOS	*N*-benzyl-3,4-bis-diphenylphosphino-pyrrolidine
DFT	Density functional theory
DIPHOS	1,2-Bis(diphenylphosphino)ethane
DIOP	4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DIPAMP	1,2-bis[(2-methoxyphenyl)(phenyl)phosphino]ethane
DMF	dimethylformamide
DMSO-d_6	dimethylsulphoxide-d_6
DNA	deoxyribonucleic acid

L-DOPA	*L*-3,4-dihydroxyphenylalanine
EA	elemental analysis
EDA	ethyl diazoacetate
ee	enantiomeric excess
EI	electron ionisation
ESI	electron spray ionization
ESPHOS	{(1R,1'R, 3aS,3'aS)-1,1'-(1,2-phenylene)bis[hexahydro-2-phenyl-1*H*-pyrrolo[1,2-c][1,3,2]diazaphosphole]}
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
GC	gas chromatography
Hex	n-hexane
HF	hydroformylation
HRMS	high resolution mass spectrometry
HSAB	hard and soft acids and bases
Hz	hertz
ICP-OES	inductively coupled plasma - optical emission spectrometer
i-Pr	iso-propyl
IR	infrared spectrometry
J	coupling constant
l	linear
LDA	Lithium diisopropylamide
m	multiplet
m/z	mass-to-charge ratio
Me	methyl
mmol	milimol
MeCN	acetonitrile
mp	melting point
MS	mass spectrometry
NEt_3	triethylamine
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NORPHOS	2,3-Bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene

OTf	triflate
OX	oxazoline
Ph	phenyl
PVA	polyvinylalcohol
ppm	parts per million (NMR)
PyBOX	pyridine bis(oxazoline)
PYRPHOS	3,4-bis-diphenylphosphino-pyrrolidine
q	quadruplet
rs	regioselectivity
rt	room temperature
s_{br}	singlet (broad signal)
SAPC	supported aqueous-phase catalysis
SILP	supported ionic liquid phase
t	tiplet (NMR), time
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-Butyl
THF	tetrahydrofuran
TMS	tetramethylsilane
t_R	retention time
UV	ultra-violet
$[\alpha]$	Optical rotation
[Rh]	Rh complex

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Chapter 1

General Introduction

1. Asymmetric Catalysis: A Historical Overview

In 1848 Louis Pasteur described Chirality for the first time, he demonstrated that tartrate enantiomers rotated the plane of polarized light in opposite directions, and only the right-handed enantiomer was present in wine lees. Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. However, there is one property in which chiral compounds differ from achiral compounds and in which enantiomers differ from each other. This property is the direction in which they rotate plane-polarized light, and this property is called optical activity which leads to the phenomenon of optical rotation.[1,2]

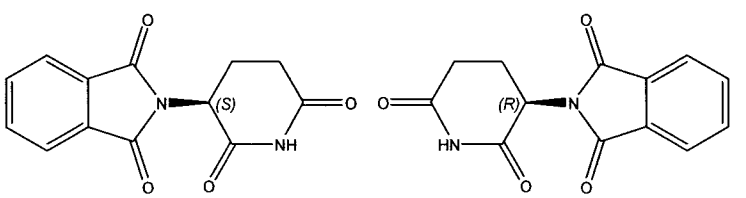
Chirality is of prime significance in biological systems, as most of the biological macromolecules of living systems occur in nature in one enantiomeric form only. A biologically active chiral compound interacts with its receptor site in a chiral manner, and enantiomers may be discriminated by the receptor in very different ways. Thus it is not surprising that the two enantiomers of a chiral drug may interact differently with the receptor, leading to different effects. Indeed, it is very important to bear in mind this concept of chiral discrimination or stereoisomeric discrimination when designing biologically active molecules.

Biological chiral receptors, for example, interact mostly with drug molecules having the correct absolute configuration, leading to distinct biological activities for the two enantiomers of the drug. The importance of the relationship between pharmacological activity and chirality was demonstrated in the early 1960s, by the tragic administration to pregnant women of thalidomide (Figure 1), in the racemic form. The (*R*)-enantiomer had the desired sedative properties, while (*S*)-thalidomide was teratogenic and led to fetal malformations.[3] However, even in 2000, only 40% of the synthetic chiral drugs on the market were sold in single enantiomeric form.[4]

There are three main approaches to synthesize single enantiomers: (i) Synthesis from the chiral pool; (ii) Resolution of racemic mixtures; (iii) Asymmetric synthesis (the use of chiral reagents, auxiliaries or catalysts).[2]

In 2001, Noyori, Sharpless and Knowles were awarded the Nobel Prize in chemistry for their achievements in the field of asymmetric organometallic catalysis.[3,5,6]

Catalytic asymmetric syntheses have a very important role to play in the preparation of enantiomerically enriched compounds, for agrochemical and pharmaceutical applications.[7,8] Fortunately, with so much research in the area, there are many methods now available with advanced asymmetric reactions being developed each year. There still are cases where asymmetric synthesis doesn't provide the best method for the preparation of a particular enantiomerically pure compound, but it surely allows for the preparation of a more diverse range of structures. Asymmetric catalysis is an especially appealing technique for the asymmetric synthesis of chiral compounds. Small amounts of a catalyst (frequently less than 1 mol %) can be used to control the stereochemistry of the bulk reaction. The use of a catalyst often makes the isolation of a product easier, since there is less unwanted material to remove at the end of a reaction.[8]

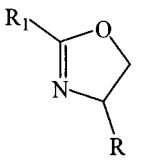


(*S*)-Thalidomide (*R*)-Thalidomide

Figure 1. Thalidomide enantiomers.

2. Chiral Oxazoline Ligands

2.1 Historical Overview



1

The first oxazoline ligand ring **1** (4,5-Dihydro-1,3-oxazole) was prepared in 1884.[9] These ligands show a number of attractive characteristics like: versatility of ligand design, easy synthesis from readily available precursors, and modulation of the chiral centers, which are located near the donor atoms, including stability towards hydrolysis and oxidation. Oxazolines are in fact chiral *N*-donor ligands that have been used successfully in asymmetric catalytic reactions. These oxazolines have been used extensively in many areas of chemistry (reviewed in 1949 and 1971[10]), given the versatility of this ring which can act as a protecting group, coordinating ligand, or activating unit. Furthermore, the oxazoline ligating group is present in certain classes of microbial iron chelators.[11] Only in the last twenty five years have oxazolines been applied in catalytic asymmetric synthesis. The first application of oxazoline-based ligands in asymmetric catalysis was in 1986 for the monophenylation of diols[12] and soon after for the hydrosilylation of ketones.[13] This was the starting point for research on the syntheses of a wide diversity of chiral ligands containing at least one oxazoline structural unit and subsequent application in asymmetric catalysis using a range of transition metals, Figure 2. [14, 15]

Similar ligands appeared in 1986, namely semicorrin ligands (Figure 3), their important application prompted several research groups to develop other structurally related ligands. Semicorrins **2-4** have C_2-symmetry and show high enantioselectivities in the copper-catalyzed cyclopropanation of olefins and cobalt-catalyzed conjugate reduction of α,β-unsaturated carboxylic esters and amides,[16] this was possible given that the stereogenic centers are held in close proximity to the metal and thus have a strong and direct influence on the stereochemical course of the metal-catalyzed process.

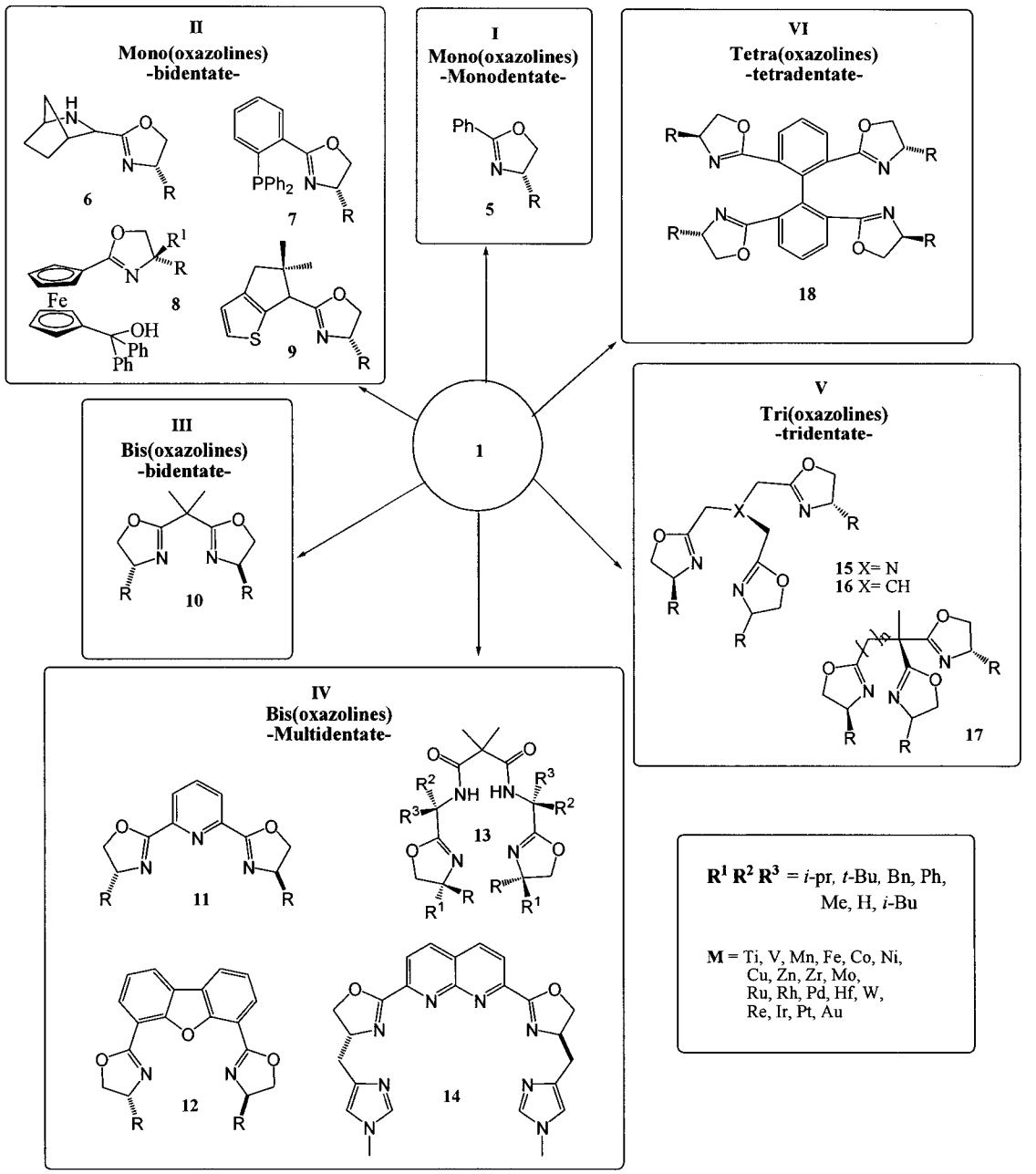


Figure 2. Types of chiral oxazolines.

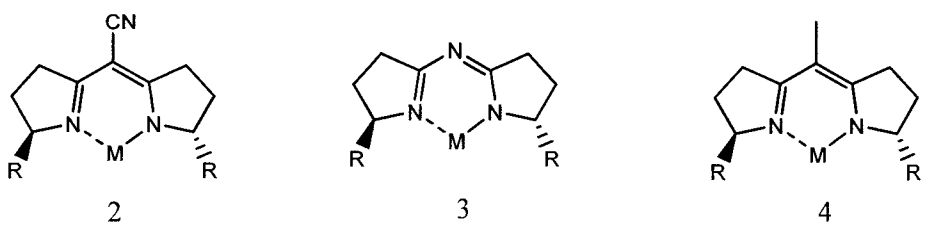


Figure 3. Metal coordinated semicorrin ligands.

A range of oxazoline-based ligands have been synthesized, they can be divided into two main classes: (i) neutral ligands, which behave as electron donors; (ii) Anionic ligands with stronger electron-donating proprieties, which can reduce the electrophilicity of a metal ion or allow coordination to early transition metals. Oxazoline-based cationic ligands have been less developed.[17]

A class of neutral oxazoline ligands was developed in this work. Within this class it is possible to distinguish six families according to the number of oxazoline units and potential coordination behavior, i.e. monodentate, bidentate, tridentate and multidentate. A few examples of oxazoline-based ligands are represented in the Figure 2. Family **I** is a monodentate mono(oxazoline) type (ligand **5**),[18] (abbreviation OX). In fact, this family is less used in asymmetric catalysis, and the only examples reported are; a Ni-catalyzed multicomponent tandem coupling,[19a] an intermolecular [2+2+2] cycloaddition of alkenes and alkynes,[19b] and a copper-catalyzed cyclopropanation of olefins.[20,21] This latter reaction will be given more attention in this thesis. Family **II** represents a series of bidentate mono(oxazolines), these ligands have only one oxazoline unit and a heteroatom (N, P, O, S) in its structure. The presence of these donor atoms in the ligand can increase the selectivity and enantioselectivity in a wide range of catalytic asymmetric reactions.[15] Ligands **6 - 9** are some examples of this family, ligand **6** (R=*i*-pr) a mono(oxazoline) *N,N*-ligand was reported by Andersson for the asymmetric transfer hydrogenation of acetophenone. Good ees (up to 79%) and a moderate conversion were obtained with $[IrCl(COD)]_2$.[22] The *P,N*-ligand **7** is an excellent ligand for a wide range of metal-catalyzed reactions.[23] Ligand **8**, is an example of an *N,O*-ligand. Hou and co-workers applied them in the asymmetric addition of phenylacetylene to aldehydes and in the alkynylation of a range of aldehydes and they gave very good yields and enantioselectivities.[24] Ligand **9**, is an example of an *N,S*-ligand, cyclopenta[*b*]thiophene-alkyloxazoline was prepared by Ricci and applied in the palladium-catalyzed allylic alkylation reaction.[25] This gave high yields of the dimethyl 1,3-diphenylprop-2-enylmalonate product, with higher reactivity rates being observed for the (*S*)-configured ligands.[25] The well known and currently most popular, Bis(oxazoline) (BOX) types, (family **III**, Figure 2) have two oxazoline units, generally with C_2-symmetry. Ligand **10** was the first ligand of this type to be developed, it has been studied in a wide range of catalytic asymmetric reactions.[14,15]

Family **IV**, includes both tridentate (ligands **11** and **12**), tetradentate (ligand **13**), and multidentate (ligand **14**) bis(oxazolines). The ligands **11** (PyBOX by Nishiyama)[26]

and **12** (DBF-BOX by Yamamoto)[27] are tridentate. PyBOX **11** gave good results in the asymmetric hydrosilylation of ketones and cyclopropanation of olefins.[26] In the case of DBF-BOX it's first application was in the preparation of cationic aqua complexes for asymmetric Diels-Alder reactions.[27] The preparation of these ligands prompted the synthesis of a wide range of other tridentate bis(oxazolines).[14,15]

Tetradentate C_2-symmetric bis(oxazoline) ligand **13**, has been investigated by Adolfsson in the titanium catalyzed addition of diethylzinc to benzaldehyde.[28] The design of polydentate oxazoline ligands has grown in importance, for example, ligand **14**, can form di- and polynuclear complexes.[29] Many studies show the considerable potential that dinuclear and cluster complexes have for catalysis, and for modeling the catalytic activity of metalloenzymes. Several examples demonstrate that dinuclear metal complexes can display distinct advantages over mononuclear metal catalysts and mixed-metal systems offer the additional potential of selective activation of two different substrates. Such complexes can mediate multi-electron transfers, activate a substrate by simultaneous coordination to two (or more) metal centers or, in the case where metal - metal bonding is present, allow direct insertion of a substrate into such a bond, a process that does not require ligand dissociation to generate coordinative unsaturation.[29]

Family **V**, trioxazoline ligands (TOX) include ligands that have three oxazolines units, the first example of a TOX ligand was reported by Katsuki and co-workers in 1995 (ligands **15**, **16**).[30] They were applied in the enantioselective allylic oxidation of alkenes (the Karasch-Sosnovsky reaction) and in the addition of diethylzinc to aldehydes.[31] Within this family the C_3-symmetric ligands (e.g. **15**, **16**) the non-C_3-symmetric oxazoline ligands of Tang's (ligand **17**) were evaluated in asymmetric Michael addition of indole to benzylidine malonatos giving good enantioselectivities.[32] In the case of family **VI**, Zhang *et al.* have developed a new class of tetra(oxazoline) containing ligands (ligand **18**). They reported their application in the Pd(II)-catalyzed asymmetric Wacker-type cyclization of allylphenols, giving excellent ees. This work has led to a new way of developing novel axially chiral catalysts.[33]

2.2 Synthesis and Application of Chiral Oxazoline Ligands

A large range of methods for the synthesis of oxazoline-based ligands have been developed since 1991. They have been applied in a wide range of catalytic asymmetric reactions. BOX ligands were the most frequently ligands to be investigated.
Gosh *et al.*[14a] and Desimoni *et al.*[14b] published reviews where they conduced a very good compilation of a diversity of methods utilized for obtaining BOX ligands.

The synthesis of oxazoline ligands can be achieved using naturally available aminoacids which give synthetic aminoalcohols. Although the oxazoline moiety is sensitive to mineral and Lewis acids, it is resistant to nucleophiles, bases and radicals, if no other labile functional groups are present in the substrate.[34]
Generally, oxazoline ligands are synthesized from aminoalcohols (easily prepared by reduction of α-aminoacids) or nitriles or carboxylic acid precursors[35] (Chart 1), although alternative procedures can be used because of the particularly sensitive functionalities present in the precursors.[36]

Several methods have been developed since 1991, most of these methods start with a cheap precursor, which is generally a malonic acid derivative and an α-amino alcohol to give a chiral bis-amide. Cyclization of this intermediate leads to the oxazoline ring. A number of methods exist. The cyclization method determines the absolute configurations of the BOX ligands.[14]

The oxazoline-based ligands that have been developed since 1989, including their application in asymmetric catalysis are presented in Chart 1 (references are included).

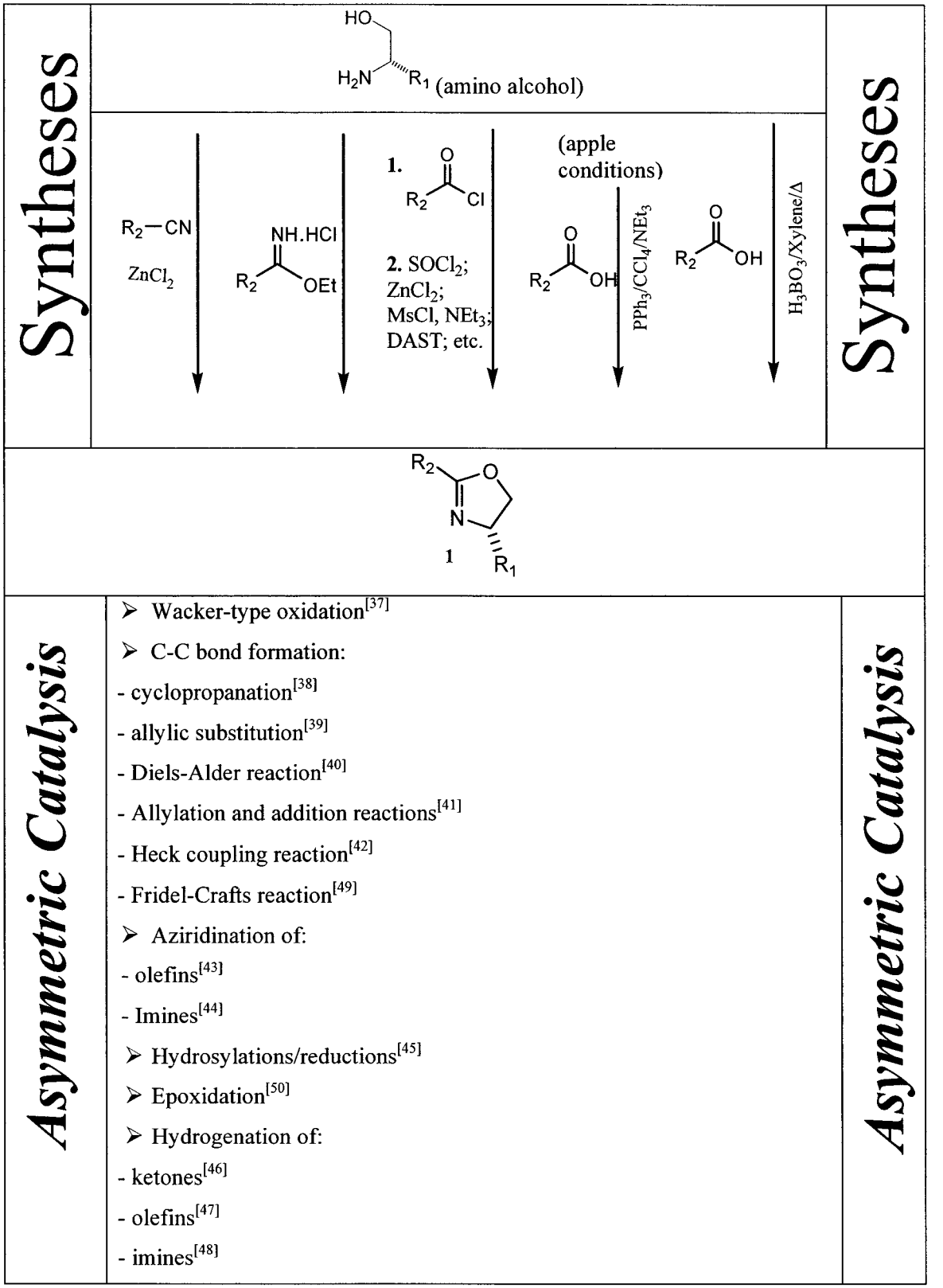
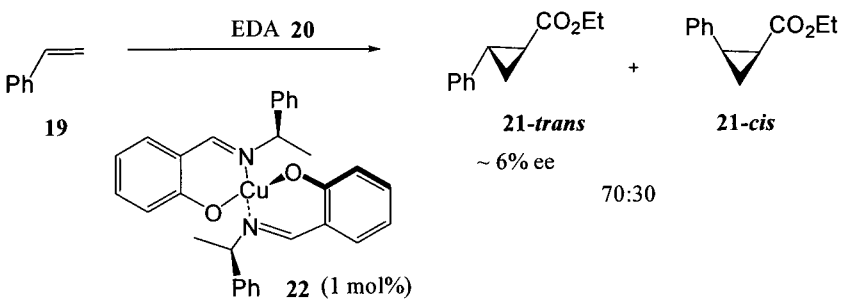


Chart 1. Summary of the most common oxazoline synthesis methods and their application.

3. Catalytic Asymmetric Cyclopropanation

Catalytic asymmetric cyclopropanation (CACP) by transition-metal-mediated carbene transfer from aliphatic diazo compounds to carbon–carbon double bonds is one of the most extensively studied reactions in the organic chemist's arsenal.[51]

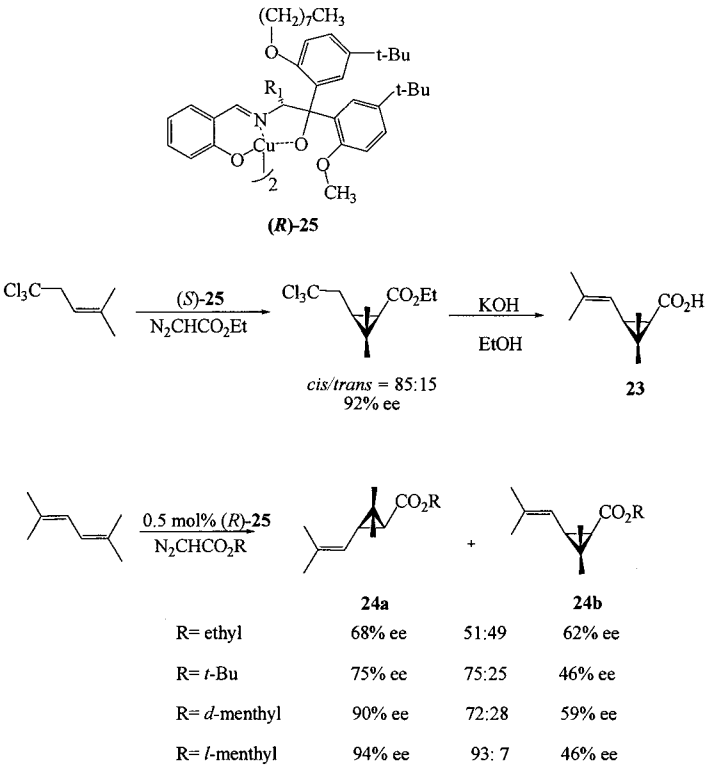
The first CACP was reported in 1966 by Nozaki, but the enantioselectivities obtained were poor (up to 10% ee).[52] A chiral copper-salicylaldimine complex **22** was used (Scheme 1). This work proved to be decisive as it demonstrated the principle that homogeneous metal-catalyzed processes can provide high enantioselectivities by attaching a chiral ligand to a metal center. CACP is one possible way of obtaining cyclopropane rings, with a large range of biological activities, like for example, enzyme inhibition, antifungal, antibiotic, antiviral and antimour activities, etc.[53]



Scheme 1. First CACP reported by Nozaki.[52]

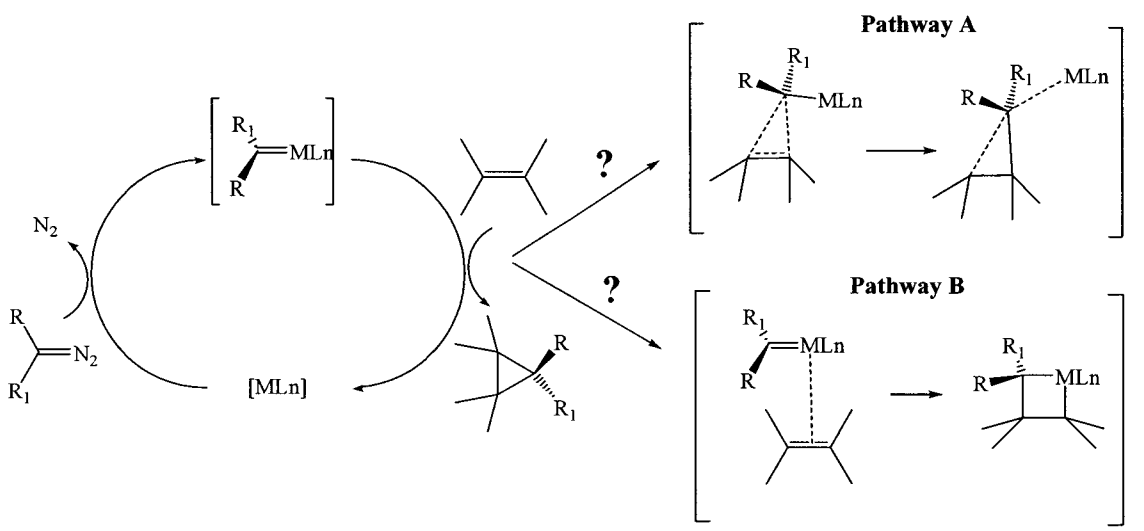
This was the starting point for the development of several catalysts. Aratani *et al.* by systematic variation and optimization of the salicylaldimine structure, developed the first practical useful catalyst for enantioselective cyclopropanation in the industrial production of certain *pyrethroids*.[54,55] Important precursors for the synthesis of *pyrethroid* insecticides, are permethrinic acid **23** and esters of chrysathemic acid **24**.[54a,b,d] They were prepared in >90% ee (Scheme 2).

After this work, highly effective and stereocontrolled syntheses of functionalised cyclopropanes have been achieved, in particular, using catalysts based on copper, rhodium and, more recently, ruthenium. Palladium-based catalysts have advantages in special cases, like for instance they are efficient catalysts for the CACP of electron-deficient C-C double bonds with diazoalkanes. Whilst Cu and Rh based catalysts are better suited for reactions with electron-rich olefins.[56] Iron and Osmium based catalysts have been reported occasionally in CACP.



Scheme 2. Catalytic asymmetric cyclopropanation giving permethrinic acid **23** and chrysathemic acid esters **24.**

The mechanism implicated in the CACP with decomposition of diazo compounds is not very well known in detail, but in general, many research groups agree that metallocarbene complexes are formed in this process, like that depicted in Scheme 3.[1b]



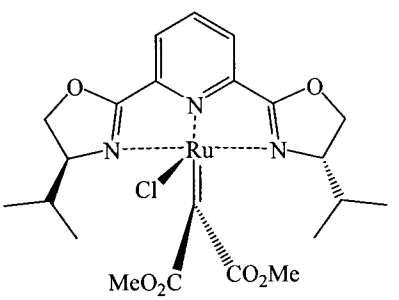
Scheme 3. Catalytic cycle of the CACP and possible mechanisms.

Some stoichiometric carbenes derived from Ru[57] and Os[58] have been prepared and characterized in solution and were shown to act as efficient catalysts for CACP. Some X-ray crystal structures of Ru carbenes have been reported,[59] for example, Nishiyama isolated a crystal of pybox Ru carbene **26**, which was shown to be an active cyclopropanation reagent under severe conditions. [59a]

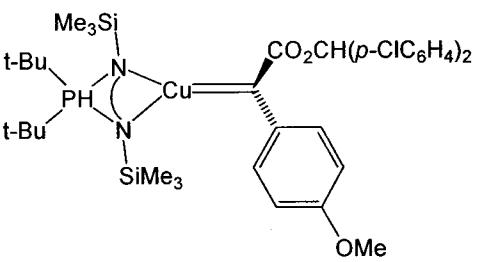
Several copper carbenes were synthethized and studied by NMR.[60a] Recently, Shishkov *et al.*[60b] isolated a Cu(I) carbene **27**, that was characterized by X-ray crystallography. The mechanistic picture presented was completely consistent with that proposed by Pfaltz and co-workers.[61]

Theoretical studies,[62] deuterium isotope effects and Hammett studies[63] have also been carried out to elucidate the mechanism of the copper (I)- catalyzed cyclopropanation of propene with diazo compounds. The two mechanistic pathways that have been proposed for the formation of the cyclopropane ring by various authors, consist in a bonding interaction between the reactive metallocarbene intermediate (electrophilic carbenoid-C) and the π-system of the C-C double bond of the alkene, as is represented as pathway A in Scheme 3 and the alternative pathway which consists in coordination of the olefin to the metal center forming a metallocyclobutane intermediate (pathway B) as the central intermediate which then suffers a reductive elimination. This pathway has been considered to be less attractive for steric reasons.[1b]

Another important aspect of this reaction in the case of copper, is the oxidation state of the copper center in the active catalyst, Cu(I) or Cu(II). Most evidence points to a Cu(I) species as the active catalyst,[64] it has been observed in many cases that under the reactions conditions, Cu(II) complexes are reduced to Cu(I) complexes by the diazo compound, or with the use of a substituted hydrazine.[64a] In pathway A, the *trans*-isomer is preferred and the selectivity usually improves when the size of the substituent



26



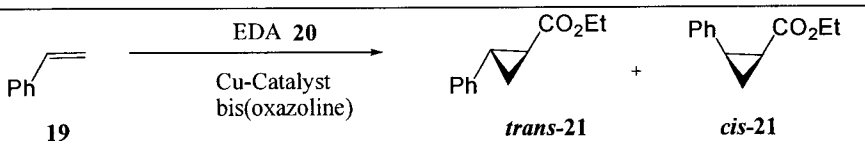
27

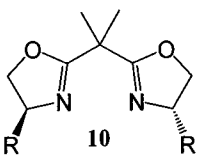
on the diazo compound is increased, as demonstred by Doyle.[64] Regarding the diazoalkanes that are used in the CACP, diazomethane (CH_2N_2) works very well with Pd(II), trimethylsilyldiazomethane ($TMSCHN_2$) and phenyldiazomethane ($PhCHN_2$) are other alternatives.[66] However, α-diazocarbonyl compounds, such as ethyl diazoacetate (EDA), are more stable and easier to handle than diazoalkanes. EDA is the most used and studied, but sometimes the diazo compounds can be a problem in high concentration as the metal-catalyzed process leads to coupling of the two diazo compounds to give an alkene. In the case of EDA, a mixture of diethyl fumarate and maleate are formed. The best way to stop this undesired reaction, is to add the diazo compound slowly over several hours, keeping the concentration of EDA low in the reaction.[1b]

The work described in this thesis concerns both Cu and Ru catalyzed cyclopropanations with EDA and chiral bis(oxazoline) and mono(oxazoline) ligands.
The use of chiral bis(oxazoline) ligands in the CACP, was introduced by Evans in 1991[38b] based on the preliminary work of Pflatz.[16]

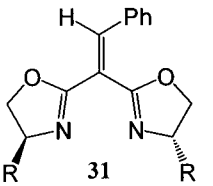
Exceptional levels of enantioselectivity have been achieved with some chiral catalysts such as copper(I)-C_2-symmetric bis(oxazoline) catalyst. On the other hand, the diastereocontrol of the intermolecular cyclopropanation reaction is more difficult to handle, because the cis/trans or syn/anti selective formation of cyclopropanes is most often controlled by the particular olefin/diazo compound combination. Nevertheless, catalysts with cleverly designed ligands have been developed, which have allowed highly selective *trans*- or *cis*-cyclopropanations, in particular cases. It must be noted that the cyclopropanation of styrene with ethyl diazoacetate (EDA) often serves as the bench-mark reaction for the evaluation of almost any new catalyst (Figure 4).

Ruthenium is another important central atom for CACP, and was the more recent metal introduced for this application.[74] In spite of the wide range of C_2-symmetric bis(oxazoline) ligands that have been developed since 1991,[14,15] only PyBOX **11**[26] and Thiobox **35**[75] have been successfully used in Ru-catalyzed enantioselective cyclopropanations. This study was conducted by Nishiyama *et al.* who showed a high proportion of *trans*-cyclopropane with an excellent ee.[76] They used a wide range of alkenes and diazo compounds, the *trans:cis* ratio increased with the increase in the bulkiness of the ester group (Me < Et < *t*-Bu = (*d*)-Ment; (*l*)-Ment) of the diazoacetates. Simpson *et al.* increased the *trans:cis* ratio and the ee of the *trans*-cyclopropane for

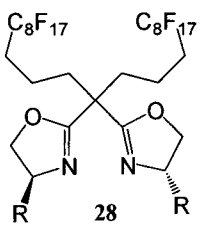




10a R= *t*-Bu: 77%
de=54%
ee(*cis*)=ee(*trans*)=99% [65];
in ionic liquids
[BMIM][BF_4]: 85%
de=44%
ee(*cis*)=ee(*trans*)=98% [66]
10b R=Ph 98% de=49%
ee(*trans*)=66%
ee(*cis*)=54% [67]

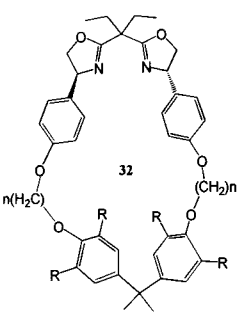


31a R=Ph: 30%
de=30%
ee(*trans*)=57%
ee(*cis*)=45%
31b R=*t*-Bu: 81%
de=24%
ee(*trans*)=84%
ee(*cis*)=77%[71]

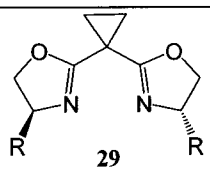


28a R= *i*-Pr: 77% de=24%
ee(*trans*)=63%
ee(*cis*)=63% [68]

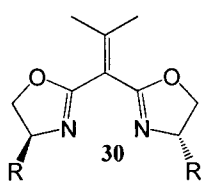
28b R=*t*-Bu: 22% de=24%
ee(*trans*)=84%
ee(*cis*)=81% [68]



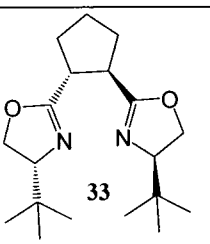
32a R=H, n=2: 55%
de=86%
ee(*trans*)=65%
ee(*cis*)=59%
32b R=Me, n=3: 65%
de=59%
ee(*trans*)=75%
ee(*cis*)=31% [72]



R= *t*-Bu: 85% de=68%
ee(*trans*)=100%
ee(*cis*)=100% [69]



30 R=*t*-Bu: 19% de=33%
ee(*trans*)=64%
ee(*cis*)=56% [70]

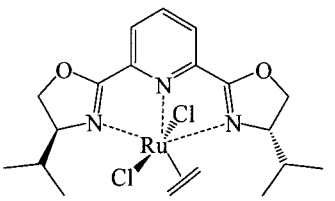


72% de=26%
ee(*trans*)=83%
ee(*cis*)=87% [73]

Figure 4. Some examples of bis(oxazoline) ligands used successfully in CACP.

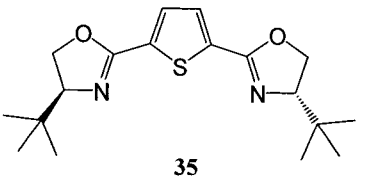
styrene and EDA with **34** (Figure 5).[77] The Thiobox **35** ligand (Figure 5) was tested by Gao *et al.* in the Ru-catalyzed enantioselective cyclopropanation of alkenes with EDA.[75] For styrene they obtained a lower de but an increase in the ee in comparison with **34** (Figure 5).

Another study with the Ru catalyst formed from PyBOX ligands **11** was developed by Nishiyama *et al.*[78] Aqueous media and protic solvents were used in the enantioselective cyclopropanation reaction. Excellent enantioselectivities and des were obtained with this system.



34
Nishiyama's Catalyst

Yield= 98% de= 92%
ee(*trans*)= 86% [77]



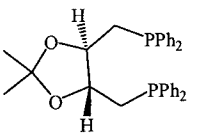
35
$[RuCl_2(p\text{-cymene})]_2$

Yield= 79% de=58%
ee(*trans*)=89% ee(*cis*)=82%
[75]

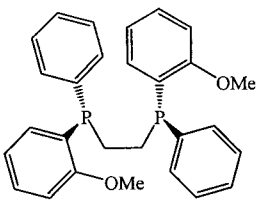
Figure 5. Ru-catalysts used in CACP of styrene with EDA.

4. Chiral Diphosphine Ligands

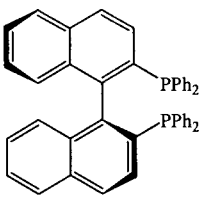
Chiral diphosphine ligands play a very important role in catalytic asymmetric synthesis. In 1972, Kagan developed the first diphosphine ligand (*S,S*)-DIOP **36**[79] and introduced the concept of C_2-symmetric ligands,[80] which diminish the number of possible catalyst-substrate conformations. This work prompted the development of new C_2-symmetric diphosphine ligands for instance, Knowles discovered (*S,S*)-DIPAMP **37**,[81] an important ligand for Rh-catalyzed asymmetric hydrogenation of dehydroamino acids. This was successfully employed in the industrial production of L-DOPA.[82] L-DOPA is used for treating Parkinson's disease. Knowles was later awarded the Nobel Prize in 2001 for this work.[5] Another diphosphine which is important for the catalytic asymmetric hydrogenation is the an axially chiral ligand, (*S*)-BINAP **38** discovered by Noyori in 1980.[83] He also won the Nobel prize for this work. This ligand was applied in the Ru-catalyzed asymmetric hydrogenation,[84] involving enantioselective reductions of various alkenes and ketones,[85] and also for the isomerization of allyl amines into enamines.[86] After the discovery of these three principle diphosphines **36-38**, a large number of other efficient chiral diphosphines have been developed for asymmetric catalytic hydrogenations,[87] hydroborations,[88] hydrosilylations,[89] allylic alkylations,[90] and hydroformylations,[91] etc.



(*S, S*)-DIOP **36**



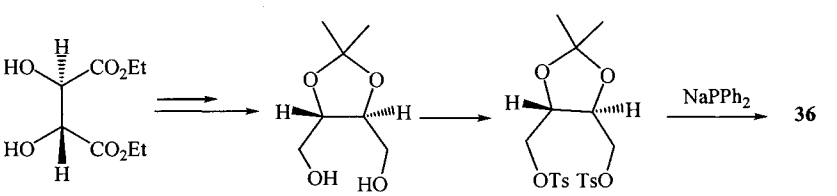
(*S, S*)-DIPAMP **37**



(*S*)-BINAP **38**

Chiral diphosphines can be prepared using four different synthetic routes: (i) S_N2 reactions, (ii) oxidative couplings, (iii) Diels-Alder reactions and (iv) Michael additions.

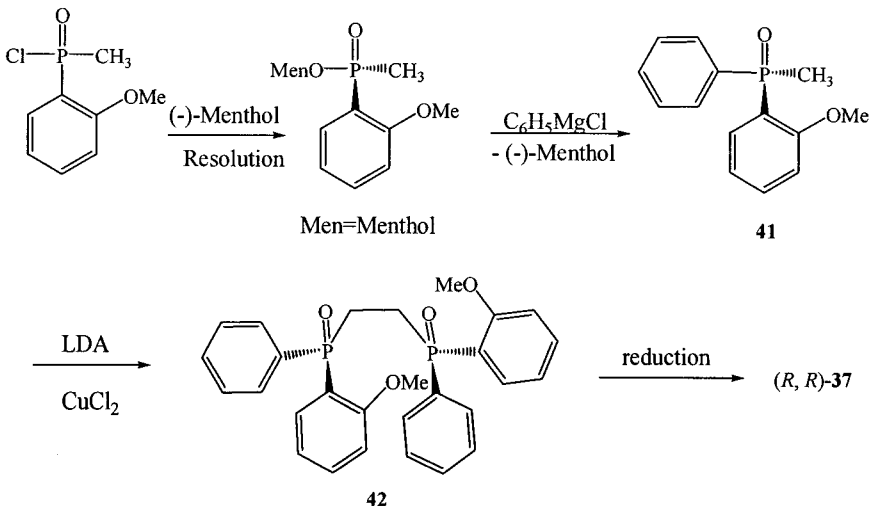
(i) Synthesis *via* the S_N2 reaction: the example used to illustrate this method is the DIOP **36**[79] synthesis (Scheme 4). It was prepared from (-)-diethyl tartrate **39** bearing stereogenic information in the carbon backbone. Sodium diphenylphosphide was used in an S_N2 type reaction with the corresponding tosylate **40** to introduce the phosphorus moiety in the last reaction step of the sequence. Under the same mechanism it is also possible to use potassium or lithium diphenylphosphide instead of sodium diphenylphosphide and other sulfonate leaving groups, like mesylate or triflate instead of tosylate.



39 **40**

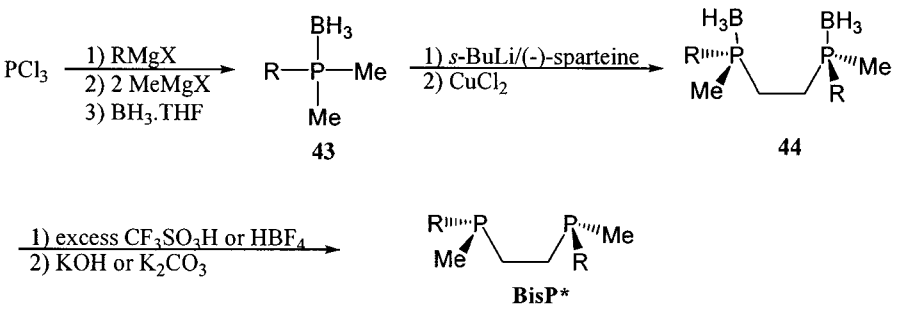
Scheme 4. Synthesis of DIOP by Kagan.[79]

(ii) Synthesis *via* oxidative couplings: A different class of chiral C_2-symmetric *P*-chirogenic phosphine ligands was introduced by Knowles. The key step in this synthesis was the oxidative coupling of (*o*-methoxyphenyl)methylphenylphosphine oxide **41** after treatment with LDA using a copper salt to give the diphosphine oxide **42**. This precursor is converted to the DIPAMP **37** ligand by reduction of **42** (Scheme 5).[81]



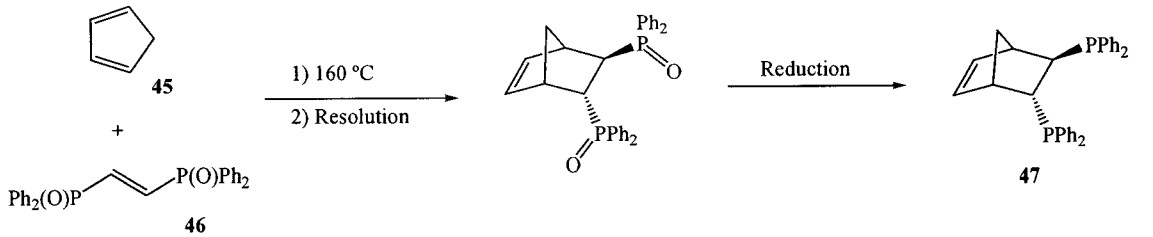
Scheme 5. Synthesis of DIPAMP **37**.[81]

Imamoto developed ligands based on the 1,2-bis-(alkylmethylphosphino)ethane framework (abbreviated **BisP*** with alkyl = *t*-butyl, 1-adamantyl, 1-methycyclohexyl, 1,1-diethylpropyl, cyclopentyl, cyclohexyl, isopropyl), which are obtained through oxidative coupling of the corresponding alkyldimethylphosphine-borane **43** in a one-pot synthesis starting from PCl_3. The chirality is elegantly introduced by a stereoselective deprotonation of phosphine-boranes **43** employing *s*-BuLi in the presence of (-)-sparteine (Scheme 6).[92] These ligands are precursors of efficient catalysts used in the asymmetric hydrogenation of dehydroamino acids and itaconic acid derivatives.[93]



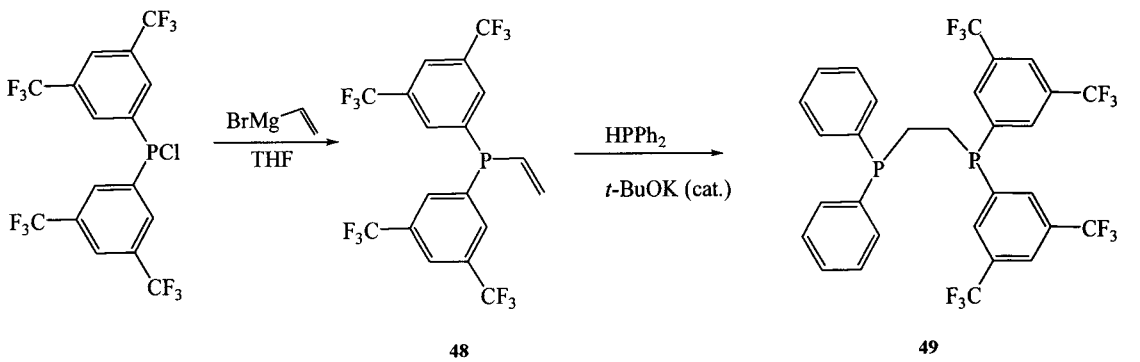
Scheme 6. Synthesis of BisP* by Imamoto.[93]

(iii) Synthesis *via* Diels-Alder reactions: Brunner synthesized NORPHOS **47**[94] using Diels-Alder reactions of a diene **45** and a dienophile **46** bearing two phosphorus atoms. NORPHOS contains two stereogenic centers in the α-position relative to the phosphorus atoms. The route is depicted in Scheme 7.



Scheme 7. Synthesis of NORPHOS **47** by Brunner.[94]

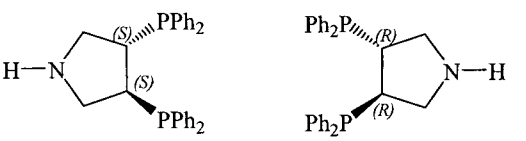
(iv) Michael additions: This method consists in the base-mediated addition of a secondary phosphine across the carbon-carbon double bond of a diarylvinylphosphine **48** giving DIPHOS-(3,5-CF_3) **49** (unsymmetric diphosphine).[95] The synthetic route is shown in Scheme 8, this ligand was evaluated in Rh-catalyzed hydroformylation reactions.



48 49

Scheme 8. Synthesis of DIPHOS-(3,5-CF_3) **49** by Casey.[95]

4.1 (*S, S*) or (*R, R*)-PYRPHOS 50



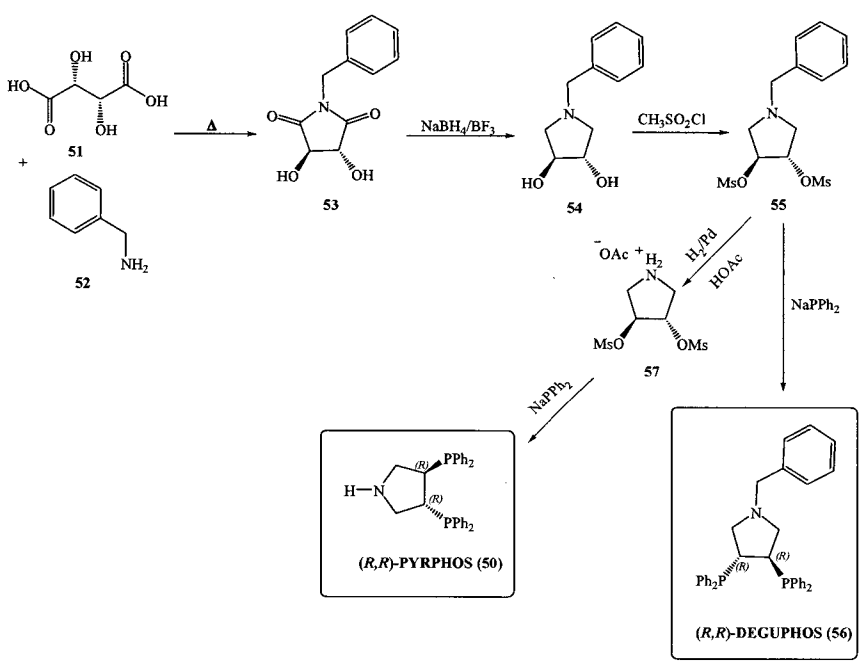
(*S, S*)-PYRPHOS (50) **(*R, R*)-PYRPHOS (50)**

Ulrich Nagel in 1984 discovered the 1,2-diphosphine PYRPHOS **50** (3,4-bis-diphenylphosphino-pyrrolidine) ligand, which showed good results in hydrogenating (*Z*)-α-acetamido cinnamic acid catalyzed by rhodium (an ee of up to 100% was obtained).[96,97] One of the advantages of PYRPHOS **50** is the possibility of

functionalization *via* its N-ring atom. The variation of substituents on the N-atom had no marked influence on the catalytic activity or the selectivity when using rhodium complexes. Several protecting groups can be introduced and the ligand can also be easily purified by recrystallization of the amino hydrochloride salt.

The synthesis of PYRPHOS **50** starts with cheap (+)-tartaric acid **51** and benzylamine, and a simple condensation forming the *N*-benzyltartrimide **53**. Nagel proposed several different methods, in this thesis only one of these is shown (Scheme 9). The (*S,S*)-*N*-benzyl-3,4-dihydroxypyrrolidine **54** was obtained by the reduction of **53** with a common hydride and lewis acid, $NaBH_4/BF_3$. The dimesylate **55** was substituted by the phosphide group, *via* an S_N2 reaction, to obtain the (*R,R*)-*N*-benzyl-3,4-bis-diphenylphosphino-pyrrolidine **56**, the well know DEGUPHOS. In order to obtain PYRPHOS **50**, it was necessary to debenzylate **55** and then introduce the diphenylphosphine groups.

PYRPHOS **50** is the starting point for obtaining several derivatives with the 3,4-bis-diphenylphosphino-pyrrolidine structure. In figure 6 some examples of PYRPHOS derivative (**50a-h**) are shown. They are obtained by simply coupling the respective carboxylic acid with the (*R,R*)-PYRPHOS **50**. All these derivatives were used in the Rh-catalyzed hydrogenation of (*Z*)-α-acetamido cinnamic acid, and excellent ees were obtained.



Scheme 9. Synthesis of PYRPHOS **50** and DEGUPHOS **56** by Nagel's Method.[96a]

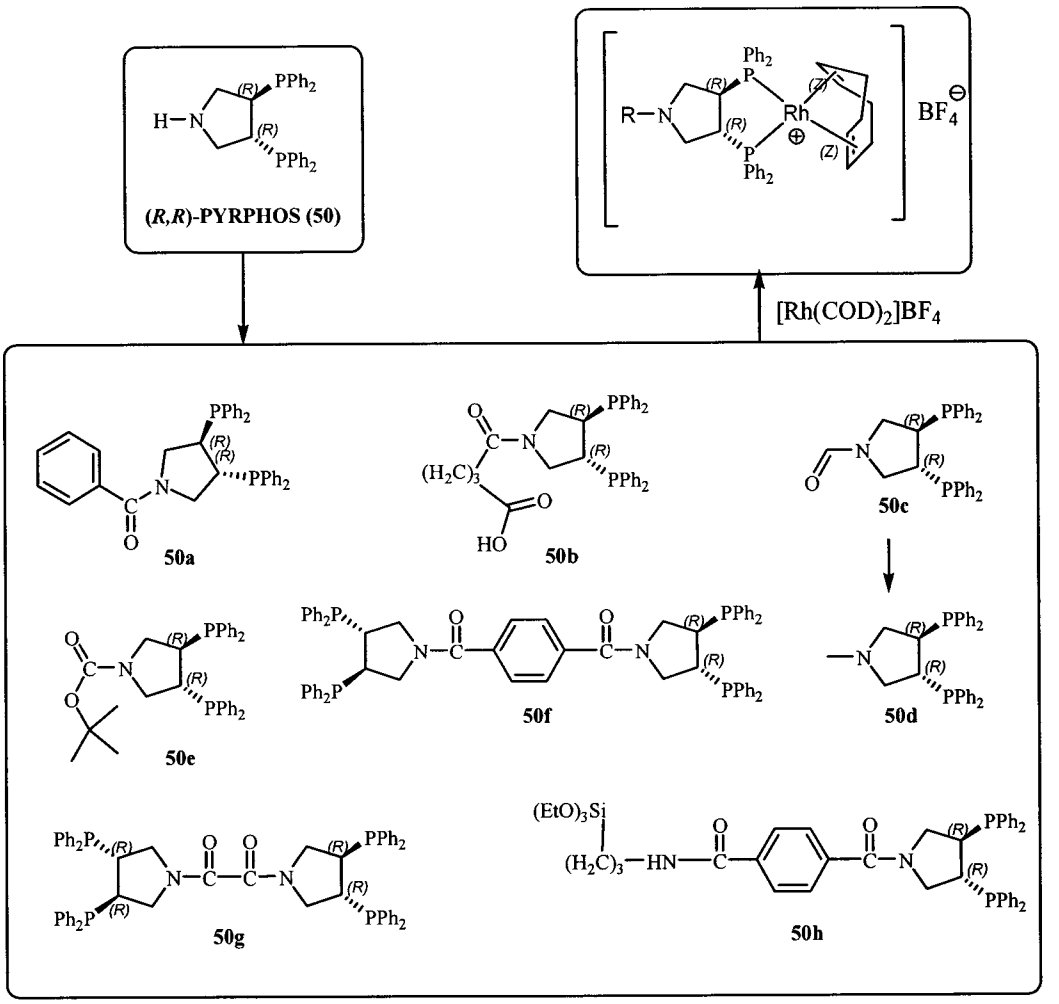
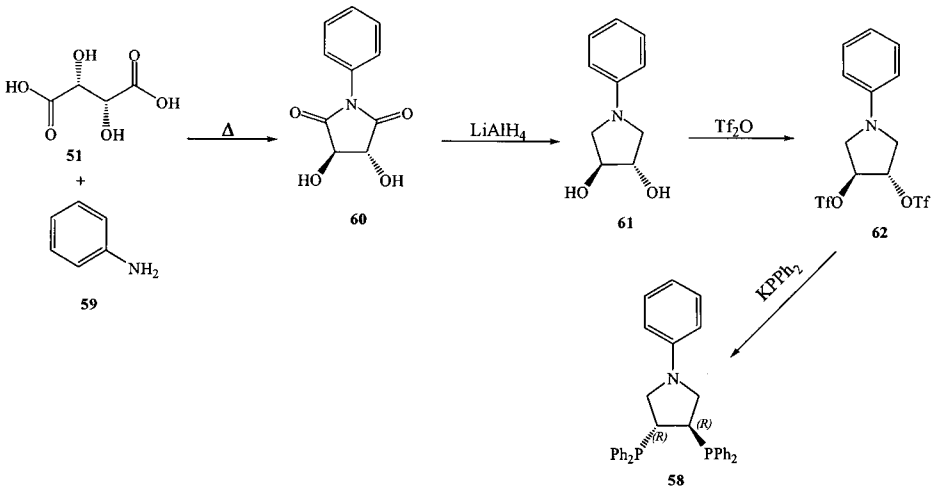


Figure 6. (*R,R*)-PYRPHOS-derivatives and the respective complexation with Rh.

In 2001, Gonsalves *et al.*[98] developed a new PYRPHOS derivative (*R,R*)-*N*-Phenyl-3,4-bis-diphenylphosphine-pyrrolidine **58**, which was prepared via a similar method but using the aromatic amine, aniline **59**. This posed quite a few problems, requiring the use of specific reduction conditions, use of the triflate leaving group instead of the mesylate and use of the more reactive potassium diphenylphosphide instead of sodium diphenylphosphide. The yield was very modest (22%). The route is depicted in Scheme 10. **58** was tested in the Rh-catalyzed enantioselective transfer hydrogenation of α-acetamido cinnamic acid and itaconic acid, but the ees were only moderate (up to 40%).



Scheme 10. Synthesis of **58** using Gonsalves' method.[98]

Based on the good results obtained using several PYRPHOS **50** derivatives in the homogeneous phase, it was of interest to immobilize this diphosphine and apply it in heterogeneous asymmetric catalysis. Despite the number of supports used to immobilize PYRPHOS (see Chart 2), in this work we studied for the first time it's immobilization to PVA and its evaluation in Rh-catalyzed enantioselective hydroformylations.

Chart 2 summarizes the various supports that have been used to immobilize PYRPHOS **50**. The first immobilization was developed by Nagel *et al.*[99] who covalently attached **50** to Silica (I, Chart 2), and evaluated this immobilized catalyst in the Rh-catalyzed enantioselective hydrogenation of α-acetamidocinnamic acid obtaining very good ees. The ees were very close to those obtained in the homogeneous version. This study prompted other research groups to immobilize **50** to other supports, like that depicted in the Chart 2 (II-IX). Generally the ligand was attached to the linker through an amide bond which facilitated the immobilization of the transition metal complexes to poly-acrylic acid (PAA),[100] polyethylene glycol,[101] dendrimers,[102,103] gold surfaces,[104] a protein cavity,[105] and even on DNA[106] including non-covalent adsorption on carbon nanotubes.[107] PYRPHOS **50** was attached to poly(acrylic acid) to give the supported ligand (III, Chart 2), which is a new water-soluble-ligand. Polymer immobilized **50** was tested in the biphasic (H_2O/EtOAc) Rh-catalyzed asymmetric hydrogenation of acetamidocinnamic acid. The hydrogenated product was obtained in 76 to 83% ee which were lower than those obtained in the homogeneous system. In 2001 Fan and Chan prepared polyethylene glycol-supported PYRPHOS (IV, Chart 2), and this soluble

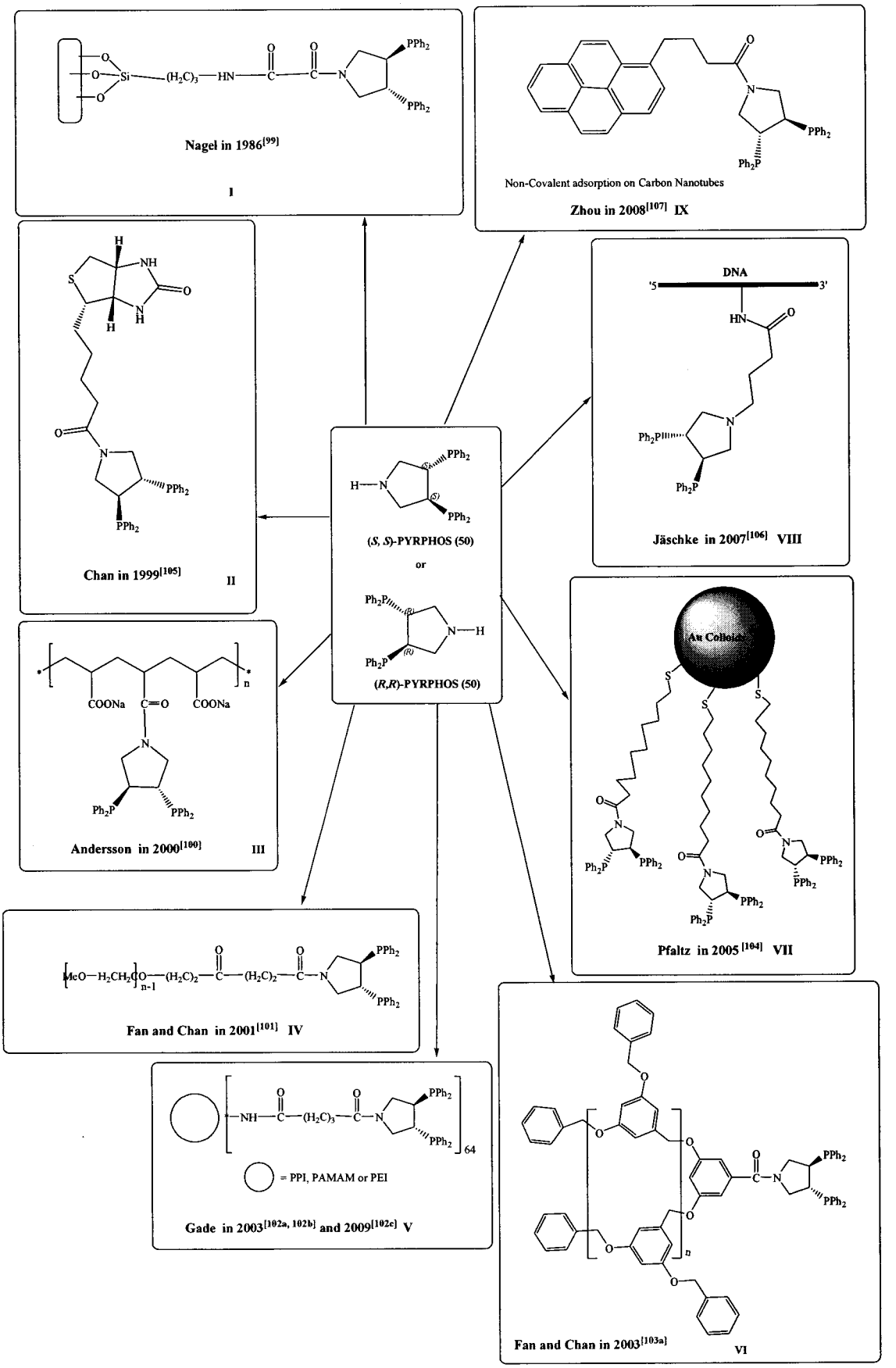


Chart 2. Examples of immobilized PYRPHOS attached to diverse supports.

polymer-supported PYRPHOS was tested in the Rh(I)-catalyzed enantioselective hydrogenation of prochiral enamides. The results showed that the supported-catalyst had high catalytic activity and enantioselectivity (ees up to 96%), and this catalyst could be recovered easily. The recycled catalyst was shown to have similar efficiency as a freshly prepared sample, indicating no catalyst deactivation.[101] The same group in 2003 described the use of a Fréchet-type polyether dendron for immobilizing PYRPHOS at the focal point of the dendrimer. This dendrimer-bond PYRPHOS ligand (VI, Chart 2) was used to prepare recoverable reusable Rh(I)-catalysts for asymmetric hydrogenation of (*R*)-acetamidocinnamic acids. The primary objective of this study was to probe the effect of the dendrimer structure and generation on the activity of a core-centered single site catalyst. The selectivity was >97% ee for all cycles, but the conversion dropped from 94% in the first cycle to 55% in the third cycle.[103a] Recently, Fan *et al.* [103b] developed a new series of dendritic PYRPHOS ligands. The preparation of these peripherally alkyl-funcionalized dendritic PYRPHOS ligands with PYRPHOS located at the focal point, was easily accomplished and they were subsequently applied in the Rh-catalyzed enantioselective hydrogenation of acetamidocinnamic acids in an organic biphasic system. Excellent catalytic activity and enantioselectivities were obtained (ees up to 98%). This system gave facile catalyst recycling, and the recovered catalyst could be reused four times without significant loss of efficiency.

Gade and coworkers[102a,102b] have developed an interesting technique which attaches **50** in the densely packed environment of a dendrimer (up to 64 metal sites can be loaded to the support). The supports were PPI [poly(propyleneimine)] and PAMAM [poly(amido amine)], the resulting polynuclear complexes were tested in the Rh-catalyzed enantioselective hydrogenation of *Z*-methyl-*N*-(acetylamino)cinnamate and dimethyl itaconate giving ees up to 93%,[102a] and in the Pd(0)-catalyzed enantioselective allylic amination of 1,3-diphenyl-1-acetoxypropene giving ees of up to 69%.[102b] Recently, they reported the immobilization of **50** on soluble hyperbranched poly(ethylene imines) (PEI), with 9 to 139 centers. The system was tested in the Rh-catalyzed hydrogenation in ionic liquids and ees of up to 86% were obtained. The system could be recycled twice without loss of activity and enantioselectivity.[102c]

Belser *et al.* immobilized Rh(I)-PYRPHOS complexes on self-assembled thiolate monolayers of a gold colloid. The immobilized system was used for the enantioselective hydrogenation of methyl α-acetamidocinnamate giving good enantiosletivities and catalytic activity (ees of up to 93% and yields of up to 98%). The

colloids could be easily recovered and reused up to three times without loss of enantioselectivity, but the yield dropped to 90%.[104]

Another interesting method, was developed by Lin *et al*,[105] this consisted of introducing a biotinylated PYRPHOS-Rh catalyst into the restricted tertiary environment of a protein cavity. The system was evaluated in the enantioselective hydrogenation of itaconic acid, and gave better ees than the biotinylated PYRPHOS complexes.

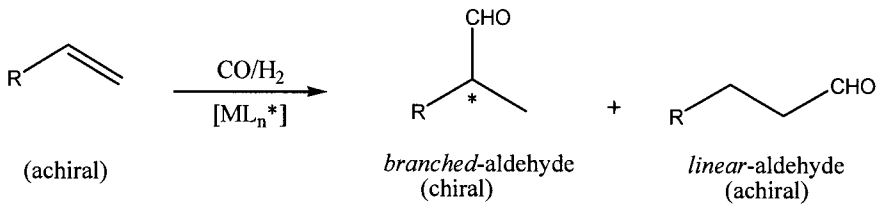
In 2007 Caprioara *et al.*[106] developed an interesting technique, consisting of a post-synthetic strategy for the site-specific incorporation of PYRPHOS into DNA sequences (VIII, Chart 2). A study on the stability after purification and isolation revealed that the system was quickly oxidized.[106]

A non-covalent immobilization method was developed by Xing *et al.*[107] This method consisted in the adsorption of pyrene-modified PYRPHOS (IX, Chart 2) Rh complexes to nanotubes *via* non-covalent adsorption (π–π stacking interactions). The system was applied in the enantioselective hydrogenation of α-dehydroamino esters. For up to nine cycles the ees remained constant.

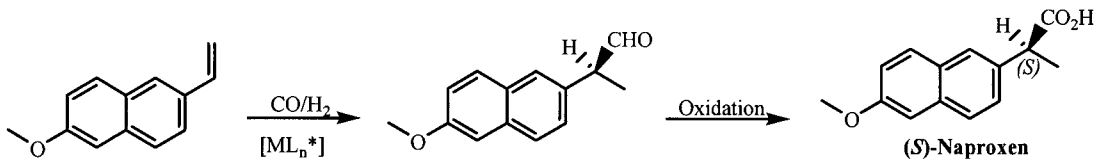
5. Catalytic Asymmetric Hydroformylation

The hydroformylation reaction (HF) was discovered by Otto Roelen in 1938 (he called it "Oxo synthesis"),[108] and it consisted in the transformation of olefins to aldehydes, by the addition of a formyl group and a hydrogen atom to C-C double bond (Scheme 11). This is a very important process in obtaining important fine chemicals. Catalytic Asymmetric Hydroformylation (CAHF) was an important extension of this reaction, furnishing chiral products, particularly for the pharmaceuticals industry. The aldehyde group is one of the most versatile functional groups, giving a known variety of useful chiral chemicals, like amines, imines, alcohols, and acids, etc. For example, the CAHF leads to 2-aryl-propionic acid drugs, one example being the anti-inflammatory drug (*S*)-Naproxen (Scheme 12). The challenges of the CAHF reaction concern not only the enantioselectivity but also the chemoselectivity (hydroformylation versus hydrogenation) and the regioselectivity (branched (*b*) versus linear (*l*) aldehyde) like that depicted in Scheme 11. Obviously, these requirements depend on the reaction conditions used, like temperature, pressure, substrate type and the chiral ligands.

Among the most significant problems encountered are: (i) decreasing the temperature leads to low reaction rates, although good selectivities are usually observed; (ii) limited substrate scope for any single ligand. These requirements are the reason at the moment why there are few applications of the CAHF on an industrial scale. [1b,109]



Scheme 11. Catalytic asymmetric hydroformylation.



Scheme 12. Synthetic route for the anti-inflammatory drug (*S*)-Naproxen involving a CAHF.

The first report on the CAHF appeared in 1972, and concerned the hydroformylation of styrene and related alkenes in the presence of a Cobalt catalyst containing a chiral Schiff base,[110] and Rhodium complexes bearing chiral monophosphine ligands.[111] The most promising system was the Rhodium catalyst as better chemo- and regioselectivities were obtained, although the enantioselectivities were rather low. In the case of the Cobalt catalyst the main reaction was hydrogenation of styrene to ethylbenzene, and the regioselectivity obtained was nearly 50:50 (*b:l*) with a very low ee.[110]

The initial results obtained for the CAHF of styrene catalyzed by Rh with chiral monophosphine ligands, prompted various research groups to use chiral diphosphine ligands. DIOP **36** was the first diphosphine tested in the Rh-catalyzed asymmetric hydroformylation.[112] Other metals have been used in the CAHF like platinum, ruthenium, iridium and palladium, but only platinum gave promising results.[113]

In this thesis the focus is on Rh-catalyzed asymmetric hydroformylation of styrene (as a model compound for vinyl aromatic substrates that could be used for the synthesis of anti-inflammatory drugs) with chiral phosphorous ligands.

A range of diphosphines (DIOP-based) was developed and used in the CAHF, despite the moderate enantioselectivities, the chemo- and regioselectivities were good.[109a] An improvement was obtained with the BINAPHOS **63**[114] (Figure 7) ligand and its analogs. These ligands furnished high enantioselectivities (up to 99% ee) for a variety of alkenes, but the regioselectivities were typically quite low.[114] See Figure 7 for examples of chiral phosphorus ligands used in CAHF. CHIRAPHITE **64**,[115] the first example of a diphosphite ligand used with success in the CAHF of styrene, gave enantioselectivities of 76% ee, with very high regioselective control (*b:l* = 47:1) but only when the reaction was carried out at room temperature.

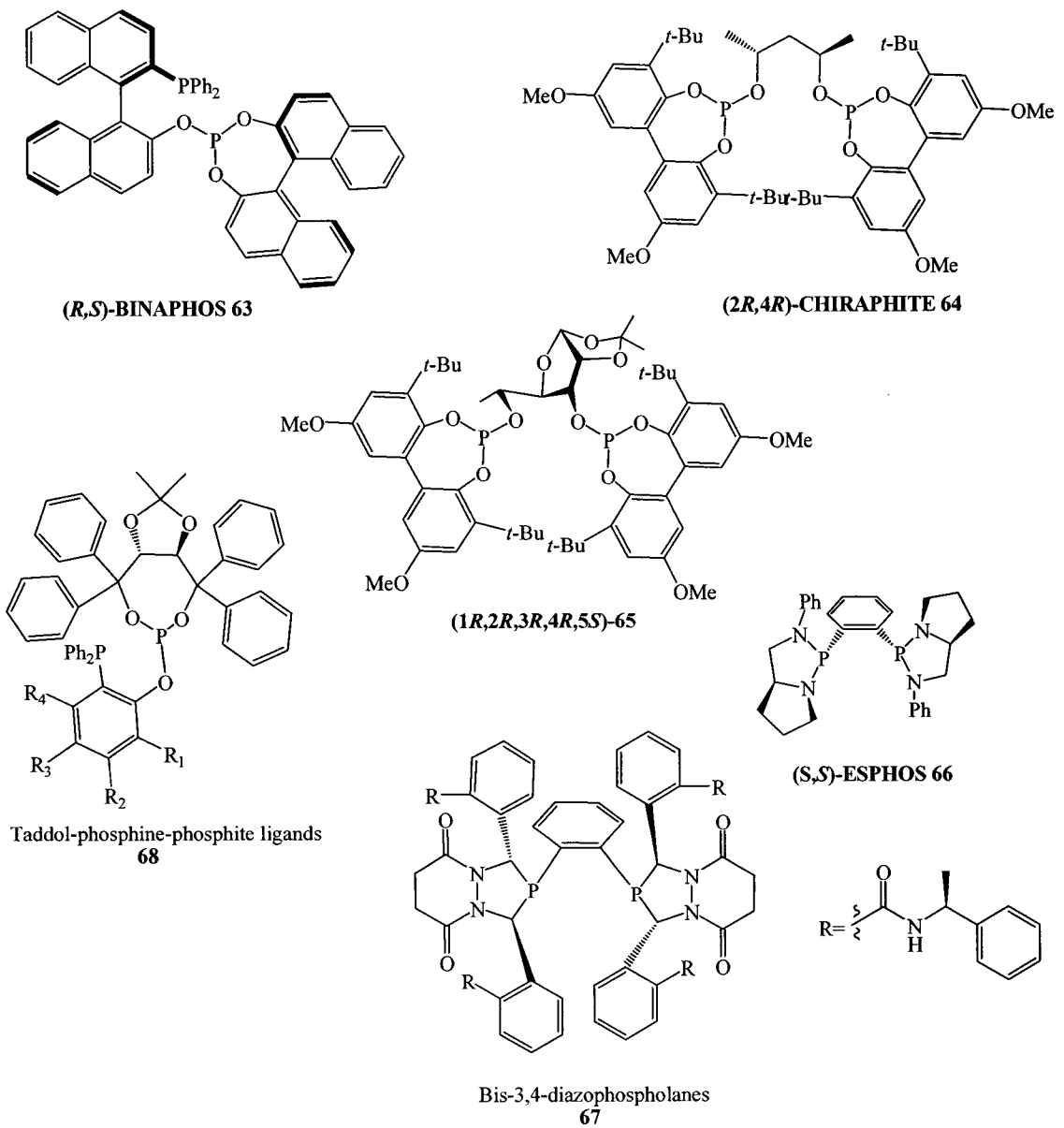
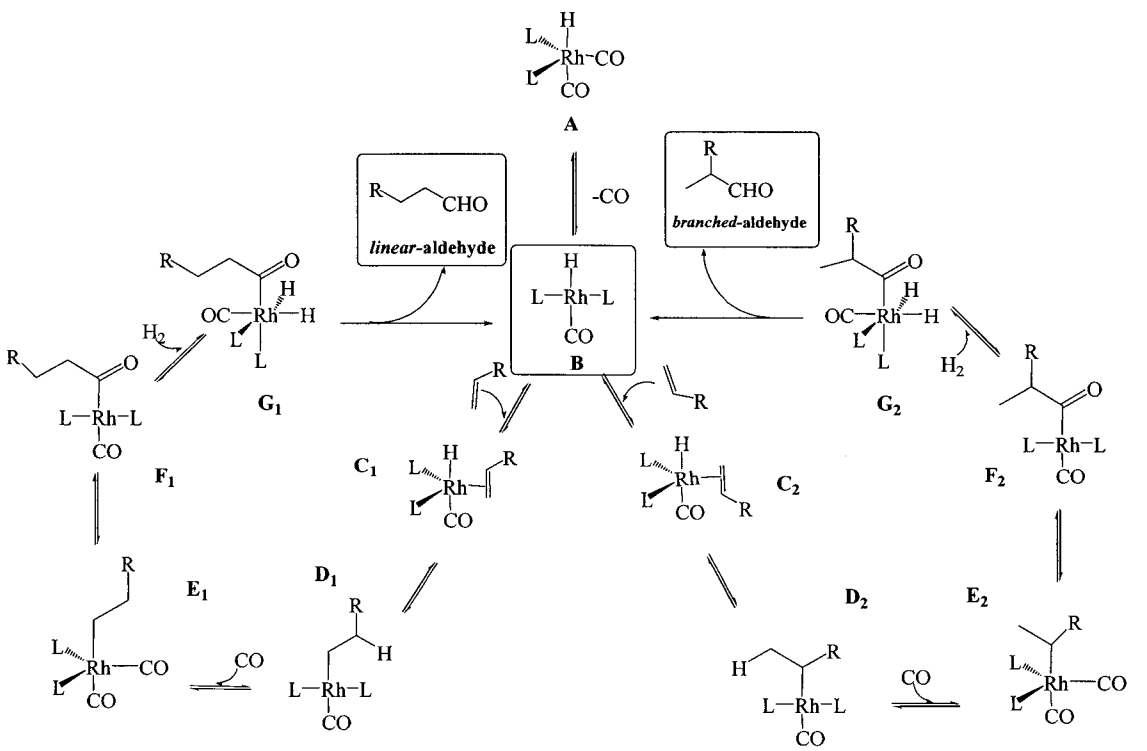


Figure 7. Chiral phosphorus ligands used in the catalytic asymmetric hydroformylation reaction.

CHIRAPHITE **64** analogs were developed by Claver and coworker,[116] these diphosphite sugar-based systems - (1*R*,2*R*,3*R*,4*R*,5*S*)-**65** - were used in the CAHF of styrene, with similar reaction conditions. The best enantioselectivity obtained was 89% ee and the best regioselectivity was 49:1 (*b:l*), the results were a little bit better than with CHIRAPHITE **64**. ESPHOS **66**, the first phospholane-type ligand tested in the CAHF gave good results for vinyl acetate (ee = 90%, *b:l* = 16:1), but it was quite unselective for styrene.[117] Bis-3,4-diazaphospholane **67** demonstrated effective regio- and enantiocontrol for styrene (82% ee, *b:l* = 6.6), vinyl acetate (96% ee, *b:l* = 37) and allyl cyanide (87% ee, *b:l* = 4.1).[118]

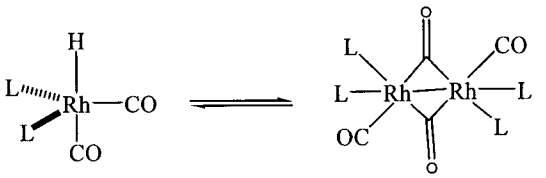
Recently, Schmalz and Reek[119] developed a new family of Taddol-based ligands **68** of the type bearing bulky substituents in the *ortho*-position of the phosphite, the application of these ligands in the CAHF gave enantioselectivities of up to 85% ee and regioselectivities of ≥ 98:2.

The first mechanism for the CAHF catalyzed by Rh(I)-phosphine complexes was proposed by Wilkinson. This dissociative mechanism, is now the generally accepted mechanism for bidentate phosphine-Rh(I) catalyzed hydroformylations.[120] This is supported by theoretical studies.[121] The catalytic cycles are depicted in Scheme 13.



Scheme 13. Wilkinson's dissociative mechanism for the Rh-phosphine catalyzed hydroformylation reaction.[120]

Ignoring the counter-anion attached to the Rh in the catalyst precursor **A** (18 e^-, inactive), the dissociation of CO from the complex gives the Rh hydride complex **B** (16 e^-, active) which coordinates to the alkene ($\mathbf{C_1}$ and $\mathbf{C_2}$). This is followed by hydride insertion to give the Rh species $\mathbf{D_1}$ and $\mathbf{D_2}$. CO coordination followed by migratory insertion leads to the Rh-acyl intermediates $\mathbf{F_1}$ and $\mathbf{F_2}$. Oxidative addition of H_2, ($\mathbf{F_1}$ and $\mathbf{F_2}$)→($\mathbf{G_1}$ and $\mathbf{G_2}$) and reductive elimination of the product aldehyde completes de catalytic cycle, ($\mathbf{G_1}$ and $\mathbf{G_2}$)→(**B**). The Rh-phosphine catalyzed reaction can often be accelerated by using higher H_2 pressures. Wilkinson has suggested that the oxidative addition of H_2 may be the rate-determining step. Dimeric species are usually formed by the Rh-phosphine complex, $RhH(CO)_2(phosphine)_2$ under the H_2/CO atmosphere (Scheme 14).



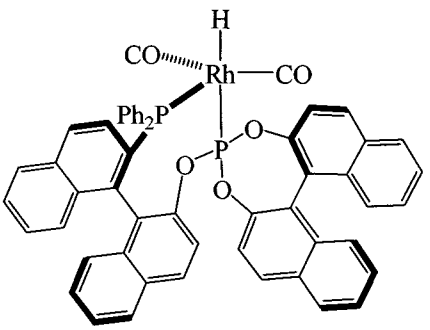
Scheme 14. Formation of $[Rh(CO)_2(phosphine)_2]_2$ compex dimers which causes loss of catalytic activity.

As depicted in the catalytic cycle of the hydroformylation reaction (Scheme 14) the active species is the monometallic one and the process of dissociation of the dimer by hydrogenolysis influences the reaction rate, this is crucial at high concentrations of the Rh catalyst at low H_2 pressure. In the same way a higher CO pressure frequently results in a low reaction rate. This is attributed to the fact that the dissociation of CO from $RhH(CO)_2(phosphine)_2$ is required to continue the cycle.

In the case of the CAHF various studies have established that the existence of a single species is essential to achieve high ees. The two monodentate phosphine or the single bidentate phosphine or phosphite ligands adopt an equatorial-equatorial and/or equatorial-apical position in the $RhH(CO)_2(phosphine)_2$ complex.

Takaya and Nozaki[114b,122] reported that $RhH(CO)_2$[(*R,S*)-BINAPHOS] **69** exists as a single form in which the phosphine occupies an equatorial position and the phosphite an apical one, the latter being *trans* to the hydride. This particular complex is definitely active in the CAHF, demonstrating high selectivity on only a single species is essential. Van Leeuwen and coworkers[123] reported an X-ray crystal structure for $RhH(CO)_2L_2$ in which L is the bulky bisphosphite. In this case, the phosphorus atoms occupy equatorial positions around the central Rh atom, and the hydride and one of the

carbonyls occupy apical positions. Systematic studies were carried out by the same research group to understand the relationship between the structure of the chiral bisphosphite ligands and the enantioselectivities obtained with the corresponding Rh(I) complexes in the CAHF. They concluded that to obtain high ees the ligands had to be exclusively coordinated in an equatorial-equatorial fashion, and the presence of an equatorial-apical isomer reduces the ees. From a number of studies it has become evident, that high ees can be obtained with chelating ligands preferring **eq-eq** coordination.[124] However, ligands coordinating in **eq-ap** mode gave good enantioselectivities as well.[125]



69 eq-ap

6. Immobilization of Chiral Catalysts

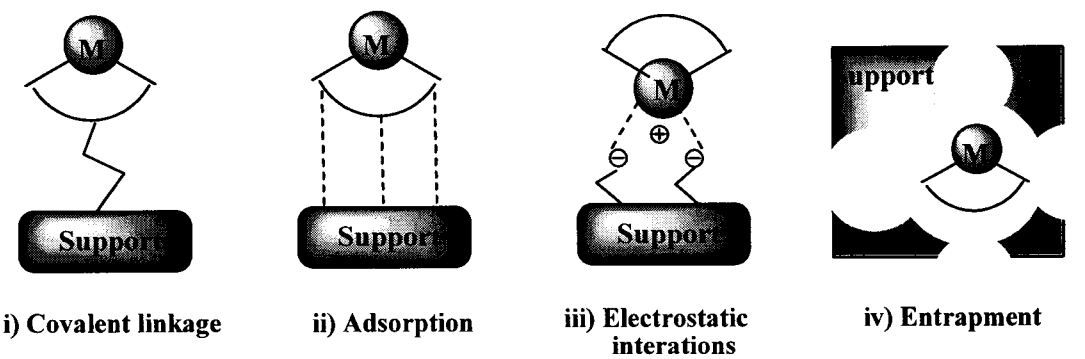
The increased importance for immobilized chiral catalysts is a consequence of the increased demand for chiral chemicals, and of great interest in both academia and industry.[126,127]

Catalyst immobilization can be defined as 'the transformation of a homogeneous catalyst into a heterogeneous one, that can be separated from the reaction mixture and preferably be reused many times'. The main reason objective for the development of an immobilized chiral catalyst is to combine the positive aspects of a homogeneous catalyst (e.g. high activity, high enantioselectivity, good reproducibility) with those of a heterogeneous catalysis (e.g. ease of separation, stability, reusability). Over the past few decades, a number of strategies have been developed for this purpose. Depending on whether the modifications are made on the catalyst structure or on the reaction medium, the immobilization techniques can be categorized into two general classes, namely heterogenized enantioselective catalysts and multiphase (or monophase) catalysis in

nonconventional media. The immobilized chiral catalysts can be further subdivided into several types:[126]

- ❖ Insoluble chiral catalysts bearing stationary supports such as inorganic materials or organic cross linked polymers, or homochiral organic – inorganic coordination polymeric catalysts without using any external support.
- ❖ Soluble chiral catalysts bearing linear polymeric supports or dendritic ligands.
- ❖ Chiral catalysts with some form of nonconventional reaction medium as the 'mobile carrier', such as, aqueous phase, fluorous phase, ionic liquid or supercritical carbon dioxide ($scCO_2$). These liquids can form biphasic systems with the immiscible organic products in the second phase, leading to the possibility of easy isolation and recovery of the chiral catalyst by phase separation.

The most common methods for immobilization of homogeneous asymmetric catalysts are by: a) Covalent linkage; b) Adsorption c) Electrostatic interactions; and d) Entrapment (Figure 8).



i) Covalent linkage **ii) Adsorption** **iii) Electrostatic interations** **iv) Entrapment**

Figure 8. Schematic representation of the common strategies for immobilizing homogeneous chiral catalysts on solid supports.

a) The immobilization *via* covalent (i, Figure 5) linkage of the ligands/catalysts onto a solid support is one the most frequent and versatile ways to heterogenise a chiral catalyst. The supports generally used are either organic polymers or inorganic solids (more robust and stable). The covalent bond formed between the catalyst and the support is very stable, which makes leaching of the catalytic complex more difficult. On the other hand the major disadvantage is that the ligand has to be functionalized, which requires a longer and sometimes complicated synthetic process. With this method, generally, the heterogenised

catalysts have slightly different activities and selectivities in comparison to the respective homogeneous catalysts. To avoid these problems, one critical problem being - limited reagent diffusion within the support matrix - it is best to place the ligand/catalyst as far as possible away from the support.

b) Adsorption (ii, Figure 5) represents the noncovalent immobilization of the ligand/catalyst. This is a very facile method, and the procedure consists of a simple impregnation. This method can subdivided into: immobilization by physisorption (weak Van der Waal type interactions with the support), immobilization by hydrogen bonding with the support (some authors consider this as an electrostatic interaction), supported liquid phase (SILP), and nanoparticles as supports for chiral catalyst. The electrostatic or coordenative interactions cannot be discarded in some of these immobilizations. Leaching can be a big problem.

c) Electroactatic interaction is another common and conceptually simple method of immobilization, which is applicable to heterogenation of ionic catalytic species. The solid support can be either anionic or cationic, and the catalyst is adsorbed by ion-pairing. Diverse supports with ion-exchange capabilities can be used, like organic or inorganic ion-exchange resins, inorganic clays (e.g. montmorillonite K10, betonite) and zeolites. Although this method can provide relatively stable immobilized catalysts, it is still limited to the catalysts which can only be immobilized through electrostatic interactions. Leaching can be a problem.

d) Entrapment (iv, Figure 5), the objective is to keep the catalytic complex enclosed inside the structure of the support without the need for an additional support-complex interaction. In this technique the size of the metal complex relative to that of the cavity of the host support is a critical factor, leading to a mechanically immobilized catalyst. The approach can be subdivided into two main methods: entrapment into a flexible polymer or entrapment into a rigid inorganic matrix. The entrapment strategy is relatively complex to implement compared with the others methods, and the size of the substrate molecules and/or reagents may cause diffusion problems within the support.

All these methods described have advantages and disadvantages, and it is difficult to predict whether a covalent or a noncovalent immobilization strategy would be preferential for a particular catalyst. Noncovalent immobilization strategies are gaining increasing recognization as a practical way to achieve good stability and reusability as

well as high selectivity and activity of the immobilized chiral catalyst, despite the fact that covalent bonding still remains the most popular approach to chiral catalyst immobilization.

Several catalysts have been immobilized using these methods, and tested in catalytic asymmetric reactions, like those referred to in several reviews.[128]

Some supports were used to immobilize key catalysts in this work.

The objective of this PhD research was to immobilize the Arylid-BOX ligands (Chapter 3) and derivatives (Chapter 4) or their resulting metal catalysts via covalent bonding, adsorption and electrostatic interactions, and subsequent evaluation in catalytic asymmetric cyclopropanation reactions. Another challenge was to immobilize PYRPHOS **50** to an organic polymer support via covalent bonding, and then evaluation in the CAHF.

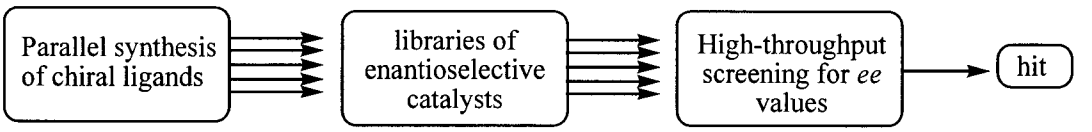
7. Combinatorial Homogeneous Catalysis

Since the end of the nineteen-eighties combinatorial chemistry as a tool for the screening of large "libraries" of new drug molecules has shown an unprecedented rapid devolvement. At one stage during the evolution combinatorial methods were believed to offer the best results in the discovery of novel drugs.

Part of this work has focused on the use of combinatorial approaches to designing the most efficacious homogeneous catalysts. However, the term "Combinatorial homogeneous catalysis" is frequently used in a very broad sense, like for instance to describe, parallel ligand/catalyst synthesis and rapid evaluation of a large number of soluble catalysts.[129] This includes not only the synthesis and the testing of structurally different ligands/catalysts, but also the study of the influence of various conditions like, temperature, pressure, solvent and additives, etc. Multiple substrate screening is a concept and current methodology introduced by Kagan and Satyanarayana[130] and is thus another practical facet of combinatorial homogeneous catalysis (see the work of Gennari reported below).

The most common combinatorial approach for designing chiral ligands for enantioselective catalysis is based on a modular approach: ligand libraries are synthesized in solution or on a solid support via the coupling of different subunits.

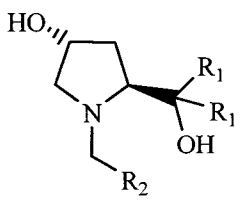
One should carefully distinguish between the combinatorial synthesis of the (chiral) ligands and the parallel assessment of the respective transition-metal catalysts formed using these molecules. The ideal situation is to combine the two processes in a sequential manner, to increase both the diversity and speed at obtaining an optimized catalyst (Scheme 15).



Scheme 15. Parallel preparation and screening of chiral catalysts.

This research is well reported in several reviews.[131] Some fundamentals will be presented here.

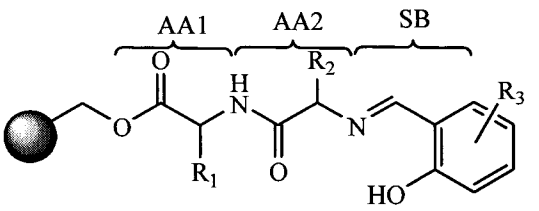
Ellman and coworkers[132] in 1995 were the first to explore the strategy of synthesising parallel libraries of chiral ligands by developing a highly modular ligand structure and screening it in enantioselective metal-catalyzed reactions. They started with a small library of substituted of pyrrolidine alcohol ligands **70**. The synthesis was carried out as a six-step parallel solid-phase process, the last step being acid-catalyzed cleavage from the solid phase. A variety of different R_1 and R_2 groups were introduced by Grignard reactions and *N*-acylation/reduction, respectively. Subsequently the modular amino alcohols were tested as catalysts in the enantioselective addition of Et_2Zn to aldehydes, with the best hits from this small library resulting in ee values of up to 85 %.



70

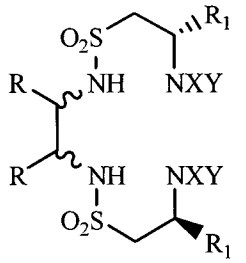
Snapper, Hoveyda and coworkers,[133] also made an important contribution using modular peptides **71**, which were comprised of three variable sub-units: Schiff base (SB), amino acid **1** (**AA1**) and amino acid **2** (**AA2**). Transition metals were expected to coordinate at the SB site. Titanium is one metal that has been studied and it has been

applied in the asymmetric ring opening of epoxides. These workers developed a screening strategy which avoids the tedious individual testing of all the possible permutations. Each of the three modular subunits was optimized successively whilst keeping the other two subunits of this type unchanged. Positional scanning of this type led to the identification of a catalyst showing 89 % *ee* in this model reaction. Since only 60 catalysts were tested, it is likely that even better results could be achieved with larger libraries. Later, this type of combinatorial search was successfully applied to other reaction types.[131b, 134]



71

Gennari *et al.*[131c,135] described another combinatorial approach. This consisted in the creation of new members of a known family of modular chiral ligands incorporating sulfonamides using solution-phase reactions and a solid-phase extraction technique. Libraries of disulfonamides **72** were then tested in the [Ti(O*i*Pr)$_4$]-mediated addition of Et_2Zn to aldehydes. This was accomplished by employing 30 reaction vessels in parallel, each containing four different aldehydes according to Kagan's concept of simultaneous screening of substrate mixtures.[130] 120 data points were collected, with the best enantioselective values amounting to about 90 % ee.

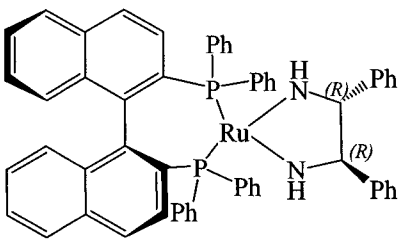


X= H, -$(CH_3)_3$-
Y= Boc, Cbz

72

Classical GC was employed as the analytical tool. This particular strategy has since been extended and refined by Gennari[131c,135] and Liskamp *et al.*[136]

The concept of utilizing libraries of modular ligands for asymmetric transition-metal catalysis was also investigated by Jacobsen,[137] Burgess,[138] Gilbertson,[139] Kobayashi,[140] Waldmann,[141] Berkessel,[142] Schmalz,[143] Ding[131d] and others.[144] The use of a mixture of monodentate ligands in a combinatorial asymmetric homogeneous catalysis was introduced in 2003 simultaneously and independently by Reetz and Feringa for asymmetric catalytic hydrogenation reactions.[145,146] This work was inspired by the previous work using mixtures of ligands for the formation of chiral catalysts, but has been limited to bidentate ligands.[147,148] Examples include; ruthenium catalyst **73** by the group of Noyori,[147] and titanium catalyst **74** developed by the group of Mikami.[148a]



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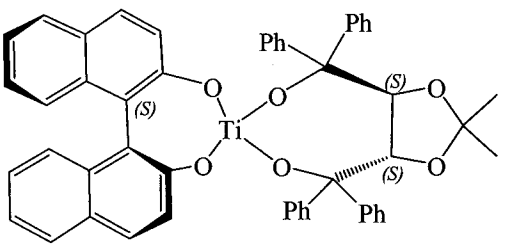

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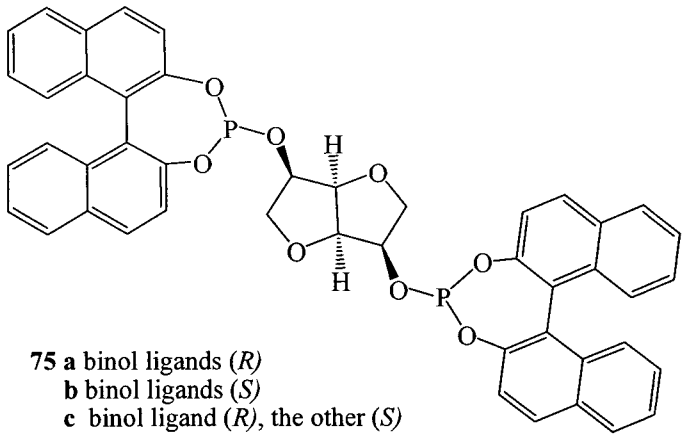
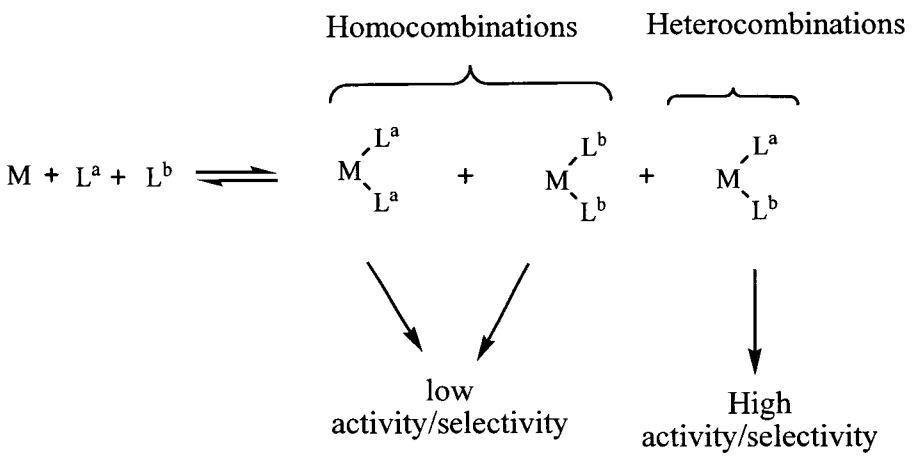
These methods differ, however, from the monodentate ligand combination approach, because these complexes were specifically designed to exist only as the heterocombination.

In the case of diastereomeric bidentate ligands containing two chiral centres, the (*R,R*), (*S,S*) *or* (*R,S*) diastereomers can be used for the study of matched (favorable) or mismatched (unfavorable) combinations in transition-metal catalysis.[149] For example, Reetz and coworkers[150] designed the diphosphites **75**, which could lead to high enantioselectivity in the Rh-catalyzed olefin hydrogenation. This ligand has two binol (2,2'-dihydroxy-1,1'-binaphtyl) units attached to an isomannide core unit. Two diastereomers **75a,b** were synthesized, allowing for the study of matched or mismatched combinations in subsequent transition-metal catalysis. For example, in the asymmetric Rh-catalyzed hydrogenation of itaconate, the diphosphite containing two (*R*)-binol units, **75a**, turned out to be the matched case (95% ee (*R*)). Mismatched **75b** led to a lower enantioselectivity (88% *ee* (*S*)) and to a distinctly lower reaction rate.[150]



75 **a** binol ligands (*R*)
b binol ligands (*S*)
c binol ligand (*R*), the other (*S*)

The use of mixtures of monodentate ligands, leads to greater diversity. For example when two chiral ligands, $\mathbf{L^a}$ and $\mathbf{L^b}$ are complexed *in situ* to a transition metal **M**, they will form three distinct catalytic entities, two homocombinations [$\mathbf{ML^aL^a}$] and [$\mathbf{ML^bL^b}$], but also the heterocombination [$\mathbf{ML^aL^b}$] (Scheme 16).



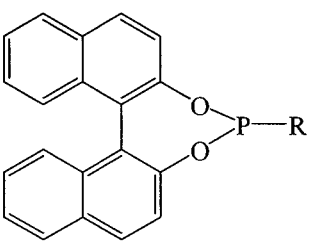
Scheme 16. The monodentate ligand combination approach – ideal situation.

It has been shown in some cases that the heterocomplex shows higher activity and selectivity than the two homocomplexes simultaneously present in the reaction mixture.[145,146] It is important to note that this approach only leads to improved results when a more selective heterocomplex is favored (predominant) and is also more active than the homocomplexes. This approach benefits greatly from combinatorial screening methods, because a relatively small number of monodentate ligands give rise to a large number of possible heterocomplexes. In a mathematical form, n monodentate ligands give rise to $\frac{n(n+1)}{2} - n$ possible heterocombinations, for example one library of 20

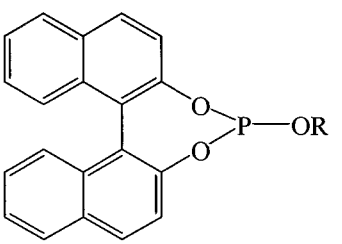
different monodentate ligands, should lead to 190 different heterocomplex catalysts.[129] This certainly is a very powerful combinatorial catalytic approach.

Reetz *et al.*,[146] investigated this new concept with a small library of eight binol-derived phosphites **76** and five phosphonites **77** and the chloride **78** as the monodentate ligands. These ligands were evaluated in the Rh-catalyzed hydrogenation of *N*-acetamido acrylates, which lead to amino acid derivatives. The results obtained revealed, generally that the heterocombinations gave similar results to the homocombinations. When the substrate was changed to the *N*-acyl enamine, to give chiral amines, mixing the ligands gave much better results. For example, with the heterocombinations, an enantioselectivity of 96.1% ee was obtained, whereas the respective homocombinations gave 75.6% ee and 13.2% ee, respectively.[146] Several substrates were screened in the Rh-catalyzed asymmetric hydrogenation,[146] libraries with other monodentate ligands like, phosphines **79**[151] and phosphoramidites **80**,[145,151,152] were screened in other catalytic asymmetric reactions.[152] In general, the improved results obtained, like the increase in ee and reaction rate, were due to the presence of the heterocomplexes.

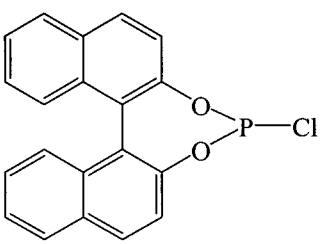
For this reason, the monodentate ligand combination approach is a new concept in asymmetric catalysis and it dramatically broadens the chiral space available for the development of new more efficient chiral catalysts.



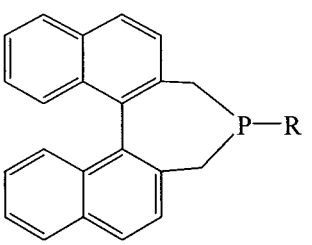
76



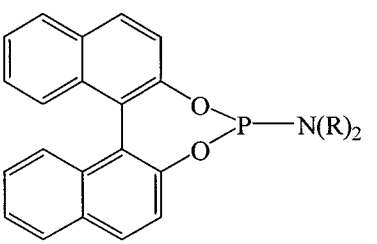
77



78



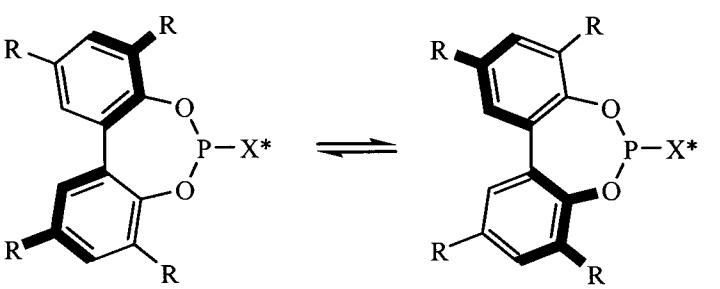
79



80

Gennari *et al.* proposed an interesting extension of the concept of mixing monodentate ligands, by exploiting the dynamic (fluxional) behavior of ligands containing a fluxional axially chiral (tropos) unit and a configurationally stable unit in a Rh-catalyzed olefin hydrogenation (Scheme 17).[153] If two different ligands of this kind are used in a mixture, an intriguing situation arises. When employing a "single" ligand, two diastereomeric homocombinations [ML^aL^a] and [$ML^{a'}L^{a'}$] as well as the heterocombination [$ML^aL^{a'}$] are possible. Consequently, three diastereomers are actually present in the mixture, which are likely to have different catalytic profiles in terms of activity and enantioselectivity (which obviously cannot be measured owing to the rapid interconversion process). In the case of two different ligands of this kind L^a and L^b, up to 10 different species may be formed: [ML^aL^a], [$ML^aL^{a'}$], [$ML^{a'}L^{a'}$], [ML^bL^b], [$ML^bL^{b'}$], [$ML^{b'}L^{b'}$], [ML^aL^b], [$ML^aL^{b'}$], [$ML^{a'}L^b$], and [$ML^{a'}L^{b'}$].[153] The application of this concept in the Rh-catalyzed hydrogenation with the mixture of phosphite and phosphoramidite, gave a best hit of 87% ee compared to 53% ee and 52% ee for the respective homocombinations.[153]

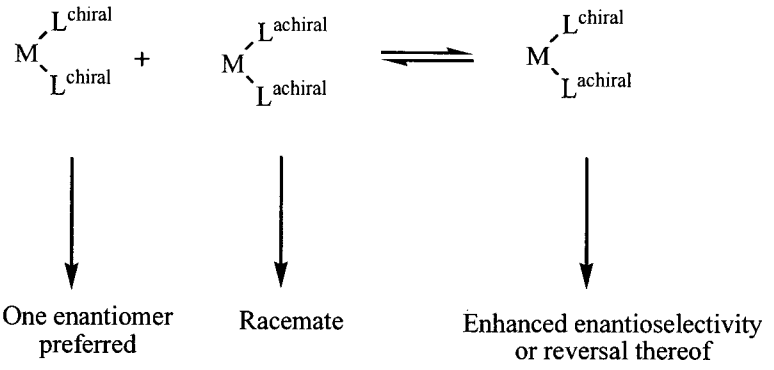
The monodentate ligand combination approach is not only limited to the use of two chiral ligands, but for instance one achiral ligand might replace one of the chiral ligands (e.g. PPh_3) in order to make the process even more efficient (Scheme 18).[154,155]



L^a $L^{a'}$

R = H or *t*-Bu
X* = Chiral alcohol or chiral secondary amine

Scheme 17. Chiral phosphate or phosphoramidite ligands based on a chiral *P*-bound alcohol or secondary amine and a fluxional (tropos) *P*-bound biphenol unit.[153]



Scheme 18. The concept of using mixtures of monodentate chiral and achiral ligands in transition-metal-catalyzed asymmetric reactions.

In this work the objective was to evaluate some monodentate mono(oxazolines) in the Cu-catalyzed asymmetric cyclopropanation of alkenes using the concept of mixing the monodentate ligands, an endeavour that has never previously been explored.

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Chapter 2

Synthesis of Chiral Mono(Oxazolines) and Evaluation in the Catalytic Asymmetric Cyclopropanation Reaction[‡]

Abstract

The objective of the work described in this chapter was to synthesize novel chiral modular monodentate oxazoline ligands, known as Arylid-OX (**1-2**) and Propen-OX (**3**). The goal was to study the behavior of these ligands in the catalytic asymmetric cyclopropanation reaction, to investigate the structure of the resulting copper complexes, and to see if there was more of a preference for formation of heterocomplexes or homocomplexes. The Arylid-OX (**1-2**) and Propen-OX (**3**) ligands were prepared in good overall yields. These ligands were screened in bench-mark Cu(I) catalyzed cyclopropanations of styrene and α-methylstyrene with ethyldiazoacetate. Surprisingly an ee as high as 58% for styrene and 74% for α-methylstyrene were obtained. The heterocomplexes were probably the most stable and active in the catalytic reaction, this was supported by NMR, kinetic and computational studies.

1. Introduction

Over the last number of years chiral monodentate ligands have proven their potential in a number of transition-metal-catalyzed asymmetric transformations. Although there is enormous application of bi-dentate chiral ligands in catalytic asymmetric synthesis, monodentate versions have rarely had the same impact, for the main reason that they fail to form compact catalytic manifolds which are pivotal for

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high asymmetric induction during the reaction. Monodentate ligands offer the advantage that they are in general less structurally complex than di- and multi-dentate ligands, thus the synthesis in principle is less demanding. Binol-based modular mono-phosphonites,[1] mono-phosphites[2] and mono-phosphoramidites[3] are the principle monodentate ligand to have been investigated, often leading to medium or high enantioselectivities when used with metals, like Rh or Cu, in diverse asymmetric catalytic reactions. In fact, some monodentate ligands give very good results, for instance, Feringa used chiral phosphoramidite ligands for copper-catalyzed dialkylzinc additions and ees of up to 98% could be obtained.[4] Also, Luan *et al.* studied a series of monodentate *N*-heterocyclic carbene (NHC) ligands in the asymmetric α-arylation of amides and obtained enantioselectivities of up to 98% ee.[5]

Oxazoline ligands are stable to hydrolysis and oxidative conditions, a considerable advantage when compared to phosphine ligands, which are converted into phosphine oxides under oxidative conditions.[6] For instance, monodentade oxazolines were applied in catalytic asymmetric cyclopropanations,[7] in catalytic enantioselective [2+2+2] cycloadditions with Ni[8] and in enantioselective Diels-Alder reactions.[9,10] All of these reactions showed moderate stereoselectivity. Recently, Glorius and co-workers introduced a new family of modular oxazolines, which are Olefin-Oxazolines (OlefOX), that were tested in conjugate additions of phenylboronic acid to cyclohexenone catalyzed by rhodium, giving very good enantioselectivities. However, despite their appearance these ligands can be considered as bidentate ligands as they coordinate to the Rh by both the N and the C-C double bond.[11]

Monodentate ligands allow a large diversity of chiral catalysts to be used, and are very amenable for catalytic combinatorial enantioselective synthesis using a mixture of chiral monodentate ligands, (see Chapter 1-section 7). The first combinatorial homogeneous asymmetric catalysis using the concept of mixing chiral monodentate ligands was reported simultaneously by Reetz[12] and Feringa.[13] Using this concept in some catalytic asymmetric hydrogenations[12,13b,14] and in conjugated additions with arylboronic acids[13a] it was possible to enhance the enantioselectivities and the reaction rate by simply mixing two known monodentate ligands, the heterocomplex formed was assumed to be the active catalyst.

The ligands studied in this project are divided into two new families of monodentate oxazolines, designated by Arylid-OX (**1, 2**) and Propen-OX (**3**), (Figure 1). The Arylid-OX family was inspired by the well known Arylid-BOX **4**[15,16] and

Isbut-BOX **5**[17] developed by our research group. The Arylid-BOX family will be considered in Chapter 3. The Arylid-OXs **1** have a double bond between the oxazoline ring and the 2,4-dimethoxyphenyl group. The novel Arylid-OX **2** has a phenyl ring instead of the 2,4-dimethoxyphenyl ring. In the case of the Propen-OX, family **3**, the oxazoline ring is attached to the prop-2-enyl chain and thus designated by Propen-OX. These ligands were tested in the catalytic asymmetric cyclopropanation of alkenes with ethyl diazoacetate (EDA) using $[Cu(MeCN)_4]PF_6$ and Cu(I)OTf as the pre-catalysts.

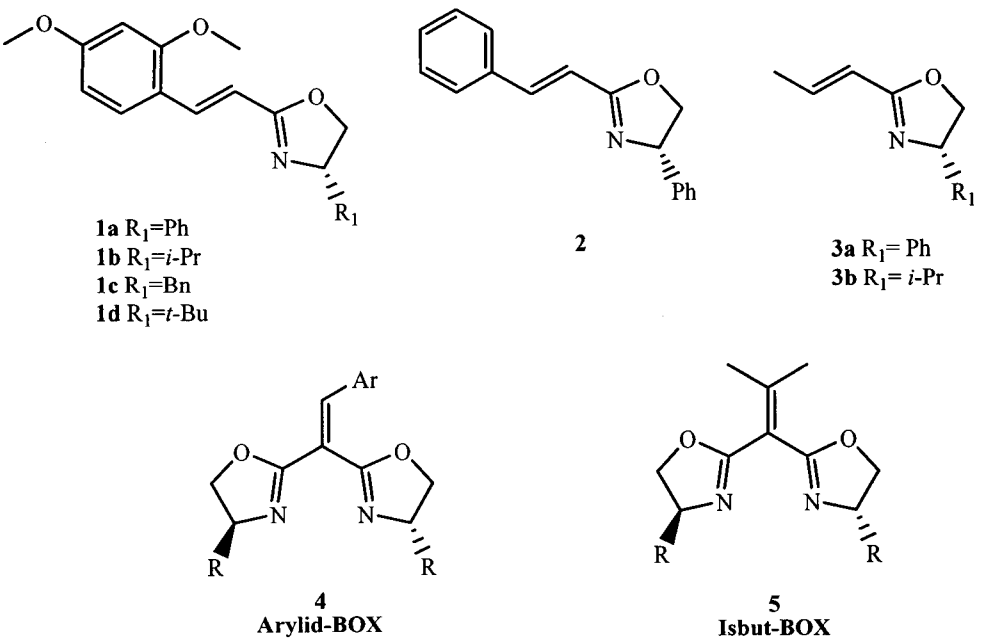


Figure 1. Mono(oxazoline) and bis(oxazoline) ligand families.

2. Results and Discussion

2.1 Synthesis and Characterization of Arylid-OX (1, 2) and Propen-OX (3)

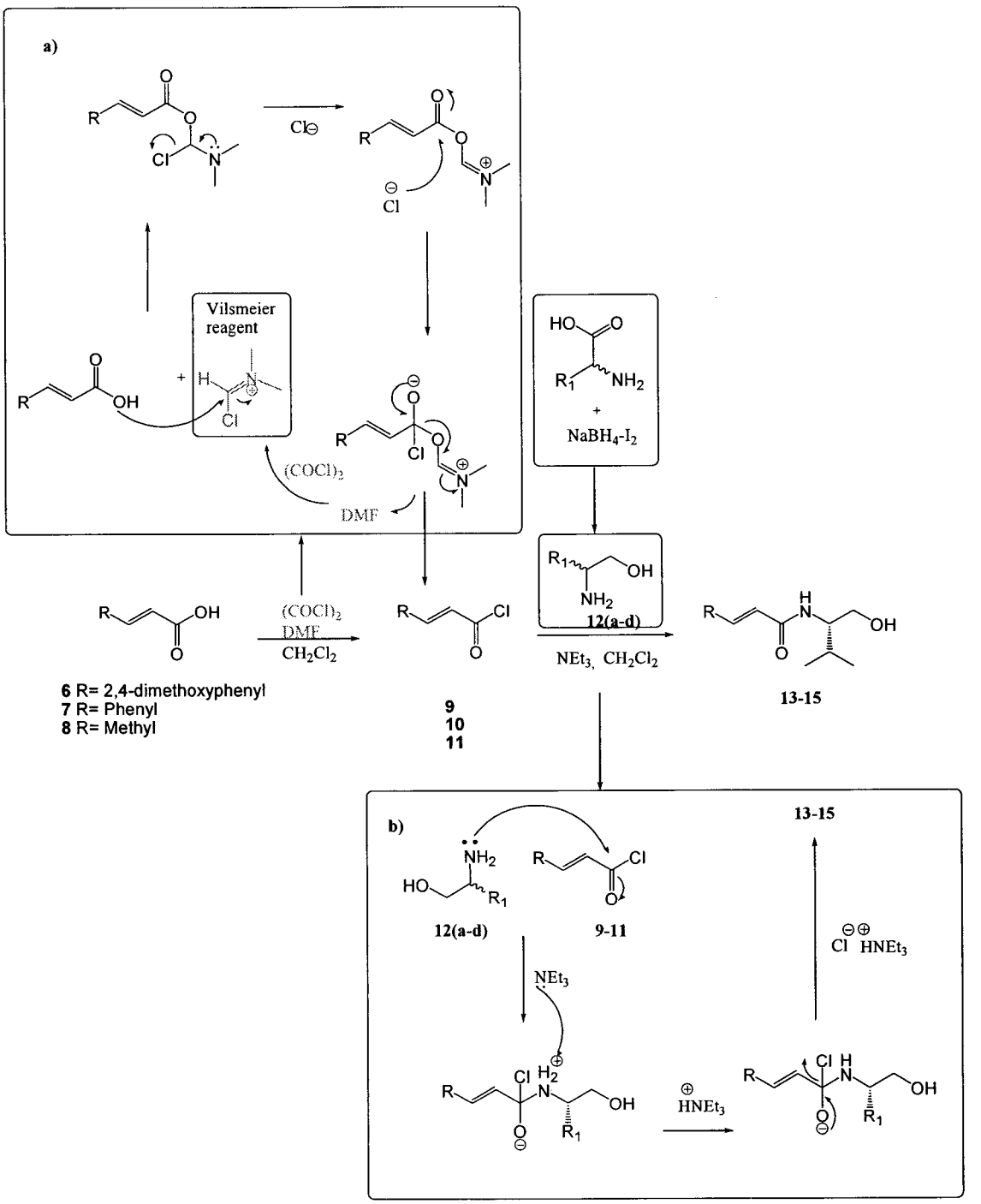
2.1.1 Synthesis of Arylid-OX (1, 2) and Propen-OX (3):

The Arylid-OX (**1** and **2**) and Propen-OX (**3**) ligand families were prepared in good yields using our established method for the synthesis of Isbut-BOX **5**[17] and Arylid-BOX **4**[15,16] ligands (Figure 1).

The cinnamic acid **6** and the four α-amino alcohols (**12a-c**) were synthesized according to the literature methods. **6** was obtained via the procedure reported by Neustadt *et al.*[18] using a simple Knoevenagel condensation with malonic acid and 2,4-dimethoxybenzaldehyde. The α-amino alcohols ((*S*)-phenylglycinol (**12a**), (*S*)-valinol (**12b**), (*S*)-phenylalaninol (**12c**) and (*S*)-*tert*-leucinol (**12d**)) were obtained using the procedure of McKennon *et al*[19] which consists in the reduction of the natural α-amino acids (*L*-valina, *L*-phenylanine, *L*-phenylglycine, *L*-*tert*-leucine) with $NaBH_4$-I_2 complex.

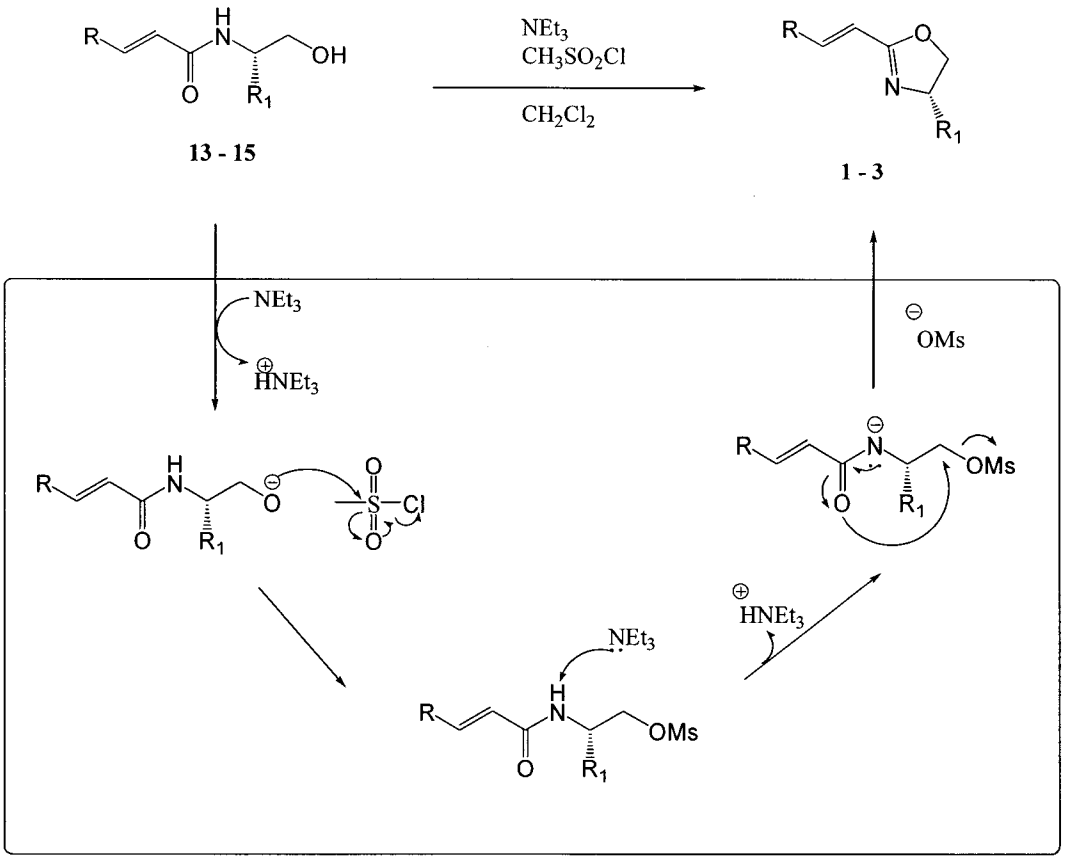
The synthesis of the modular oxazolines **1 - 3** consists of two important steps: formation of the hydroxyamide (**13 - 15**) and cyclization to afford the oxazoline.

In the synthesis of the hydroxyamides **13 - 15** the carboxylic acids **6 - 8** are transformed into the acid chlorides **9 - 11** using the Vilsmeier reagent, generated *in situ* from oxalyl chloride and DMF (Scheme 1, **a)**).[20] The resultant acid chloride was coupled without any purification with the α-amino alcohol in the presence of NEt_3, forming the hydroxyamides in good yields; the mechanism is depicted in the Scheme 1 **b)**. The second step is the cyclization of the hydroxyamide to give the oxazoline, this was conducted in a one-pot manner using an excess of base and mesyl chloride (Scheme 2).[20]



13 (R=2,4-dimethoxyphenyl)	Yield (%)	14 (R=Ar)	Yield (%)	15 (R=Me)	Yield (%)
a R_1=Ph	81	R_1=Ph	52	**a** R_1= Ph	78
b R_1=*i*-Pr	81			**b** R_1= *i*-Pr	33
c R_1=Bn	47				
d R_1=*t*-Bu	61				

Scheme 1. Synthesis of hydroxyamides **13 - 15**.



1 (R=2,4-dimethoxyphenyl)	Yield (%)	2 (R= Ar)	Yield (%)	3 (R= Me)	Yield (%)
a R_1=Ph	98	R_1=Ph	76	**a** R_1= Ph	72
b R_1=*i*-Pr	70			**b** R_1= *i*-Pr	62
c R_1=Bn	90				
d R_1=*t*-Bu	55				

Scheme 2. Synthesis of Arylid-OX **1 - 2** and Propen-OX **3**.

2.1.2 Characterization of Arylid-OX (1, 2) and Propen-OX (3):

All compounds were characterized by various analytic techniques such as FTIR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. These techniques confirmed the structures of the novel mono(oxazolines) synthesized in this project.

FTIR spectroscopy was performed using KBr pellets scanned at the full wave length range from 4000 – 400 cm^{-1}. The absorption bands were assigned on the basis of our earlier publications.[15-17]

The hydroxyamides **13a-d**, **14** and **15a-b** showed as the most conspicuous feature, a strong and sharp band around 1626 cm^{-1} this was probably due to C=O stretching, along with a medium/strong band in the region 1550 cm^{-1}, which resulted

from the interaction of the N-H bending and C-N stretching of the C-N-H group. A weaker band near 1238 cm^{-1} probably also resulted from the interaction between N-H bending and C-N stretching. The *trans*-alkene configuration was confirmed by the presence of a medium band above 2950 cm^{-1} due C-H stretching and, a weak band near 1640 cm^{-1} due to bond stretching vibrations in conjugated systems (C=C), and a strong band near 980 cm^{-1} (C-H).[21]

In the case of the ^1H NMR spectra of compounds **13a-d**, **14** and **15a-b** (Figure 2), the H^1 and H^2 protons give well defined doublets with a respective coupling constant of 16 Hz, which indicated the *trans*-configuration. The hydroxyamide proton of (N-H) was well defined as a broad doublet with J=7 Hz. Generally, all the hydroxyamides have these characteristic signals. The H^4 and $H^{4'}$ protons are diastereotopic protons, and consequently have different chemical shifts with the same multiplicity (dd or m) and respective coupling constant. The ^{13}C NMR spectra showed the presence of the C=O group with a chemical a shift of around 166 ppm which is common in all these compounds.

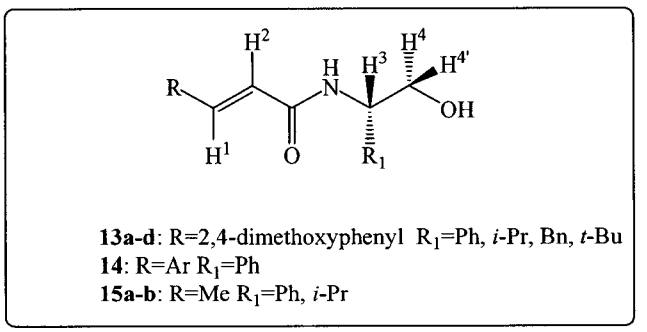


Figure 2. Representative structure of hydroxyamides **13 - 15**.

In the case of the mono(oxazoline), compounds **1a-d, 2, 3a-b** (Figure 3), FTIR spectroscopy was conducted using NaCl disks as the compounds were non-solid, and in the case of oily compounds, NaCl cells with $CHCl_3$ or CH_2Cl_2 as solvent were used. A medium intensity band appeared between 1710-1730 cm^{-1} which was characteristic of the C=N group of the oxazoline ring. To confirm the presence of a C=C bond, there appeared, a weak band near 1640 cm^{-1}. In the ^1H NMR spectra of Arylid-OXs (**1** and **2**) the presence of two doublets in the low field region with coupling constants of 16 Hz, confirmed the *trans*-alkene configuration. In the case of the Propen-OX ligand the H^1 proton appeared as a double quadruplet with J= 14 and 7 Hz, respectively, this was

clearly due to coupling with the methyl protons. H^2 was defined by a doublet with a similar coupling constant to H^1.

In the case of the oxazoline ring the H^4 and $H^{4'}$ are diastereotopic protons (H^4 and $H^{4'}$), having different chemical shifts but with the same multiplicity (dd or m) and with the same constant coupling. In the ^{13}C NMR spectrum the C=N carbon gives a signal of 162 ppm, and the carbons of the double bond appear in the region 120-140 ppm.

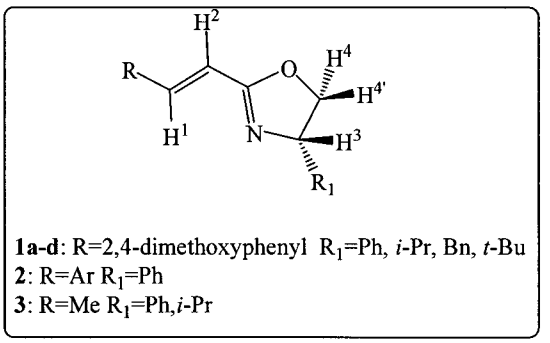
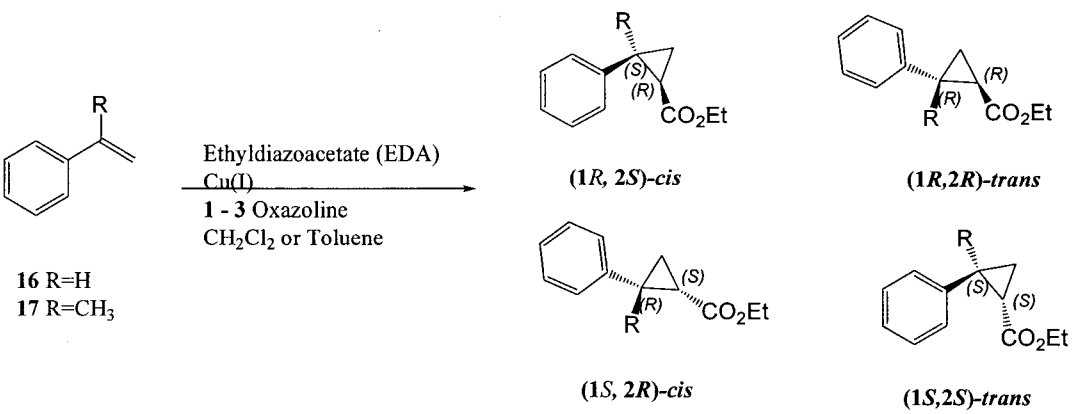


Figure 3. Representative structure of mono(oxazolines) **1 - 3**.

2.2. Evaluation of Arylid-OX (1, 2) and Propen-OX (3) in Catalytic Asymmetric Cyclopropanations

The novel monodentate mono(oxazolines) were evaluated in Cu(I)-catalyzed asymmetric cyclopropanation of styrene and α-methylstyrene using ethyldiazoacetate (EDA) (Scheme 3).



Scheme 3. Cu(I) catalyzed asymmetric cyclopropanation of alkenes — the benchmark reaction for this study.

The CACP consists in the decomposition of the α-diazo esters using a Cu(I) catalyst (see Chapter 1). The catalyst was generated *in situ* by the addition of the pre-catalyst, $[Cu(MeCN)_4]PF_6$ or Cu(I)OTf, and the chiral mono(oxazoline) **1** - **3** in catalytic quantities, followed by the addition of an alkene in excess, and the slow addition of EDA. The alkene was used in excess in order to avoid dimerization. The method here had been previously established and optimized by our research group in the case of the bisoxazolines **4** - **5**.[15-17] The reactions were conducted in both CH_2Cl_2 and toluene to determine the influence of both polar and apolar solvents, as well as to check for π–π interactions, which are sometimes important to increase the reaction stereoselectivities.[22] For this reason we focused on three types of Arylid-OX or Alkylid-OX ligands, namely, **1**, **2** and **3** (Scheme 2). The Arylid-OX ligands **1** contained a very electron-rich π-system. In fact, computational studies *(vide infra)* show that the aryl group is co-planar with the C=C. It was hoped that this extensive π-electron delocalization would promote significant π-π interactions, leading to more compact Cu-catalysts that would promote better asymmetric induction. To test this hypotheis, two more ligand families were prepared, type **2**, with only a phenyl group in the back-bone, and thus expected to show less intense π-π interactions, and type **3**, bereft of an aryl-backbone group. The reactions with toluene required heating for activation, but, unfortunately as the results showed, heating probably destroyed or deactivated the catalyst.

2.2.1 Homocombinations of Ligands

CACP of styrene 16

In terms of enantioselectivity an ee as high as 58% for the *trans*-product could be obtained using the homocombination of Arylid-OX **1d/1d** at a loading level of 6.3 mol%. (Table 1, entry 12) with $[Cu(MeCN)_4]PF_6$ as the pre-catalyst. In all cases, the *trans*-isomer was the predominant isomer. The highest de obtained was 38% (Table 1, entry 12). Generally, **1d/1d** gave better ees than **1a/1a - 1c/1c** and this can be ascribed to the presence of a bulkier substituent. The yields were only moderate and this was due to the formation of significant quantities of maleate/fumarate products, and it proved difficult to control dimerization.

Table 1. Catalytic asymmetric cyclopropanation of styrene **16** using homocombinations of mono(oxazolines) **1** and **3**.[a,e]

Entry	Ligand (mol%)	Pre-catalyst (mol%)	Yield[b] (%)	*cis:trans*[c]	*cis* (ee %) (1*R* 2*S*)[c,d]	*trans* (ee %) (1*R*, 2*R*)[c,d]	Cyclopropanes: dimers[c]
1	**1a/1a** (2.2)	Cu(I)OTf (1)	13[b]	32:68	3	5	89:11
2	**1a/1a** (2.2)	$CuPF_6$ (2)	18[b]	36:64	15	20	84:16
3	**1d/1d** (2.1)	$CuPF_6$ (2)	27[e]	33:67	29	26	91:9
4	**1a/1a** (3.14)	Cu(I)OTf (1)	18[b]	38:62	13	16	75:25
5	**1a/1a** (3.14)	$CuPF_6$ (2)	26[b]	36:64	38	32	92:8
6	**1a/1a** (4.2)	Cu(I)OTf (1)	15[b]	35:65	19	22	78:22
7	**1a/1a** (4.2)	$CuPF_6$ (2)	17[b]	34:66	33	32	86:14
8	**1d/1d** (4.2)	Cu(I)OTf (1)	32[e]	39:61	6	7	72:28
9	**1d/1d** (4.2)	$CuPF_6$ (2)	31[e]	40:60	43	45	82:18
10	**1b/1b** (6.3)	$CuPF_6$ (2)	12[e]	39:61	48	37	97:3
11	**1c/1c** (6.3)	$CuPF_6$ (2)	10[e]	37:63	32	25	10:90
12	**1d/1d** (6.3)	$CuPF_6$ (2)	34[e]	31:69	51	58	86:14
13	**3a/3a** (6.3)	$CuPF_6$ (2)	10[e]	34:66	46	32	78:22
14	**3b/3b** (6.3)	$CuPF_6$ (2)	17[e]	44:56	42	33	84:16

[a]Styrene (4 eq), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1eq), CH_2Cl_2, rt, 24h.

[b]Determined by gas chromatography using di-n-buthylether as the internal standard.

[c]Determined by chiral GC.

[d]The major isomer is indicated in parenthesis.

[e]Yield determined from the mass of isolated crude product isomers.

In order to find the optimized conditions, different ratios of ligand to Cu(I) were investigated. In the case of **1a/1a** using Cu(I)OTf (entries 1, 4 and 6) an increase in the ee was observed when the proportion of ligand was increased. The same was true for the other pre-catalyst, $[Cu(MeCN)_4]PF_6$, (entries 2, 5 and 7). The diastereoselectivities remained generally the same. In the case of **1d/1d** with $[Cu(MeCN)_4]PF_6$ (entries 3, 9 and 12) the ee increased on increasing the quantity of ligand. The best ees were obtained using a 6.3:2 ratio (mol%) of mono(oxazoline):Cu(I). In this case the quantity of free Cu(I) was reduced this was undoubtly due to the formation of a greater quantity of dicoordinated complex. In the case of **1b/1d** the best ee obtained was 48% for the *cis*-cyclopropane with 6.3 mol% of ligand. On comparing the homocombinations **3a/3a** and **3b/3b**, it was **3a/3a** that gave the best ee (46% for the *cis*-cyclopropane), and the best de, but the yield was inferior due to an increase in the dimerization side-reaction giving maleate/fumarate products (entry 13).

In some cases, the *cis*-cyclopropane had higher ees than the *trans*-cyclopropane (the predominant isomer).

Some years ago Dakovic *et al.*[7] tested some mono(oxazolines)-Cu(I) complexes in the CACP of styrene, the best ee obtained was 38% for the *trans*-cyclopropane product. These authors concluded that π–π interactions were important to stabilize the

derived Cu(I) complex. In fact, our Arylid-OX ligands were designed on the basis that π–π interactions would stabilize the resulting metal complexes making them more compact and more likely to give higher enantioselectivities and yields, like was explained previously.

The Arylid-OX ligands **1a-d**, by the way, gave similar or better ees than the mono(oxazolines) studied by Dakovic *et al.*[7]

CACP of α-methylstyrene 17

For the CACP using α-methylstyrene **17**, with all homocombinations of the mono(oxazoline) ligands were tested in the same proportion ((6.3:2) ligand:Cu(I)PF_6) (Table 2). Generally they gave very good conversions. Curiously, the *trans*-cyclopropane (the predominant isomer) gave the best ees. The best ee obtained was 74% with only 1.13 mol% of homocombination **1d/1d** (Table 2, entry 4), this was undoubtly due to the presence of a bulky *tert*-butyl group. In the case of **3a/3a** and **3b/3b**, the difference in the ees obtained was small, ligand **3b** gave the best ee for the *trans*-cyclopropane product, but the de was the same, and the conversion for the products was slightly higher. Toluene was used with homocombination **3a/3a**, but the ees for both isomers decreased approximately by half, this was probably due to the higher temperature used in the reaction, that probably led to (i) reduced asymmetric induction and/or (ii) catalyst decomposition.

Table 2. Catalytic asymmetric cyclopropanation of α-methylstyrene **17** using homocombinations of mono(oxazolines) **1-3**.[a]

Entry	Oxazoline (mol%)	$CuPF_6$ (mol%)	Conversion (%)[c]	ee *cis* (%)[c]	ee *trans* (%)[c]	*cis:trans*[c]	Dimers: cyclopropanes[c]
1	**1a/1a** (6.3)	2	100	34	44	46:54	4:96
2	**1b/1b** (6.3)	2	94	22	42	45:55	2:98
3	**1c/1c** (6.3)	2	86	41	63	42:58	21:79
4	**1d/1d** (1.13)	0.36[b]	100	42	74	43:57	9:91
5	**2/2** (6.3)	2	98	27	37	47:53	9:91
6	**3a/3a** (6.3)	2	92	35	39	47:53	12:88
7	**3a/3a** (6.3)	2[d]	98	12	24	46:54	12:88
8	**3b/3b** (6.3)	2	98	32	44	50:50	10:90

[a] α-Methylstyrene (4 eq), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1eq), CH_2Cl_2, rt, 24h.

[b] α–Methylstyrene (0.7eq), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1eq), CH_2Cl_2, rt, 24h.

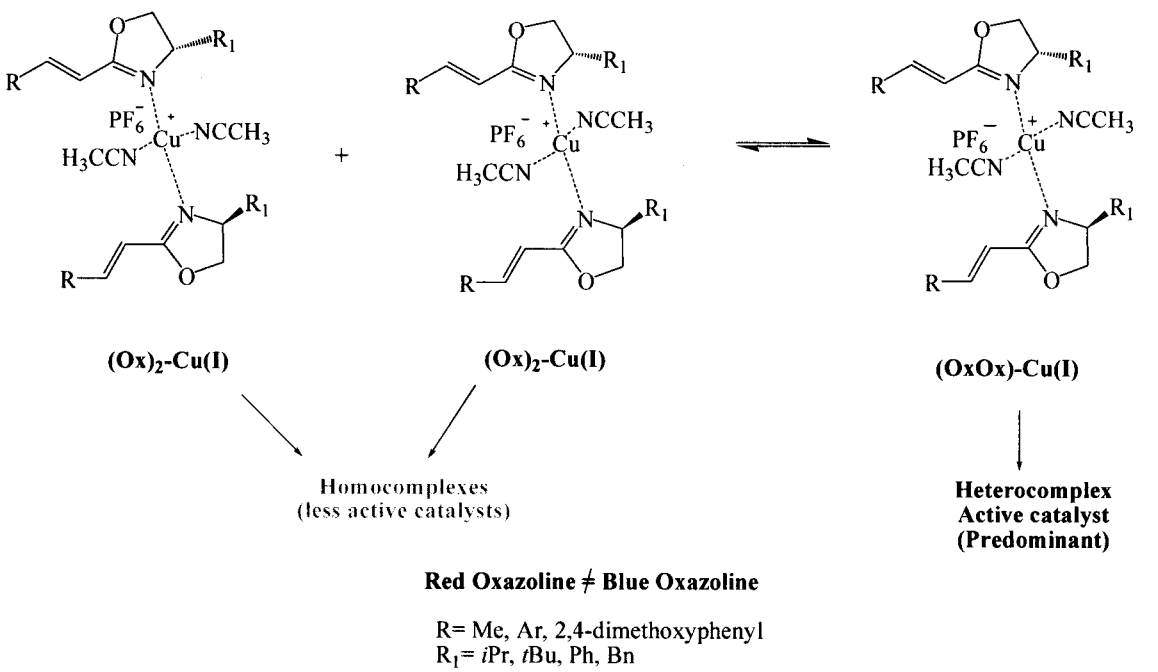
[c] Determined by chiral GC.

[d] Toluene, T=40°C, t=48h.

Analysis of the results shown in either Table 1 or 2, in fact show no direct correlation between the structure of the ligand and the enantioselectivity, diastereoselectivity or yield. There was no family that could be singled out to give the highest enantioselectivity. For example, the combination of **3b/3b** (Table 1, entry 14) gave similar ees and des as the **1b/1b** combination (Table 1, entry 10). The same applies to the combination **2/2** (Table 2, entry 5) with **3a/3a** (Table 2, entry 6). Thus it seems that the aromatic π–π interactions that could make the catalyst more compact as was hoped from the beginning, was not very important. Computational studies (*vide infra*) suggested that there should be no π–π interactions.

2.2.2 Heterocombinations of Ligands

Using the concept of mixing monodentate ligands introduced by Reetz[12] and Feringa,[13] our objective was to apply these novel mono(oxazoline) ligands as mixtures in the CACP (Scheme 4).



Scheme 4. The monodentate oxazoline ligand combination approach.

Table 3. Catalytic asymmetric cyclopropanation of styrene **16** using heterocombinations of Arylid-OXs **1**.[a]

Entry	Ligand (mol%)	Pre-catalyst (mol%)	Yield[b] (%)	*cis:trans*[c]	*cis* (ee %) (1*R* 2*S*)[c,d]	*trans* (ee %) (1*R*, 2*R*)[c,d]	Cyclopropanes: dimers[c]
1	**1b/1c** (1.13)	$CuPF_6$ (0.36)	11	30:60	40	32	90:10
2	**1b/1d** (1.13)	$CuPF_6$ (0.36)	37	34:66	37	30	92:8

[a] Styrene (0.7 eq), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1eq), CH_2Cl_2, rt, 24h.

[b] Yield determined from the mass of isolated crude product isomers.

[c]Determined by chiral GC.

[d]The major isomer is indicated in parenthesis.

Two types of **1a-d** ligands were combined in equimolar amounts (3.15 mol% of each ligand), together with 2 mol% of Cu(I) pre-catalyst, with the intention of giving better enantioselectivities in the cyclopropanation reaction than the corresponding homocombinations. In the CACP of styrene only two heterocombination were tested (Table 3, entries 1 and 2). Unfortunately, in both heterocombinations **1b/1c** and **1b/1d**, the ees obtained were not as high as the homocombinations (Section 2.2.1). In the case of the **1b/1c** combination the ees obtained were the average of the ees obtained with both homocombinations of these ligands. Perhaps, it may have been due to the fact that one ligand was actually enhancing the enantioselectivity were as the other was reducing the enantioselectivity. (sort of "push-pull effect") This result indeed supports the belief that the heterocomplex was the most reactive.

In the CACP of α-methylstyrene **17** seven heterocombinations were investigated (Table 4). In the heterocombinations of **1a** with **1b**, **1c**, **2** and **3a**, the best ee obtained was 38% for the *cis*-isomer and 57% for the *trans*-isomer using the **1a/1c** heterocombination.

Table 4. Catalytic asymmetric cyclopropanation of α-methylstyrene **17** using heterocombinations of mono(oxazolines) **1-3**.[a]

Entry	Oxazoline (mol%)	$CuPF_6$ (mol%)	Conversion (%)[c]	ee *cis* (%)[c]	ee *trans* (%)[c]	*cis:trans*[c]	dimers: Cyclopropanes[c]
1	**1a/1b** (6.3)	2	80	24	46	44:56	57:43
2	**1a/1c** (6.3)	2	89	38	57	44:56	26:74
3	**1b/1c** (6.3)	2	90	31	52	44:56	6:94
4	**1a/2** (6.3)	2	87	29	44	44:56	35:65
5	**1a/3a** (6.3)	2	94	38	44	45:55	18:82
6	**2/3a** (6.3)	2	100	37	44	45:55	7:93
7	**3a/3b** (6.3)	2	95	37	43	47:53	16:84

[a] α-Methylstyrene (4 eq), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1eq), CH_2Cl_2, rt, 24h.

[b] α–Methylstyrene (0.7eq), Chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1eq), CH_2Cl_2, rt, 24h.

[c] Determined by chiral GC.

This result is superior to that with **1a/1a**, but inferior to that with **1c/1c**. In the case of the heterocombinations **1a/2** and **1a/3a**, the ees obtained were close to the best ees obtained for the homocombination systems. The same was observed in the other heterocombination **2/3a** and **3a/3b**. These results seemed to indicate an equilibrium between the homo and heterocomplexes in solution.

These results can be compared with some cases in the literature, not all heterocombinations gave significant improvements (superior ees and yields) compared to the respective homocombinations.[12] The NMR spectra of the heterocombination case showed the presence of the three possible catalysts, but the heterocomplex as the predominant catalyst.[12]

2.2.3 Kinetic study

A kinetic study was carried out with the homocombination of ligand **1a** (Figure 4) and the heterocombination of ligands **1b** and **1c** with Cu(I) (Figure 5) for the CACP of α-methylstyrene **17**. Both the homo- and heterocombination systems were analyzed at intervals during a 24 hour period. On comparing the results of these studies it was observed that in the case of the first system the ee remained constant during the reaction (*cis* 30% ee and *trans* 40% ee), but for the second system it reached it's optimum level only after 4 hours (*cis* 30% ee and *trans* 50% ee). This result seems to indicate that in the heterocombination system there was competition between the homocombination of $(\mathbf{1b})_2$-Cu(I) and $(\mathbf{1c})_2$-Cu(I), and the heterocombination of (**1b1c**)-Cu(I). The conversions and selectivities (% of products – % of maleate/fumarate) for the homocombination systems were basically the same increasing during the first 3 hours and remaining constant till the end. The same didn't apply to the heterocombination system as, the conversion increased over the first six hours to a maximum of 72%, then dropped during the next hour and then reaching the maximum conversion of 89% after 22 hours. A similar trend was observed with the selectivity. Over the first 4 hours it increased to 88%, then decreased by 10% during the next 18 hours, and in the last 2 hours increased by 6%. These flucuations can be attributed to an equilibrium/competition between the three complexes in solution. These results do not indicate which of the complexes is the most catalytically active in the case of the heterocombinations.

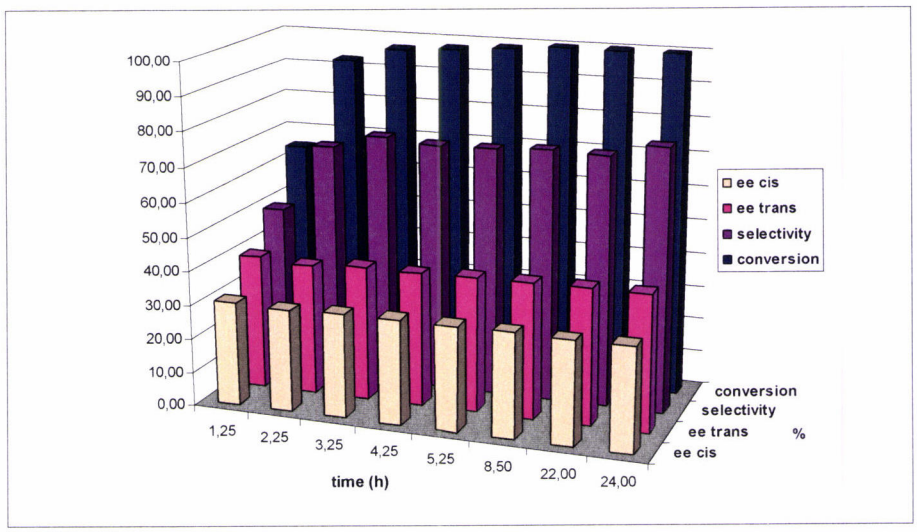


Figure 4. Kinetic study for the catalytic asymmetric cyclopropanation of α-methylstyrene using ligand **1a** with $[Cu(MeCN)_4]PF_6$ (Homocombination).

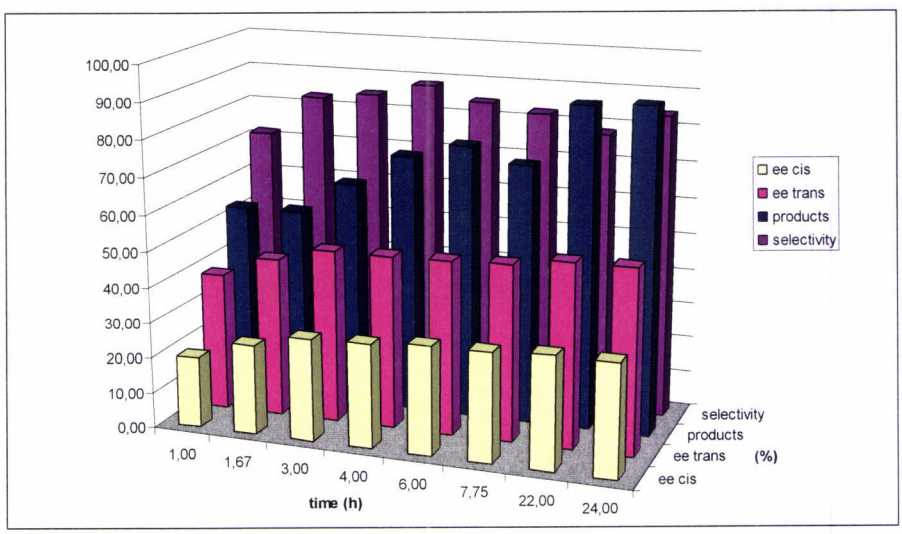


Figure 5. Kinetic study for the catalytic asymmetric cyclopropanation of α-methylstyrene using ligands **1b** and **1c** with $[Cu(MeCN)_4]PF_6$ (Heterocombination).

2.2.4 NMR study

To gain an insight into the structure of the active catalyst involved on using the heterocombination system in this reaction, both ^1H NMR and computational studies were carried out. Three types of complexation were conducted, using ligand **1a** and $[Cu(MeCN)_4]PF_6$, in the following ratios; 1:1, 2:1 and 3:1 ligand (Figure 6). (**1a** was

mixed with the pre-catalyst in CH_2Cl_2 at r.t. for 30 mins, the solvent was removed and the remaining solid dried carefully). In all cases the NMR spectra were clean and it was obvious that complexation had taken place, as the spectra were different from that of the free ligand. The observed chemical shifts for the principal signals are shown in Table 5. In the case of both 1:1 and 2:1 **1a**:pre-catalyst, the difference in the chemical shifts was quite small. The fact that some solid precipitated when a 1:1 mixture of **1a** to pre-catalyst was used indicated formation of a di-Arylid-OX-coordinated complex, ie. Cu(I)-**1a**$_2$(MeCN)$_2$ (Figure 6). In the case of the system which comprised 3:1 **1a**:pre-catalyst, the resolution was poorer than in the previous cases, leading us to believe that an equilibrium was established between the excess free ligand and the di-coordinated complex. There did not seem to be any evidence of the presence of the Cu(I)-**1a**$_3$(MeCN) complex (Figure 6). The ^{1}H NMR studies indicate that the MeCN coordinates with the metal through vacant coordination sites on the metal.

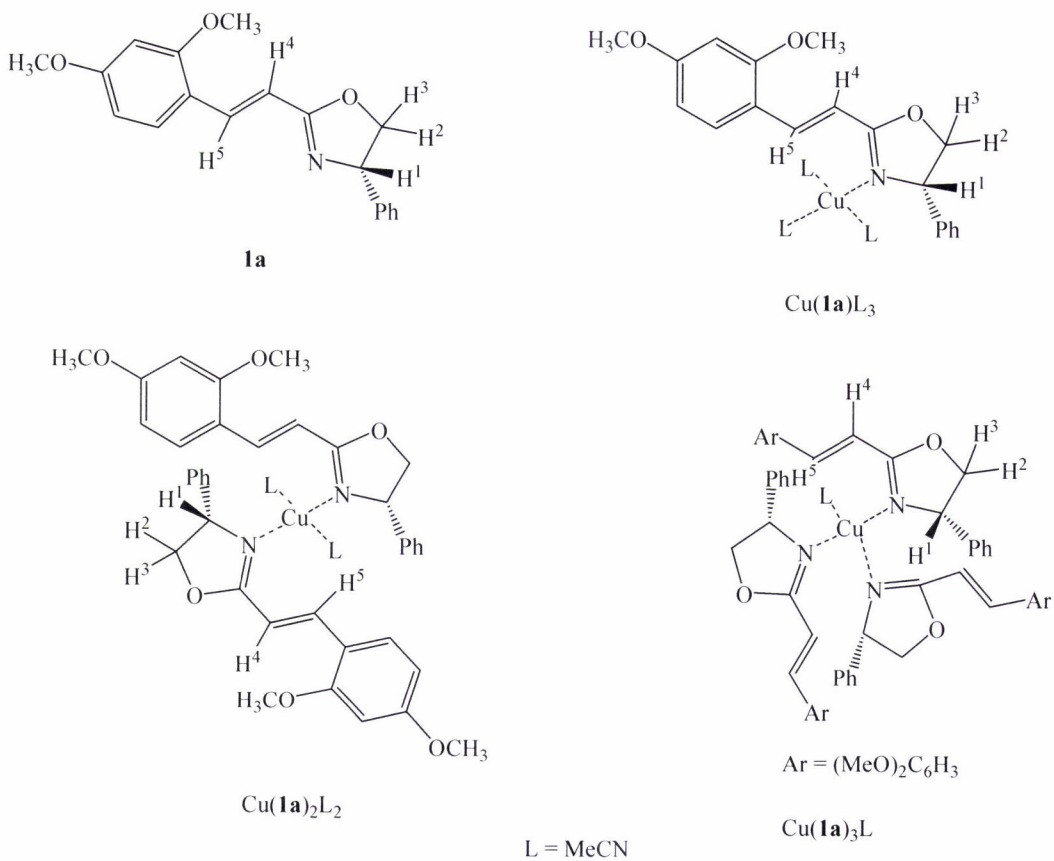


Figure 6. Structures of the possible complexes formed between Cu(I) and **1a**.

Table 5. ^{1}H NMR data for Cu(I) complex formation.

1a:Cu(MeCN)$_4$]PF$_6$	δ_H (ppm)				
	H^1	**H^2**	**H^3**	**H^4**	**H^5**
1:0	5.295	4.179	4.697	6.750	7.676
1:1	5.370	4.950	4.410	6.330	7.875
2:1	5.350	4.927	4.412	6.349	7.858
3:1	5.143	4.777	4.306	6.375	7.807

An NMR study of the homocomplexes (**1b**)$_2$-Cu(I) and (**1c**)$_2$-Cu(I), and of a mixture of **1b**, **1c** and Cu(I) was also carried out (Figure 7). The complexes were prepared in the NMR tube with dry $CDCl_3$ and the ligands were combined in equimolar amounts, together with 1 equiv of the Cu(I) pre-catalyst. The results are shown in the Figure 8. The objective was to confirm if the catalytic active species was **1b1c**-Cu(I) (derived from the heterocombination of ligands **1b** and **1c**) in solution. Although, this complex should exist in equilibrium with the other two possible homocombination catalysts, namely (**1b**)$_2$-Cu(I) and (**1c**)$_2$-Cu(I) (Figure 7) the goal was to try and observe this complex by ^{1}H NMR. Analysis of the ^{1}H NMR data obtained using a (2:1) mono(oxazoline):Cu(I) mixture suggested the presence of the (**1b1c**)-Cu(I) complex, as two well defined doublets for the H^3 protons with similar coupling constants (15 Hz (δ= 6.69 ppm) and 16.8 Hz (δ = 6.57 ppm)) were observed. This proton (H^3) is overlapped in the (**1b**)$_2$-Cu(I) complex with the aromatic peaks. Another indication is the signals for H^1 in the homocomplexes (**1b**)$_2$-Cu(I) and (**1c**)$_2$-Cu(I) appeared at 4.61 and 4.66 ppm, respectively, but these protons in the heterocomplex **1b/1c**-Cu(I) appeared at 4.74 and 4.07 ppm. Coordination of the ligands with Cu is expected to increase the chemical shifts of the H^1 signals due to electron donation from the oxazoline group. The H^1 signals for both ligands in the putative heterocomplex show a greater separation. When the ratio of ligand to Cu(I) was increased to (4:1) under the same conditions as the other experiments. The chemical shifts decreased in the case of the putative H^1, H^2, and H^3 protons in the (**1b/1c**)$_2$-Cu(I) complex, indicating an equilibrium with the free ligand.

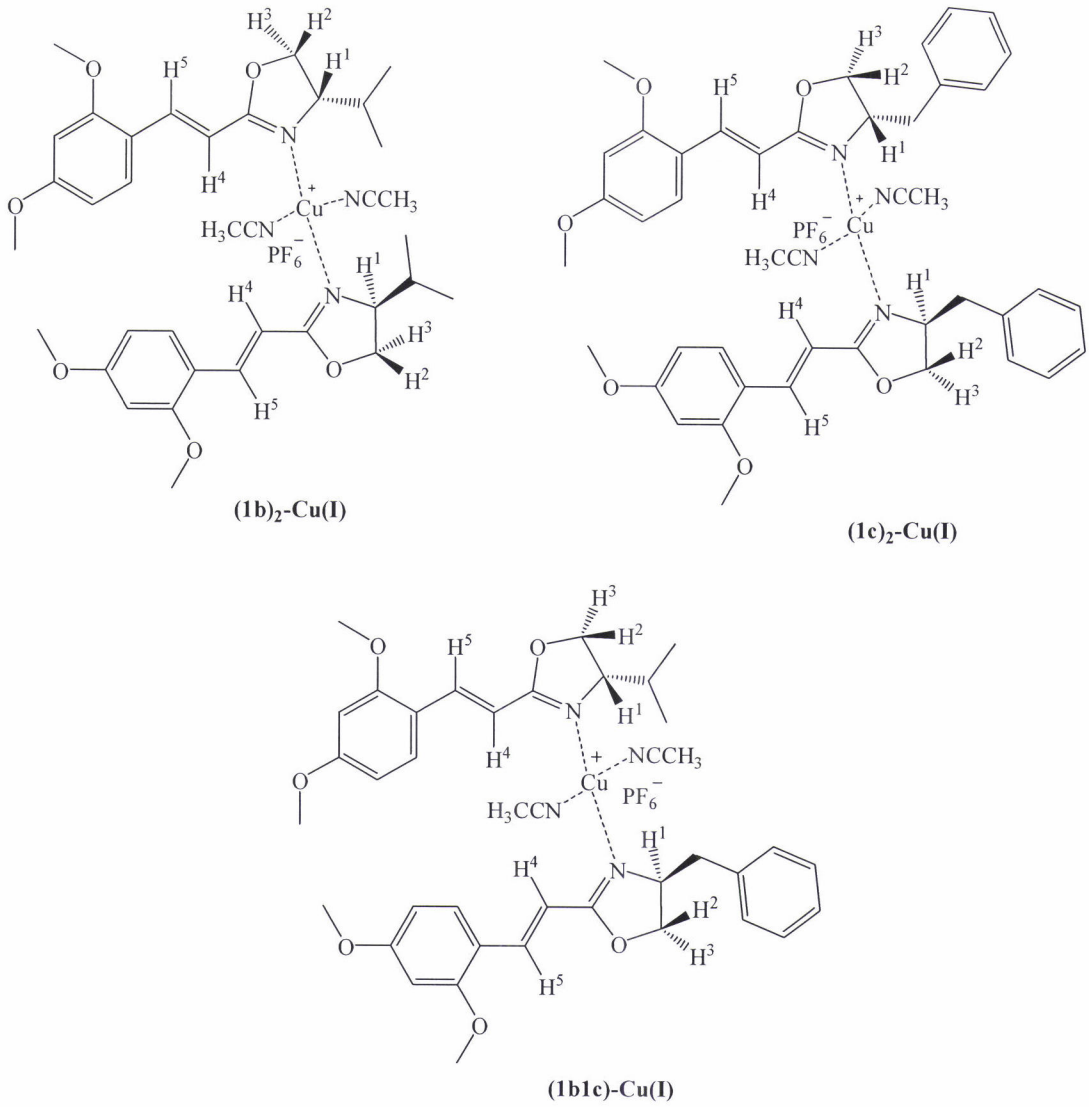
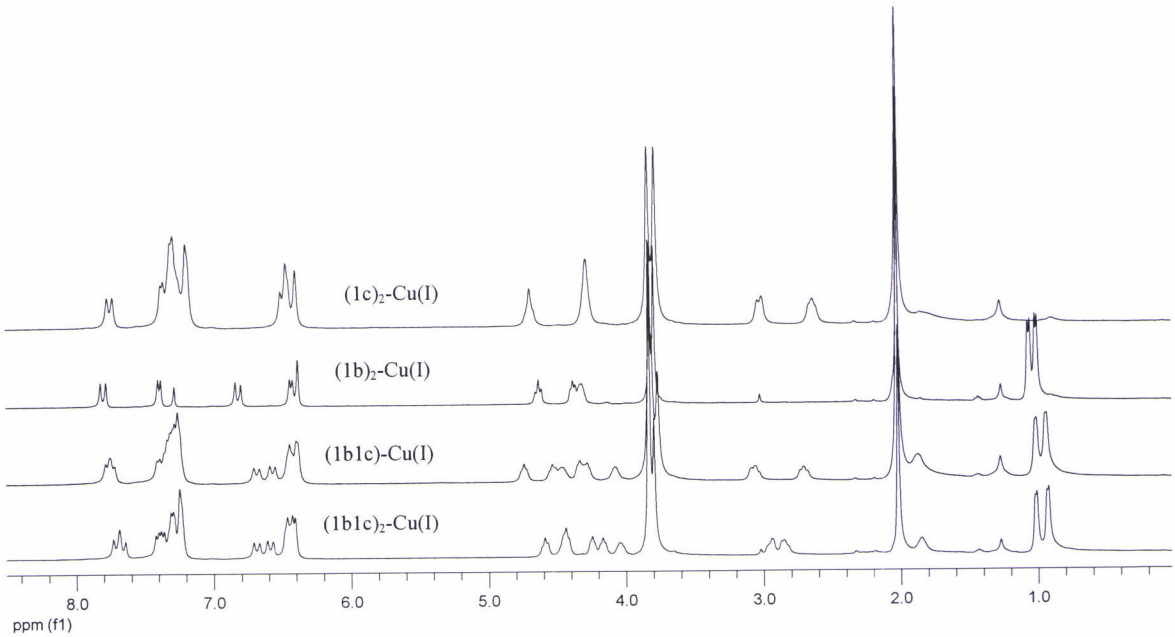


Figure 7. Putative structures for complexes Cu(I)-**1b**$_2$(MeCN)$_2$, Cu(I)-**1c**$_2$(MeCN)$_2$ and Cu(I)-**1b1c**(MeCN)$_2$ analyzed by ^{1}H NMR.

The spectra for the heterocomplex are different to those of the homocomplexes, because the diagnostic signals (H^1, H^2, H^3 and H^4) appeared twice. Low temperature experiments were also conducted (to -25°C) in an effort to try and calculate the equilibrium constant for this process, but they were inconclusive.



These are the diagnostic signals:

Ligand/complex	δ (ppm)						
	H^1		H^2	H^3	H^4		H^5
1b	4.32		4.00	[a]	6.66		7.54
1c	4.51		4.04	4.28	6.66		7.58
Cu(I)-(1b)$_2$	4.61		4.36		6.80		7.78
Cu(I)-(1c)$_2$	4.66		4.25		6.42		7.72
Cu(I)-(1b1c)	4.74	4.07	4.51	4.31	6.69	6.57	7.75
Cu(I)-(1b1c)$_2$	4.60	4.05	4.45	4.22	6.70	6.60	7.70

[a] Not observed, presumably hidden by the phenyl signal.

Figure 8. ^{1}H NMR spectra of homo- and heterocomplexes.

In the case of the heterocomplex (Cu(I)-(**1b1c**)) some comments need to be made regarding the increase in the chemical shift for one of the H^1 signals (to 4.74 ppm), and the decrease in the chemical shift in the case of the other H^1 signal (to 4.07 ppm). This is most probably due to a deshielding or shielding effect. Analysis of the calculated structure for Cu(I)-(**1b1c**) (see: section 2.2.5) showed that the H^1 of **1b** appears to be close to the C=C bond of the other ligand, and probably lying in the deshielding zone of the latter. The distance calculated between H^1 and H^4 (other ligand) was only 2.662Å. In the case of the second H^1, analysis of the same model, seems to indicate that it lies in the shielding zone of one of the nitrile ligands.

2.2.5 Computational study

An important computational study was conducted to substantiate the observations obtained from ^{1}H NMR spectroscopy. The following four complexes were studied: $Cu(MeCN)_4$, Cu(I)-**1a**$(MeCN)_3$, Cu(I)-**1a**$_2(MeCN)_2$ and Cu(I)-**1a**$_3$(MeCN) to determine the relative energies in an attempt to establish the most stable complex and thus the most likely involved in these catalytic reactions. In order to determine the structure of the complex that exists predominally in solution, the energies of formation for each were calculated. Considering the number and size of these systems, coupled with the computational capabilities available at this time, a semi-empirical method proved to be the best choice for geometry optimization. The novel PM6 Hamiltonian[23] included in the recent version of MOPAC 2007[24] was employed in this study, followed by single point calculations at Density Functional Theory (DFT) level.

The geometries were fully optimized in Cartesian coordinates and the stationary points obtained were further characterized by frequency calculations as minima.
Following the initial geometry optimization with the PM6 method, DFT calculations were carried out on all complexes. The DFT calculations were performed using the hybrid Becke exchange functional[25] and the correlation functional B3LYP[26] as contained in the Gamess package.[27] The Lanl2DZ effective core basis set was employed for the metal atom while the 6-31G** basis set was used for all the other atoms.

All the Cu(I)-complexes studied were found to have a tetrahedral structure as illustrated in Figure 9 which is in agreement with what is found experimentally for the majority of Cu(I) complexes.[28,29] The Cu(I)-N bond distances are depicted in Table 4. For the known tetrahedral complex $[Cu(I)(MeCN)_4]ClO_4$, Cu-N distances of 1.99 Å were experimentally observed[30] and are to be compared with the Cu-N distances in the first column of Table 6. The good agreement observed here supports the suitability of the PM6 method to determine the molecular geometries of these complexes. The calculated Cu-N(oxazoline) distances are slightly longer that the calculated Cu-N(MeCN) distances for all the oxazoline containing complexes. The binding energy for each complex was obtained by calculating the difference in energy between the optimized structure for each complex and the sum of the energies of the optimized isolated moieties. Selected energy values calculated with the B3LYP/Lanl2DZ, 6-31G**//PM6 method are depicted in Table 7. This study clearly shows that it is the di-

Table 6. Selected bond lengths (Å) for complexes Cu(I)(MeCN)$_4$, Cu(I)-**1a**(MeCN)$_3$, Cu(I)-**1a**$_2$(MeCN)$_2$ and Cu(I)-**1a**$_3$(MeCN)

	Cu(I)(MeCN)$_4$	Cu(I)-1a(MeCN)$_3$	Cu(I)-1a$_2$(MeCN)$_2$	Cu(I)-1a$_3$(MeCN)
Cu-N$_1$	1.971	2.044*	2.050*	2.024*
Cu-N$_2$	1.971	1.964	2.023*	2.033*
Cu-N$_3$	1.971	1.961	1.955	2.043*
Cu-N$_4$	1.971	1.968	1.969	1.965

* Nitrogen atom belonging to the **1a** moiety.

oxazoline coordinated complex - Cu(I)-**1a**$_2$(MeCN)$_2$ - which has the lowest ΔE value indicating a higher stability for this complex. It is presumably the most active also. This result strongly supports our previous hypothesis based on ^{1}H NMR spectroscopy.

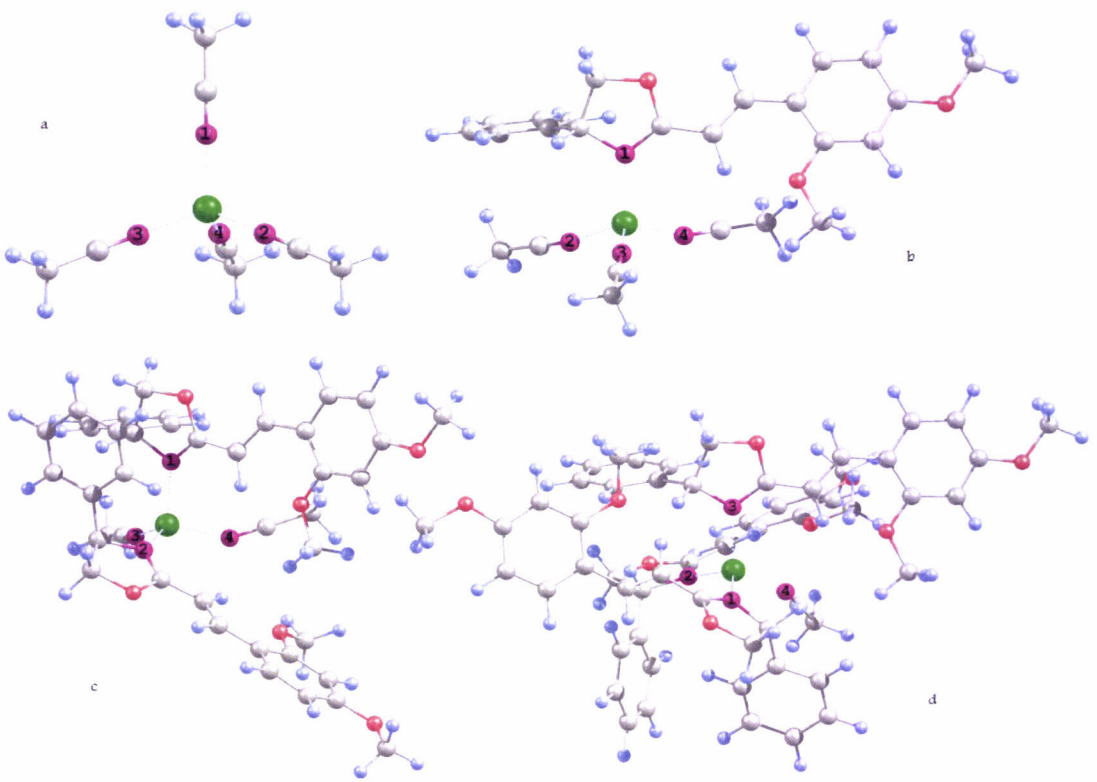


Figure 9. Calculated structures for the Cu(I) complexes a) Cu(I)(MeCN)$_4$, b) Cu(I)-**1a**(MeCN)$_3$, c) Cu(I)-**1a**$_2$(MeCN)$_2$ and d) Cu(I)-**1a**$_3$(MeCN).

Table 7. Calculated energies for complexes Cu(I)(MeCN)$_4$, Cu(I)-**1a**(MeCN)$_3$, Cu(I)-**1a**$_2$(MeCN)$_2$ and Cu(I)-**1a**$_3$(MeCN) at the B3LYP/G-31G*//PM6 level

Chemical Unit	Total Energy (a.u.)	ΔE (kcal/mol)	ΔE_{rel} (kcal/mol)
Cu(I)	-195.7599954	-	-
1a	-1015.2558668	-	-
MeCN	-132.6776021	-	-
Cu(I)(MeCN)$_4$	-726.7069097	-148.410	0.000
Cu(I)-**1a**(MeCN)$_3$	-1609.2982735	-156.629	-8.220
Cu(I)-**1a**$_2$(MeCN)$_2$	-2491.8870626	-163.234	-14.820
Cu(I)-**1a**$_3$(MeCN)	-3374.4607609	-160.368	-11.960

These results and this conclusion is supported by the work of Ricci and co-workers[9] who conducted a theoretical study at the DFT level on the *cis*-oxazoline ((3a*R*,7a*R*)-2-phenyl-7,7a-dihydro-3a*H*-thieno[3',2':4,5]cyclopenta-[1,2-*d*][1,3]oxazole):Cu(I) complex. The calculation showed that the metal is coordinated by only two of the four donor atoms, namely the oxazoline N atoms. The Cu-N bond lengths for the complex were calculated to be 1.885 Å and the relative energy was zero (kcal.mol^{-1}). These results are similar and support the conclusions borne out by the studies described in 2.2.4 and 2.25.

Another important theoretical study was carried out to verify if the heterocomplex is the predominant equilibrium species in solution. The binding energy for each heterocomplex was obtained by calculating the difference in energy between the optimized structure for each complex and the sum of the energies of the optimized isolated moieties (Figure 10). Selected energy values calculated with the B3LYP/Lanl2DZ, 6-31G**//PM6 method are depicted in Table 8. This study shows that it is the heterocomplex - Cu(I)-**1b1c**(MeCN)$_2$ - which has the lowest ΔE value, indicating a higher stability for this complex. These results support the conclusions obtained from both the kinetic and ^{1}H NMR spectroscopy experiments.

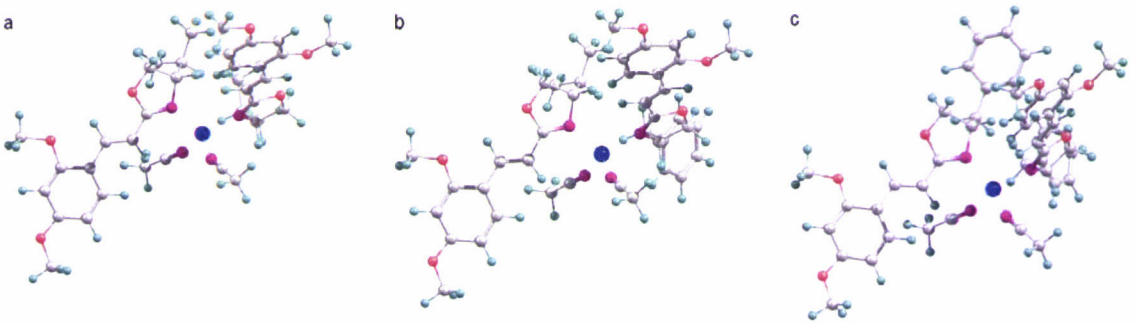


Figure 10. Calculated structures for the Cu(I) complexes: a) Cu(I)-**1b**$_2$(MeCN)$_2$, b) Cu(I)-**1c**$_2$(MeCN)$_2$ and c) Cu(I)-**1b1c**(MeCN)$_2$.

Table 8. Calculated energies for complexes Cu(I)-**1b**$_2$(MeCN)$_2$, Cu(I)-**1c**$_2$(MeCN)$_2$ and Cu(I)-**1b1c**(MeCN)$_2$ at the B3LYP/Lanl2DZ, 6-31G*//PM6 level

Chemical Species	Total Energy (a.u.)	ΔE (kcal/mol)	ΔE_{rel} (kcal/mol)
Cu(I)-(**1b**)$_2$	-2265.7216795	-157.370	0.000
Cu(I)-(**1b1c**)	-2418.0626597	-161.709	-4.339
Cu(I)-(**1c**)$_2$	-2570.3924010	-158.996	-1.626
1b	-902.1820275	-	-
1c	-1054.5160923	-	-
MeCN	-132.6734221	-	-
Cu(I)	-195.7599954	-	-

4. Conclusion

The two mono(oxazoline) families, Arylid-OX **1** - **2** and Propen-OX **3**, demonstrated significant application for catalytic asymmetric cyclopropanation of alkenes.

These ligands have much potential and applicability for use as heterocomplexes. In fact, the combination of kinetics, NMR spectroscopy and computational studies revealed the probable predominant presence of the heterocomplex in solution.

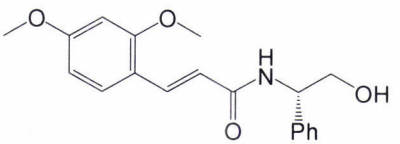
5. Experimental Section

General Remarks

trans-2,4-Dimethoxycinnamic acid **6** was obtained using the literature method.[9] All reagents were obtained from Aldrich, Fluka, Alfa Aesar or Acros. Solvents were dried using common laboratory methods.[31] Column chromatography was carried out on silica gel (sds, 70-200 μm) and flash column chromatography (Merck, 40-63 μm and sds, 40-63 μm). TLC was carried out on aluminium backed Kisel-gel 60 F254 plates (Merck). TLC plates were visualised either by UV light or phosphomolybdic acid in ethanol. Gas chromatographic (GC) analyses of the products were performed on a Hewlett Packard (HP) 6890 series instrument equipped with a flame ionization detector (FID). The chromatograph was fitted with a cyclosil-B capillary column (30 m, 250 μm, 0.25 μm) (Agilent 112-2532). The melting point was recorded on a Barnstead Electothermal 9100 apparatus and was uncorrected. The ^{1}H NMR spectra were recorded on either a Bruker AMX300 (^{1}H: 300.13 MHz and ^{13}C: 75 MHz) instrument or a Bruker Avance instrument (^{1}H: 400 MHz and ^{13}C: 100 MHz) using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on a VG Autospec M(Waters-Micromass) spectrometer using the FAB technique and Waters-Micromass GC-TOF and MicroTOF Focus (Bruker Daltonics) using the TOF technique electron spray ionization (ESI) mass spectra were performed on a Brucker Daltonics Apex-Qe instrument at 300.0. Infra-red spectra were measured with a Perkin Elmer Paragon 1000 model. Specific rotations were measured on a Perkin-Elmer 241 polarimeter.

Synthesis of Arylid-OX 1:

(+)-(*S*)-*trans*-*N*-(2-hydroxy-1-phenylethyl)-2,4-dimethoxycinnamamide 13a:



13a

dimethylformamide (0.08 mL, 1.03 mmol) and CH_2Cl_2 (20 mL). The solution was cooled to 0°C, and oxalyl chloride (1.73 mL, 1.98 mmol) was added drop-wise over a 30 min period and the solution was stirred at room temperature until the evolution of gas ended. The solvent was evaporated in *vacuo* to give *trans*-2,4-dimethoxycinnamoyl chloride **9** as a dark green solid (due to the unstable nature of this compound it was stored in the freezer at –10°C). Yield: 2.17 g (100%). A two necked round bottom flask (50 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (1.25 g, 9.12 mmol) and dry CH_2Cl_2 (20 mL) and the solution was cooled to 0°C using an ice bath. Dry triethylamine (1.27 mL, 9.12 mmol) was added via syringe. A solution of *trans*-3-(2,4-dimethoxyphenyl)cinnamoyl chloride **9** (1.06 g, 4.68 mmol) in CH_2Cl_2 (5 mL) was slowly added via syringe to the vigorously stirred reaction mixture over 30 mins. The ice bath was removed, and the reaction mixture was stirred at room temperature for a further 4 h. The reaction mixture was washed with 2M HCl (12 mL), saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with brine (15 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give (*S*)-*trans*-*N*-(2-hydroxy-1-phenylethyl)-2,4-dimethoxycinnamamide **13a** as an orange solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford *title compound* **13a** as a white solid (1.23 g, 81%); **mp** 152.2 – 153.3°C;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.8 (d, 1H *J*=15.7 Hz, RC*H*=CRH), 7.35 – 7.25 (m, 6H, C*H*(Ar), 6.54 – 6.41 (m, 4H, N*H*, RCH=C*H*R, C*H*(Ar)), 5.18 – 5.14 (m, 1H, C*H*), 3.95 – 3.82 (m, 2H, CH_2), 3.80 (s, 3H, -OCH_3), 3.79 (s, 3H, -OCH_3) ppm.

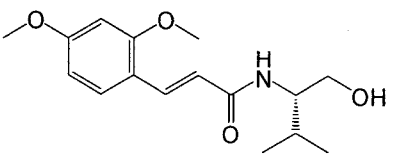
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.67, 162.20, 159.75, 139.16, 137.37, 130.78, 128.82, 127.78, 126.81, 118.44, 116.74, 105.03, 92.42, 66.80, 56.41, 55.38, 55.35 ppm.

IR (KBr) υ_{max}: 3291, 3064, 3031, 2960, 2939, 2873, 2839, 1652, 1616, 1575, 1544, 1502, 1455, 1420, 1351, 1318, 1290, 1212, 1161, 1118, 1037, 975, 836, 798, 751, 698, 523 cm^{-1}.

$[\alpha]^{22}_D$ = +13.69 (*c* = 1.22, $CHCl_3$).

FAB-MS *m/z*: 328.16 $[M+H]^+$.

(-)-(*S*)-*trans*-*N*-(1-hydroxy-3-methylbutan-2-yl)-2,4-dimethoxycinnamamide 13b:



13b

The same procedure as described previously was used in the reaction of *trans*-2,4-dimethoxycinnamoyl chloride **9** (1.0 g, 4.41 mmol) with *(S)*-valinol (0.796 g, 7.72 mmol) and dry triethylamine (1.08 mL, 7.72 mmol) to give (*S*)-*trans*-*N*-(1-hydroxy-3-methylbutan-2-yl)-2,4-dimethoxycinnamamide **13b** as an yellow solid. The crude product was purified by recrystallization (EtOAc/Hexane) to afford the *title compound* **13b** as a white solid. Yield: 0.492 g (81%); **mp** 140.4 – 141.8 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, 1H *J*=15.6 Hz, RC*H*=CRH), 7.39 (d, 1H *J*=8.4 Hz, C*H*(Ar)), 6.52 – 6.45 (m, 3H, RCH=C*H*R, C*H*(Ar)), 5.81 (d, 1H *J*=8.1 Hz, N*H*), 3.86 – 3.83 (m, 1H, C*H*), 3.86 (s, 3H, -OCH_3), 3.83 (s, 3H, -OCH_3), 3.77 – 3.69 (m, 2H, CH_2), 1.99 – 1.93(m, 1H, C*H*), 1.02(s, 3H, -(CH_3)$_2$), 1.00(s, 3H, -(CH_3)$_2$) ppm.

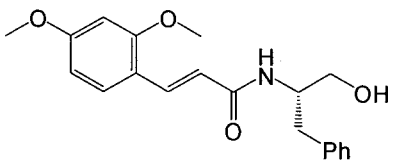
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.01, 162.07, 159.75, 136.63, 130.36, 119.7, 116.80, 104.99, 98.31, 63.86, 57.0, 55.35, 29.16, 19.52, 19.00 ppm.

IR (KBr) υ_{max}: 3371, 3311, 2960, 2864, 1643, 1603, 1568, 1531, 1460, 1417, 1355, 1304, 1260, 1216, 1163, 1138, 1075, 1042, 977, 934, 847, 800, 680, 639, 600 cm^{-1}.

$[\alpha]^{22}_D$ = -85.22 (*c* = 0.67, $CHCl_3$).

FAB-MS *m/z*: 294.17 $[M+H]^+$.

(-)-(*S*)-*trans*-*N*-(1-hydroxy-3-phenylpropan-2-yl)-2,4-dimethoxycinnamamide 13c:



13c

The same procedure as described previously was used in the reaction of *trans*-2,4-dimethoxycinnamoyl chloride **9** (1.0 g, 4.41 mmol) with (*S*)-phenylalaninol (1.167 g, 7,72 mmol) and dry triethylamine (1.08 mL, 7.72 mmol) to give (*S*)-*trans*-*N*-(1-hydroxy-3-phenylpropan-2-yl)-2,4-dimethoxycinnamamide **13c** as a white solid after purification by recrystallization (EtOAc/Hexane). Yield: 0.702 g (47%); **mp** 145.0 – 146.7 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, 1H, *J*= 15.6 Hz, RC*H*=CHR), 7.36 (d, 1H, *J*= 8.4 Hz, C*H*(Ar)), 7.31 – 7.21 (m, 5H,C*H*(Ar)), 6.48 – 6.36 (m, 3H, RCH=C*H*R, C*H*(Ar)), 5.91 (d, 1H, *J*= 7.5 Hz, N*H*), 4.28 (s_{broad}, 1H, C*H*), 3.83 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3), 3.78 – 3.63 (m, 2H, CH_2), 2.95 (d, 2H *J*=7.2 Hz, CH_2) ppm.

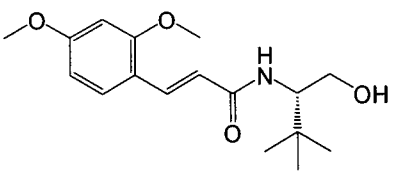
^{13}C NMR (75 MHz, $CDCl_3$/MeOD): δ = 167.75, 161.98, 159.37, 137.82, 136.19, 129.92, 128.97, 128.16, 126.12, 118.28, 116.49, 104.95, 98.06, 62.82, 55.05, 52.47, 36.63 ppm.

IR (KBr) υ_{max}: 3399, 3017, 2955, 2859, 1637, 1591, 1534, 1504, 1439, 1300, 1280, 1048, 980, 827, 759, 646, 596 cm^{-1}.

$[\alpha]^{22}_D$ = -63.37 (*c* = 0.98, $CHCl_3$).

TOF-MS *m/z*: 342.1698 $[M+H]^+$.

(-)-(*S*)-*trans*-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-(2,4-dimethoxycinnamamide 13d:



13d

The same procedure as described previously was used in the reaction of *trans*-2,4-dimethoxycinnamoyl chloride **9** (1.12 g, 4.96 mmol) with (*S*)-*tert*-leucinol (0.64 g, 5.45 mmol) and dry triethylamine (1.06 mL, 7.44 mmol) to give (*S*)-*trans*-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl) -(2,4-dimethoxycinnamamide **13d** as a white solid after purification by column chromatography (silica gel, EtOAc). Yield: 0.92 g (61%); **mp** 64 – 65 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, 1H, *J*= 15 Hz, RC*H*=CHR), 7.36 (d, 1H, *J*= 9 Hz, C*H*(Ar)), 6.53 (d, 1H, *J*= 16 Hz, RCH=C*H*R), 6.39 (t, 2H, *J*= 6.6 Hz, C*H*(Ar)), 6.15 (d, 1H, *J*= 9 Hz, N-*H*), 4.03 – 3.88 (m, 2H, C*H*, C*H*H), 3.80 (s, 3H, -OCH_3), 3.79 (s, 6H, -OCH_3), 3.65 – 3.58 (m, 1H, CH*H*), 0.99 (s, 9H, (CH_3)$_3$) ppm.

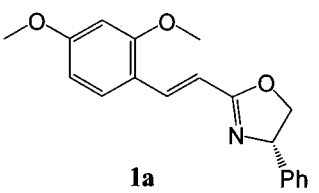
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.39, 162.04, 159.57, 136.81, 130.43, 118.79, 116.81, 104.95, 98.31, 63.01, 59.66, 55.35, 33.75, 26.97 ppm.

IR (KBr) υ_{max}: 3290, 3075, 2961, 2838, 1651, 1605, 1545, 1545, 1505, 1420, 1356, 1299, 1268, 1211, 1160, 1139, 1033, 986, 833, 798, 731, 635, 598 cm^{-1}.

$[\alpha]^{21}_D$ = -3.33 (*c* = 1.17, $CHCl_3$).

TOF-MS *m/z*: 308.19 $[M+H]^+$ HRMS (TOF) found, 308.18563; $C_{17}H_{26}NO_4$ requires 308.17836.

(+)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-phenyloxazoline-2-yl)ethene 1a:



1a

A solution of methanesulfonyl chloride (0.21 g, 1.8 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of cinnamamide **13a** (0.3 g, 6.12 mmol) and dry triethylamine (0.51 mL, 3.67 mmol) in dry CH_2Cl_2 (15 mL) and the solution was stirred between −5 and −10°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude product. The crude product was purified by column chromatography (silica gel, EtOAc:Hex (1:1)) giving the (+)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-phenyloxazoline-2-yl)ethene **1a** as a white semi-solid. Yield: 0.278 g (98%);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, 1H, *J*= 16.4 Hz, RC*H*=CHR), 7.41 (d, 1H, *J*= 8.6 Hz, C*H*(Ar)), 7.33 – 7.29 (m, 2H, C*H*(Ar)), 7.26 – 7.21 (m, 3H, C*H*(Ar)), 6.71 (d, 1H, *J*= 16 Hz, RCH=C*H*R), 6.48 (dd, 1H, *J*= 8.5 and 2.3 Hz, C*H*(Ar)), 6.42 (d, 1H, *J*= 2.3 Hz, C*H*(Ar), 5.26 (dd, 1H, *J*= 10 and 8 Hz, CH*H*), 4.66 (dd, 1H, *J*= 10 and 8 Hz, C*H*H), 4.14 (t, 1H, *J*= 8.2 Hz, C*H*), 3.81 (d, 3H, *J*= 6 Hz, -OCH_3), 3.78 (d, 3H, *J*= 6 Hz, -OCH_3) ppm.

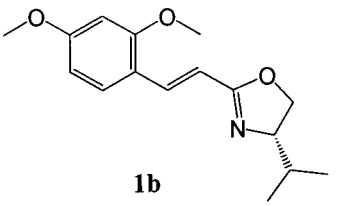
^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.30, 162.08, 159.22, 142.51, 135.69, 129.50, 128.96, 128.64, 127.43, 126.63, 117.21, 112.94, 105.13, 98.38, 74.24, 69.82, 55.37 ppm.

IR (NaCl, $CHCl_3$): υ_{max} 3035, 3025, 3016, 2963, 1646, 1608, 1576, 1504.34, 1466, 1421, 1364, 1270, 1162, 1034, 994, 840, 790, 776, 701, 666 cm^{-1}.

$[\alpha]^{22}_D$ = +7.72 (*c* = 0.57, $CHCl_3$).

FAB-MS *m/z*: 310.17 $[M+H]^+$.

(+)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-isopropyloxazoline-2-yl)ethene 1b:



1b

Using the same procedure as described previously, cinnamamide **13b** (0.40 g, 1.36 mmol) was reacted with methanesulfonyl chloride (0.234 g, 2.04 mmol) and dry triethylamine (0.57 mL, 4.08 mmol) to give the (+)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-isopropyloxazoline-2-yl)ethene **1b** as a yellow oil, after purification by column chromatography (silica gel, EtOAc:Hex (1:1)). (0.374 g, 70%);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, 1H, *J*= 16.4 Hz, RC*H*=CHR), 7.41 (d, 1H, *J*= 8.7 Hz, C*H*(Ar)), 6.66 (d, 1H *J*=16.4 Hz, RCH=C*H*R), 6.51 – 6.43 (m, 2H, C*H*(Ar)), 4.33 (m, 1H,C*H*), 4.02 – 4.00 (m, 2H, CH_2), 3.84 (s, 3H, -OCH_3), 2.92 (s, 3H, -OCH_3), 1.7 – 1.8 (m, 1H, C*H*), 1.01 (d, 1H *J*= 6.7 Hz, -(CH_3)$_2$), 0.91 (d, 1H *J*= 6.7 Hz, -(CH_3)$_2$) ppm.

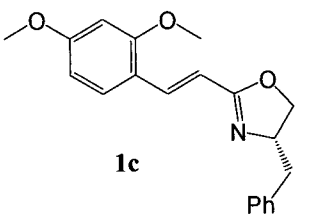
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.95, 161.83, 159.03, 134.74, 129.24, 117.27, 114.0, 104.98, 98.29, 72.40, 69.69, 55.00, 32.78, 18.87, 18.23 ppm.

IR (NaCl, CH_2Cl_2): υ_{max} 3055, 2969, 1743, 1604, 1505, 1465, 1301, 1214, 1162, 1033, 777, 669 cm^{-1}.

$[\alpha]^{22}_D$ = -51.56 (*c* = 1.44, $CHCl_3$).

FAB-MS *m/z*: 276.16 $[M+H]^+$.

(+)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-benzyloxazoline-2-yl)ethene 1c:



1c

Using the same procedure as described previously, cinnamamide **13c** (0.40 g, 1.17 mmol) was reacted with methanesulfonyl chloride (0.20 g, 1.76 mmol) and dry triethylamine (0.49 mL, 3.51 mmol) to give the (*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-benzyloxazoline-2-yl)ethene **1c** as a yellow oil after purification by column chromatography (silica gel, EtOAc:Hex (1:1)). Yield: 0.339 g (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, 1H, *J*= 16.4 Hz, RC*H*=CHR), 7.42 (d, 1H, *J*= 8.5 Hz, C*H*(Ar)), 7.34 – 7.22 (m, 5H, C*H*(Ar)), 6.65 (d, 1H, *J*= 16.4 Hz, CRH=C*H*R), 6.52 – 6.44 (M, 2H, C*H*(Ar)), 4.55 – 4.44 (m, 1H, C*H*), 4.03 (t, 1H, *J*= 8 Hz, C*H*H), 4.26 (t, 1H, *J*= 8 Hz, CH*H*), 3.85 (s, 3H, -OCH_3), 3.83 (s, 3H, -OCH_3), 3.21 – 3.13 (m, 1H, CH*H*), 2.69 (dd, 1H *J*= 8.7 and 13.7 Hz, C*H*H) ppm.

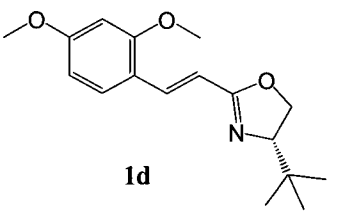
^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.56, 161.90, 159.04, 138.18, 135.21, 129.41, 129.16, 128.55, 126.43, 117.30, 113.27, 105.09, 98.40, 71.42, 67.65, 55.42, 41.90 ppm.

IR (NaCl, CH_2Cl_2): υ_{max} 3055, 2955, 1714, 1640, 1603, 1506, 1460, 1248, 1214, 1031, 939, 842, 775, 693 cm^{-1}.

$[\alpha]^{22}_D$ = +159.0 (*c* = 0.52, $CHCl_3$).

ESI-MS *m/z*: 324.16 $[M+H]^+$.

(-)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-*tert*-butyloxazoline-2-yl)ethene 1d:



1d

Using the same procedure as described previously, cinnamamide **13d** (0.40 g, 1.3 mmol) was reacted with methanesulfonyl chloride (0.22 g, 1.95 mmol) and dry triethylamine (0.55 mL, 3.91 mmol) to give the (-)-(*S*)-*trans*-2-(2,4-dimethoxyphenyl)-(4-tert-butyloxazoline-2-yl)ethene **1d** as a yellow semi-solid after purification by column chromatography (silica gel, EtOAc:Hex (1:2)). Yield: 0.21 g (55%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, 1H, *J*= 16.4 Hz, RC*H*=CHR), 7.42 (d, 1H, *J*= 8.5 Hz, C*H*(Ar)), 6.68 (d, 1H, *J*= 16.4 Hz, CRH=C*H*R), 6.5 (dd, 1H, *J*= 7.5 and 3 Hz, C*H*(Ar)), 6.44 (d, 1H, *J*= 2.3 Hz, C*H*(Ar)), 4.30 – 4.23 (m, 1H, C*H*), 4.13 (t, 1H, *J*= 9 Hz, C*H*H), 3.97 (dd, 1H, *J*= 8 and 9 Hz, CH*H*), 3.85 (s, 3H, -OCH_3), 3.83 (s, 3H, -OCH_3), 0.93 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.01, 161.90, 159.04, 134.84, 129.22, 113.13, 105.02, 98.26, 75.83, 68.13, 55.22, 33.72, 25.75 ppm.

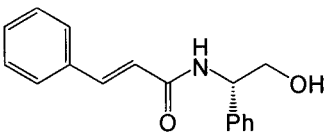
IR (NaCl, $CHCl_3$): υ_{max} 3030, 3020, 2968, 1640, 1602, 1505, 1458, 1301, 1278, 1206, 1163, 1122, 1034, 93, 841, 781, 663 cm^{-1}.

$[\alpha]^{21}_{D}$ = -38.26 (*c* = 1.44, $CHCl_3$).

TOF-MS *m/z*: 290.18 $[M+H]^+$. **HRMS** (TOF) found 290.17507 $C_{17}H_{24}NO_3$ requires 290.16779.

Synthesis of Arylid-OX 2:

(-)-(*S*)-*trans*-*N*-(2-hydroxy-1-phenylethyl)-cinnamamide 14:



14

A dry two-necked round bottom flask (25 mL) equipped with a magnetic stirring bar was charged with *trans*-cinnamic acid **7** (1.5 g, 10 mmol), dimethylformamide (0.1 mL, 1.3 mmol) and CH_2Cl_2 (15 mL). The solution was cooled to 0 °C, and oxalyl chloride (1.1 mL, 12,7 mmol) was added drop-wise over a 30 min period and the solution was stirred at room temperature until the evolution of gas ended. The solvent was evaporated in *vacuo* to give *trans*-cinnamoyl chloride **10** as a dark green solid (due to the unstable nature of this compound it was stored in the freezer at –10°C). A two necked round bottom flask (25mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (2.06 g, 15 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0°C using an ice bath. Dry triethylamine (2.01 mL, 15 mmol) was added via syringe. A solution of *trans*-cinnamoyl chloride **10** (all quantity, 10 mmol) in CH_2Cl_2 (5 mL) was slowly added via syringe to the vigorously stirred reaction mixture over 30 mins. The ice bath was removed, and the reaction mixture was stirred at room temperature for a further 4 h. The reaction mixture was washed with 2M HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with brine (15 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give (*S*)-*trans*-*N*-(2-hydroxy-1-phenylethyl)-cinnamamide **14** as an yellow solid. The crude product was purified by recrystallization (EtOAc/Hexane) to afford amide **14** as a white solid. Yield: 1.389 g (52%); **mp** 190.1 – 191.1°C;

^{1}H NMR (400 MHz, MeOD): δ = 7.54 – 7.24 (m, 12H, C*H*(Ar), N*H*, RC*H*=CRH), 6.73 (d, 1H *J*=15.7 Hz, RCH=C*H*R), 5.11 (s_b, 1H, C*H*), 3.81 – 3.77 (m, 2H, CH_2) ppm.

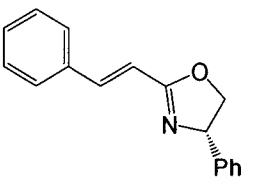
^{13}C NMR (100 MHz, MeOD): δ = 168.47, 142.05, 141.31, 136.43, 130.82, 129.95, 129.55, 128.88, 128.47, 128.11, 122.04, 66.27, 57.30 ppm.

IR (KBr) υ_{max}: 3304, 3062, 3028, 3062, 2953, 2859, 1654, 1623, 1547, 1494, 1450, 1355, 13345, 1233, 1215, 1160, 1074, 1058, 972, 863, 700, 528 cm^{-1}.

$[\alpha]^{21}_D$ = -20.12 (*c* = 0.815, MeOH).

TOF-MS *m/z*: 268.14 $[M+H]^+$.

(-)-(*S*)-*trans*-2-phenyl-(4-phenyloxazoline-2-yl)ethene 2:



2

A solution of methanesulfonyl chloride (0.411 g, 3.59 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of cinnamamide **14** (0.64 g, 2.39 mmol) and dry triethylamine (1 mL, 7.17 mmol) in dry CH_2Cl_2 (15 mL) and the solution was stirred between −5 and −10°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude product. The crude product was purified by column chromatography (silica flash, EtOAc:Hex (1:9)) giving the (+)-(*S*)-*trans*-2-phenyl-(4-phenyloxazoline-2-yl)ethene **2** as a white solid. Yield: 0.455 g (76%). **mp:** 59 – 60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 – 7.49 (m, 3H, C*H*(Ar) and RC*H*=CHR), 7.45 – 7.33 (m, 5H, C*H*(Ar)), 7.31 – 7.27 (m, 3H, C*H*(Ar)), 6.75 (d, 1H *J*=16.3 Hz, RCH=C*H*R), 5.33 (dd, 1H *J*= 8.4, 10 Hz,C*H*H), 4.72 (dd, 1H *J*=8.4, 10 Hz, CH*H*), 4.2 (t, 1H *J*= 8.2 Hz, C*H*) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.38, 142.22, 140.45, 135.13, 129.52, 128.81, 128.71, 127.54, 127.48, 126.61, 114.96, 74.34, 69.97 ppm.

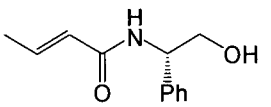
IR (KBr): υ_{max} 3057, 3030, 2955, 2889, 1650, 1605, 1492, 1474, 1450, 1361, 1244, 1201, 1074, 997, 981, 851, 760, 698, 536 cm^{-1}.

$[\alpha]^{20}_{D}$ = -12.12 (*c* = 0.99, $CHCl_3$).

TOF-MS *m/z*: 250.13 $[M+H]^+$.

Synthesis of Propeno-OX 3:

(+)-(*S*)-*trans*-*N*-(2-hydroxy-1-phenylethyl)-but-2-enamide 15a:



15a

General Procedure for the synthesis of amides (15a, 15b): A dry two-necked round bottom flask (25 mL) equipped with a magnetic stir bar was charged with *trans*-but-2-enoic acid **8** (1.0 g, 12 mmol), dimethylformamide (0.15 mL, 1.95 mmol) and CH_2Cl_2 (15 mL). The solution was cooled to 0 °C, and oxalyl chloride (1.27 mL, 15 mmol) was added drop-wise over a 30 min period and the solution was stirred at room temperature until the evolution of gas ended. The solvent was evaporated *in vacuo* to give *trans*-but-2-enoyl chloride **11** as a green oil (due to the unstable nature of this compound it was stored in the freezer at –10°C). A two necked round bottom flask (25 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (2.06 g, 15 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0°C using an ice bath. Dry triethylamine (2.1 mL, 15 mmol) was added via syringe. A solution of *trans*-but-2-enoyl chloride **11** (12 mmol) in CH_2Cl_2 (5 mL) was slowly added via syringe to the vigorously stirred reaction mixture over 30 mins. The ice bath was removed, and the reaction mixture was stirred at room temperature for a further 4 h. The reaction mixture was washed with 2M HCl (12 mL), saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with brine (15 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give (*S*)-*trans*-*N*-(2-hydroxy-1-phenylethyl)-but-2-enamide **15a** as a yellow solid. The crude product was purified by column

chromatography (silica flash, EtOAc:Hex (7:2) and AcOEt) to afford amide **15a** as a white solid. Yield: 1.924 g (78%). **mp** 95.5 – 96.9 °C;

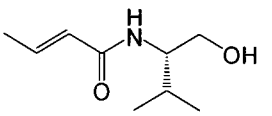
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.22 (m, 5H, H(Ar)), 6.81 (dq, 1H *J*=6.8, 15 Hz, MeC*H*=CHR), 6.61 (d, 1H *J*=6.8 Hz, N*H*), 5.83 (dd, 1H *J*=1.5, 15 Hz, MeCH=C*H*R), 5.06 (q, 1H *J*=5.4, 6 Hz, C*H*), 4.07 – 3.77 (m, 2H, CH_2), 1.83 (dd, 3H *J*=6.8, 20.2 Hz, Me) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 166.53, 140.73, 139.10, 128.70, 127.92, 127.66, 126.69, 124.69, 66.20, 55.86, 17.70 ppm.

IR (KBr) υ_{max}: 3292, 3080, 3030, 2918, 1671, 1631, 1545, 1494, 1448, 1359, 1333, 1283, 1235, 1120, 1074, 1051, 968, 917, 850, 7550, 7000, 666, 524 cm^{-1}.

$[\alpha]^{20}_D$ = +68.01 (*c* = 0.965, $CHCl_3$).

TOF-MS *m/z*: 206.12 $[M+H]^+$.

(-)-(*S*)-*trans*-*N*-(1-hydroxy-3-methylbutan-2-yl)-but-2-enamide 15b:



15b

The same procedure as described previously was used in the reaction of *trans*-but-2-enoyl chloride **11** (8.6 mmol) with (*S*)-valinol (1.14 g, 11 mmol) and dry triethylamine (1.54 mL, 11 mmol) to give (*S*)-*trans*-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-but-2-enamide **15b** as a white solid after purification by column chromatography (silica flash, EtOAc). Yield: 0.49 g (33%). **mp** 92.3 – 93.8 °C;

^{1}H NMR (400 MHz, $CDCl_3$):δ = 6.78 (dq, 1H *J*=6.8, 15.2 Hz, MeC*H*=CHR), 6.23 (d, 1H *J*=9.6 Hz, N*H*), 5.84 (dd, 1H *J*=1.6, 15.2 Hz, MeCH=C*H*R), 3.76 – 3.70 (m, 1H, C*H*), 3.67 – 3.59 (m, 2H, CH_2), 1.82 – 1.90 (m, 1H, C*H*), 1.8 (dd, 3H *J*=1.5, 6.9 Hz, Me), 0.92 (d, 3H *J*=6.8 Hz, $CH(CH_3)_2$), 0.89 (d, 3H *J*=6.8 Hz, $CH(CH_3)_2$) ppm.

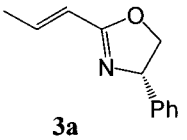
^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.99, 140.00, 125.06, 63.39, 56.91, 28.84, 18.83, 17.61 ppm.

IR (KBr) υ_{max}: 3433, 3296, 3064, 3028, 2953, 2872, 1670, 1620, 1597, 1542, 1464, 1445, 1391, 1375, 1357, 1226, 1066, 975, 921, 839, 728, 685, 653, 523 cm^{-1}.

$[\alpha]^{20}_D$ = -44.56 (*c* = 0.86, $CHCl_3$).

TOF-MS *m/z*: 172.13 $[M+H]^+$.

(-)-(*S*)-*trans*-(4-phenyloxazoline-2-yl)prop-2-ene 3a:



3a

A solution of methanesulfonyl chloride (0.42 g, 3.65 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of amide **15a** (0.5 g, 2.44 mmol) and dry triethylamine (1 mL, 7.32 mmol) in dry CH_2Cl_2 (20 mL) and the solution was stirred between −5 and −10°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude product. The crude product was purified by column chromatography (silica flash, EtOAc:Hex (1:9)) giving the (+)-(*S*)-*trans*-(4-phenyloxazoline-2-yl)prop-2-ene **3a** as a colorless oil. Yield: 0.33 g (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.26 (m, 5H, *H*(Ar)), 7.25 – 7.23 (m, 5H, *H*(Ar)), 6.69 (dq, 1H *J*=6.9, 13.7 Hz, MeC*H*=CHR), 6.1 (dd, 1H *J*=6.9, 13.7 Hz, MeCH=C*H*R), 5.22 (t, 1H *J*=9 Hz, C*H*H), 4.62 (dd, 1H *J*=8.4, 10 Hz, CH*H*), 4.1 (t, 1H *J*=8.2 Hz, C*H*), 1.9 (dd, 3H *J*=1.7, 6.8 Hz, CH_3) ppm.

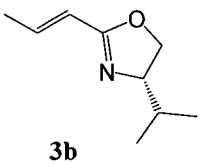
^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.95, 142.36, 139.78, 128.41, 127.46, 126.58, 126.27, 126.16, 118.89, 74.19, 69.67, 18.35 ppm.

IR (NaCl): υ_{max} 3272, 3061, 3030, 2968, 2912, 1732, 1676, 1644, 1612, 1585, 1494, 1474, 1454, 1360, 1178, 997, 968, 903, 761, 734, 701, 667, 542 cm^{-1}

$[\alpha]^{20}_D$ = -113.80 (*c* = 1.28, $CHCl_3$).

TOF-MS *m/z*: 188.11 [*M*+H]$^+$.

(-)-(*S*)-*trans*-(4-isopropyloxazoline-2-yl)prop-2-ene 3b:



3b

Using the same procedure as described previously, amide **15b** (0.35 g, 2.04 mmol) was reacted with methanesulfonyl chloride (0.35 g, 3.07 mmol) and dry triethylamine (0.86 mL, 6.13 mmol) to give the (*S*)-*trans*-(4-isopropyloxazoline-2-yl)prop-2-ene **3b** as a colorless oil after purification by column chromatography (silica flash, EtOAc:Hex (1:5)). Yield: 0.193 g (62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (dq, 1H *J*=6.9, 13.7 Hz, MeC*H*=CHR), 5.96 (d, 1H *J*=15.8 Hz, MeCH=C*H*R), 4.28 – 4.18 (m, 1H, C*H*), 3.94 – 3.89 (m, 2H, CH_2), 1.82 (d, 3H *J*=6.9 Hz, Me), 1.75 – 1.70 (m, 1H, C*H*(CH_2)$_2$), 0.94 (d, 3H *J*=6.8 Hz, CH(CH_2)$_2$), 0.89 (d, 3H *J*=6.8 Hz, CH(CH_2)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.71, 138.81, 119.10, 72.19, 69.63, 32.68, 18.82, 18.24, 18.15 ppm.

IR (NaCl):υ_{max} 3272, 2961, 2912, 2874, 1722, 1679, 1648, 1614, 1468, 1446, 1357, 1309, 1250, 1192, 1178, 1103, 995, 970, 911, 815, 795, 733, 668, 529 cm^{-1}.

$[\alpha]^{21}_D$ = - 69.06 (*c* = 0.96, $CHCl_3$).

TOF-MS *m/z*: 154.13 $[M+H]^+$.

Representative Cyclopropanation using $[Cu(MeCN)_4]PF_6$ pre-catalyst

$[Cu(MeCN)_4]PF_6$ (0.0133 mmol, 0.36 mol%) or (0.0133 mmol, 2 mol%) was added to a two-neck round-bottomed flask containing the chiral oxazoline (1.13 – 6.3 mol%) in CH_2Cl_2 (1 ml) and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Alkene **16** or **17** (2.66 mmol) and a solution of ethyl diazoacetate (7.45 mmol) or (0.665 mmol) in CH_2Cl_2 (1 ml) was then added to the reaction mixture over a period of 8 h using a syringe pump. After the addition of ethyl diazoacetate, the mixture was stirred for 16 h. The reaction mixture was firstly passed through a short pad of silica gel (washed with CH_2Cl_2) to remove the catalyst complex, the products were then isolated by column chromatography (hexane/EtOAc 9:1). All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers, the ratio was determined using GC analysis. Isolated yields, diastereoselectivities, and enantioselectives are given in Tables 1-4.

GC conditions:

CACP of styrene **16**:

Oven temperature: 120°C

Split: 120:1

t_R ((1*S*,2*R*)-ethyl 2-phenylcyclopropanecarboxylate)= 47.803 min

t_R ((1*R*,2*S*)-ethyl 2-phenylcyclopropanecarboxylate)= 50.830 min

t_R ((1*R*,2*R*)-ethyl 2-phenylcyclopropanecarboxylate)= 62.416 min

t_R ((1*S*,2*S*)-ethyl 2-phenylcyclopropanecarboxylate)= 64.010 min

CACP of α-methylstyrene **17**:

Oven temperature: 140°C

Split: 120:1

t_R (*cis*-ethyl 2-methyl-2-phenylcyclopropanecarboxylate) = 12.240 and 12.464 min

t_R (*trans*-ethyl 2-methyl-2-phenylcyclopropanecarboxylate) = 15.438 and 15.694 min

t_R (Maleate/Fumarate)= 3.955 and 4.969 min

t_R (**17**)= 2.395 min

t_R (EDA) = 2.133 min

Kinetics Studies:

Catalytic Asymmetric Cyclopropanation of α-methylstyrene with $(1a)_2$-Cu(I) (Monitoring by GC)

$[Cu(MeCN)_4]PF_6$ (15 mg, 0.039 mmol, 2 mol%) was added to a two-neck round-bottomed flask containing **1a** (39 mg, 0.063 mmol, 1.26 mol%) CH_2Cl_2 (6 ml) and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Alkene (1.03 mL, 7.96 mmol, 4eq) and a solution of ethyl diazoacetate (227 mg, 1.99 mmol) CH_2Cl_2 (1 ml) were then added to the reaction mixture over a period of 8 h using a syringe pump. After the addition of ethyl diazoacetate, the mixture was stirred for 16 h. During the reaction, aliquots (0.1 mL) were taken at 1h, 2h, 3h, 4h, 6h, 8h, 22h and 24h, and analyzed by GC in order to determine the conversion, enatioselectivities of the *cis* and *trans* diastereomers, diastereoselectivity and selectivity. The results are given in Figure 4.

Catalytic Asymmetric Cyclopropanation of α-methylstyrene with a mixture of 1b and 1c with Cu(I) (Monitoring by GC)

$[Cu(MeCN)_4]PF_6$ (14.4 mg, 0.039 mmol, 2 mol%) was added to a two-neck round-bottomed flask containing **1b** (17 mg, 0.063 mmol, 3.15 mol%) and **1c** (20 mg, 0.063 mmol, 3.15 mol%) in CH_2Cl_2 (6 ml) and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Alkene (1.03 mL, 7.96 mmol, 4eq) and a solution of ethyl diazoacetate (227 mg, 1.99 mmol) in CH_2Cl_2 (1 ml) were then added to the reaction mixture over a period of 8 h using a syringe pump. After the addition of ethyl diazoacetate, the mixture was stirred for 16 h. During the reaction aliquots (0.1 mL) were taken at 1h, 2h, 3h, 4h, 6h, 8h, 22h and 24h, and analyzed by GC in order to determine the conversion, enatioselectivities of the *cis* and *trans* diastereomers, diastereoselectivity and selectivity. The results are given in Figure 5.

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Chapter 3

Synthesis and Immobilization of Modular Arylid-BOX ligands: Catalytic Asymmetric Cyclopropanation[‡]

Abstract

Two novel *ortho*-substituted Arylid-BOX ligands **10a** and **10b** were synthesized in very good yields. These ligands were tested in the CACP of styrene with Cu(I) and Ru(II). It was found that the yields using the *ortho*-methoxy substituited Arylid-BOX ligands were the best, indicating an electrodonating effect. Both the enantioselectivities and diastereoselectivities obtained with these *ortho*-substituted ligands were in line with those previously obtained with the *para*-substituted series. The CACP with Ru(II) in biphasic media (toluene/H_2O) gave a highest enantioselectivity of 89% ee for the *cis*-cyclopropane, including a satisfactory diastereoselectivity of 58% de, but the yield was low.

Copper(I) and copper(II) complexes of two Arylid-BOX ligands were immobilized on Montmorillonite K10 (MK10) and silica via non-covalent bonding. The catalytic activity of the immobilized catalysts in the benchmark cyclopropanation reaction was observed. The results seemed to depend on the nature of both the chiral unit and the support. In the case of MK10 the highest enantioselectivities were, 62% ee for the *trans*-cyclopropane and 65% ee for the *cis* cyclopropane and in the case of silica gel, the highest enantioselectivities were 50% ee for the *trans*-cyclopropane and 43% ee for the *cis*-cyclopropane.

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1. Introduction

The Arylid-BOX **1** family of chiral non-racemic *pseudo-*C_2 symmetric bidentate bis-oxazoline ligands was introduced by our research group in 2006 (Figure 1).[1,2] They have shown significant applicability in some asymmetric catalytic reactions, like styrene cyclopropanation, demonstrating good enantioselectivities,[1,2] the Friedel–Crafts alkylation of indole with phenylidenemalonates[3a] and the Henry reaction between nitromethane and benzaldehyde.[3b]

This family of bis(oxazoline) ligands **1**, where the two oxazoline units are tethered geminally to an arylidene bridging unit with a variety of *para*-substituted phenyl rings can be tuned electronically in order to improve the performance of the resulting catalyst. The Arylid-BOX **1** was inspired by our first generation family a C_2 symmetric bis(oxazoline) system, known as Isbut-BOX **2**,[4] bearing an isobutylene bridge between the oxazoline rings. This was screened in the Cu(I) catalysed asymmetric cyclopropanation reaction.

One important structural factor for achieving good enantioselectivities is the ligand "cleft"[§] angle Θ, and this angle should affect the ligand bite angle Φ with the metal (N–Metal-N).[2,4,5-7] Several research group have investigated this structural parameter in bis(oxazoline) ligands, Figure 1.[2,4-7] In fact Denmark's paper has led to some confusion in that the term "coordination angle" was used instead of "bite angle".

In this field Davies *et al.*,[6] found that variation of the ring size of certain spiroocyclic bis(oxazolines) **3** provide different ligand geometries. They tested these ligands in copper-catalyzed asymmetric Diels-Alder reactions, and the results showed that by increasing the ligand "cleft" angle Θ, the ee increased as well. The explanation given for this behavior, was that a large value for Θ may promote a change in geometry away from an idealized square-planar shape at the copper(II)-centre.

[§] This is a new term introduced by us.

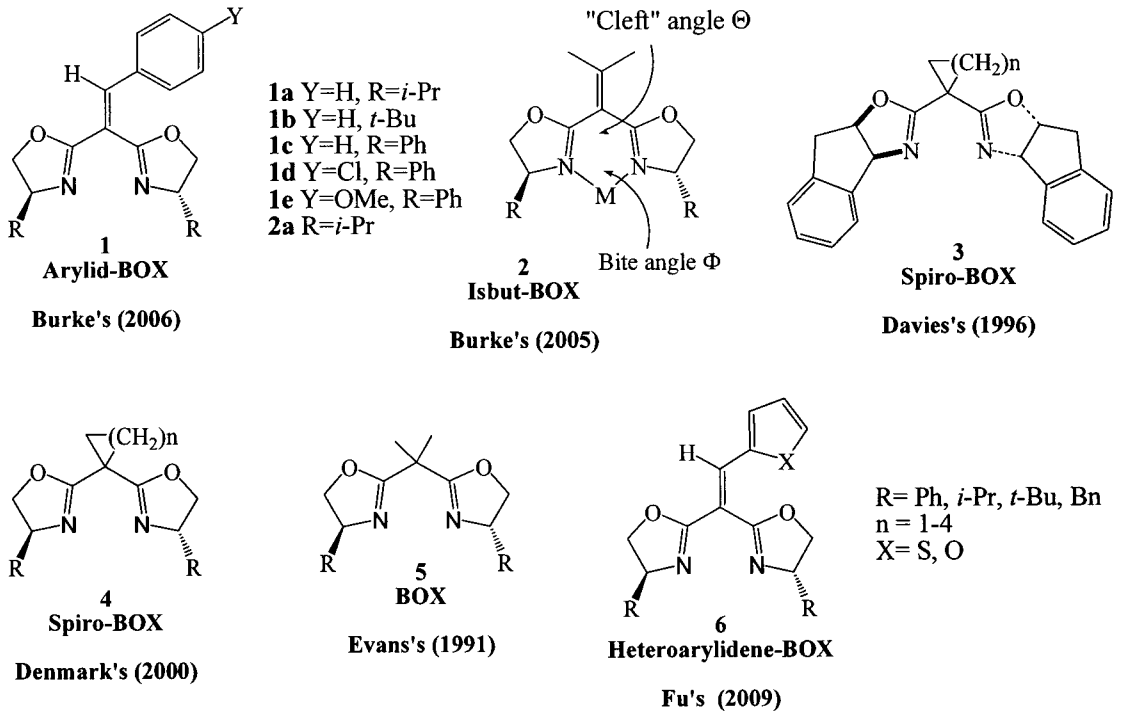


Figure 1. Bis(oxazoline) ligands.

The "cleft" angle (Θ) was predicted by computational methods for the uncomplexed ligand, a highest Θ of 110.6° was obtained for ligand **3** with n=1.[6]

In 2000 Denmark *et al.*[7] showed contradictory behaviour with the bis(oxazoline) ligands **4**. They conducted a similar study to that of Davies *et al.*,[6] but for the asymmetric addition of methyllithium to imines. In this case the large bite angle of the metal (Φ) gave poor ees.

In 2005 our research group developed the Isbut-BOX **2**,[4] in which the two oxazoline units are attached via an sp^2 hybridized carbon which was designed to provide a larger "cleft" angle (Θ) than those with sp^3 hybridized carbon at the bridge. DFT calculations were carried out for ligands **2** and **5** (Evans' BOX) copper(I)-complexes (Figure 2) and the ligand "cleft" angles (Θ) calculated were, 117.7° (for Isbut-BOX **2**) and 117.1° (for BOX **5**), and the respective bite angle of the metal Φ were, 105.5° and 104.2°. The considerable difference between the dihedral angles Cu-N1-C5-C4 (32.1°) and Cu-N2-C6-C7 (64.1°) is due to one of the oxazoline rings being slightly tilted out of the plane. The Isbut-BOX was tested in the catalytic asymmetric cyclopropanation and only gave moderate ees.

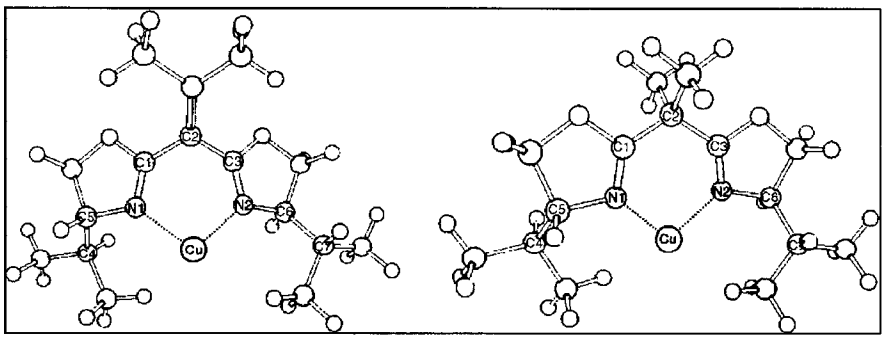


Figure 2. Calculated structural features (DFT) for the Cu(I)-Isbut-Box **2a** (left) and Cu(I)-*i*PrBox **5** (Evans) (right).[4]

The Arylid-BOX **1**[1,2] was developed with both electron donating and withdrawing groups (Cl and OMe) in the *para* position of the "tail-end" phenyl ring. These ligands were tested in Cu(I) and Cu(II)-catalyzed asymmetric cyclopropanation reactions, and gave ees up to 89% and des up to 40%.[1,2] Both inductive and resonance effects were expected, but were not confirmed in these CACP. Density functional theory (DFT) calculations conduced at the B3LYP level, suggested the arylidene phenyl unit is slightly tilted out of the plane and thus would prevent any significant resonance effects from the back-bone aryl groups in such complexes. The considerable distance between the "tail-end" phenyl substituents and the metal reduced obviously the intensity of the inductive effect. The DFT study was carried out on the Arylid-BOX **1b**-Cu(I) complex using the GAMESS-US package with the 6-31G* basis-set for C, N, O and H and applying the Stuttgart RSC 1997 effective core potential for Cu. The structure is depicted in Figure 3 with some selected measurements. These results were similar to the theoretical results obtained by Rasmussen *et al.*[8] and the X-ray crystallographic analysis of oxazoline-Cu(I) by Evans.[9]

On analysis of these theoretical results, the dihedral angle for C(3)-C(1)-C(2)-C(5) of 28.6°, demonstrated the degree to which the phenyl ring was forced out of the plane.

Recently, in 2009 Sun *et al.*[3a] developed similar bis(oxazoline) ligands to our Arylid-BOX **1**, termed, heteroarylidene-BOX **6**. These ligands had a thiophene or furan ring instead of a phenyl ring. They evaluated these ligands and our Arylid-BOX **1a** in copper (II)-catalyzed enantioselective Friedel-Crafts reactions of indole.

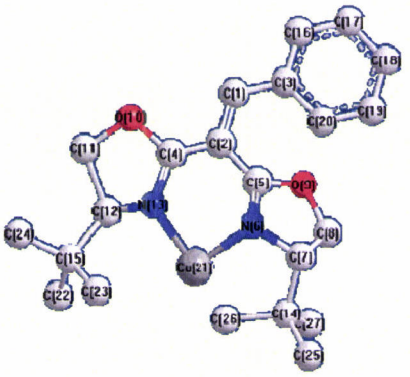
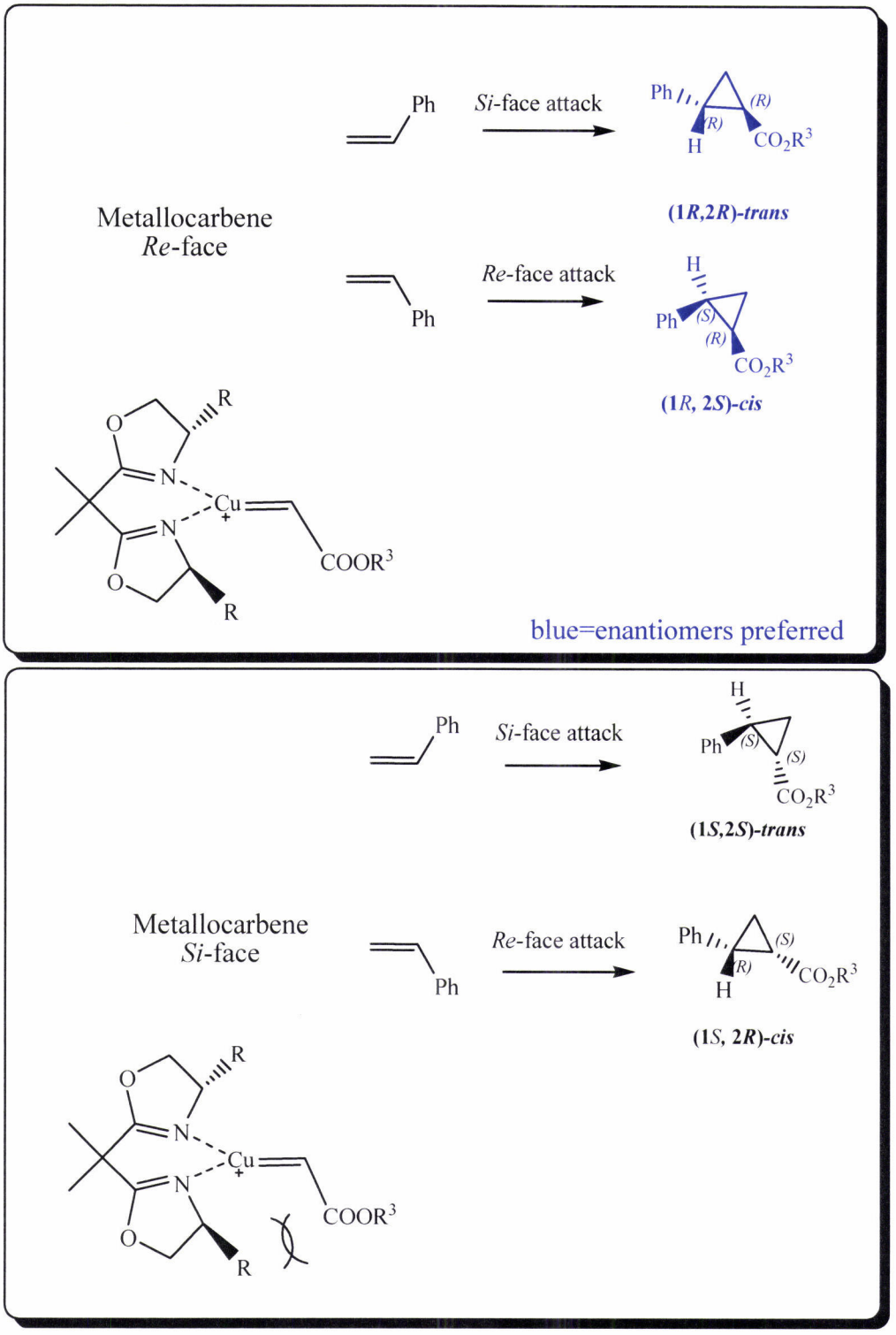


Figure 3. Chem-3D representation of the Cu(I)-Arylid-BOX **1b** model complex (Hs are omitted for clarity) whose optimized structure was determined using DFT. Selected bond lengths (Å) and bond angles (°): Cu-N13, 1.932; Cu-N6, 1.931; C1-C2, 1.372; N(13)-Cu(21), 1.932; C(4)-C(2)-C(5), 121.2; N(13)-Cu(21)-N(6), 107.5; C(3)-C(1)-C(2)-C(5), 28.6.[2]

Ees of up to 99% for their system and 65% for our Arylid-BOX ligand were obtained. This difference doesn´t seem to be due to the "cleft" Θ angle, nor the metal bite angle Φ, because they are similar having an angle of around 120°. These workers proposed that the heterocyclic moiety may participate in intermolecular coordination in solution acting as a weak ligand.

Another important aspect is the structure of the metallocarbene and how this can influence the enantioselectivities and diastereoselectivity in catalytic asymmetric cyclopropanations. In Chapter 1, the catalytic cycle was explained, but no working model to explain the stereochemical outcome of the reaction was advanced, and thus will be described in this chapter.

The theoretical studies developed by Fraile *et al.*[10] and Rasmussen *et al.*[8] are in agreement with the model depicted in the scheme 1, which has many similarities with that formulated by Pfaltz.[11b] Based on the DFT calculations on a chiral bis(oxazoline)-Cu(I) model, the steric interaction between the ester group and one of the substituents of the bis(oxazoline) ligand is supposed to be the origin of the enantioselectivity. The metallocarbene can suffer attacks from the two faces *Re*- and *Si*-face. In the Scheme 1 the attack from the carbene-*Si* face show some steric hindrance between the substituent R from the bis(oxazoline) and the carboxylate from the ester group. This steric interaction is enhanced by the axial deviation of the Cu=C carbene bond in relation to the complex. On the other hand, the *cis*/*trans* selectivity in the final cyclopropanes is governed by the steric interaction between the carbene ester group and the substituents on the olefinic double bond (Scheme 1).[8,9,12b]



Scheme 1. Stereochemical model for Evans' Cu (BOX) Catalyst.[8,10]

DFT calculations on the model Cu(I)-metallocarbene complexes **7** and **8** (Figure 4) which are basically approximations of the Cu(I)-metallocarbene species derived from Cu(I)-Arylid-BOX ligands and Evans' gem-dimethyl malonate derived ligands were quite revealing.

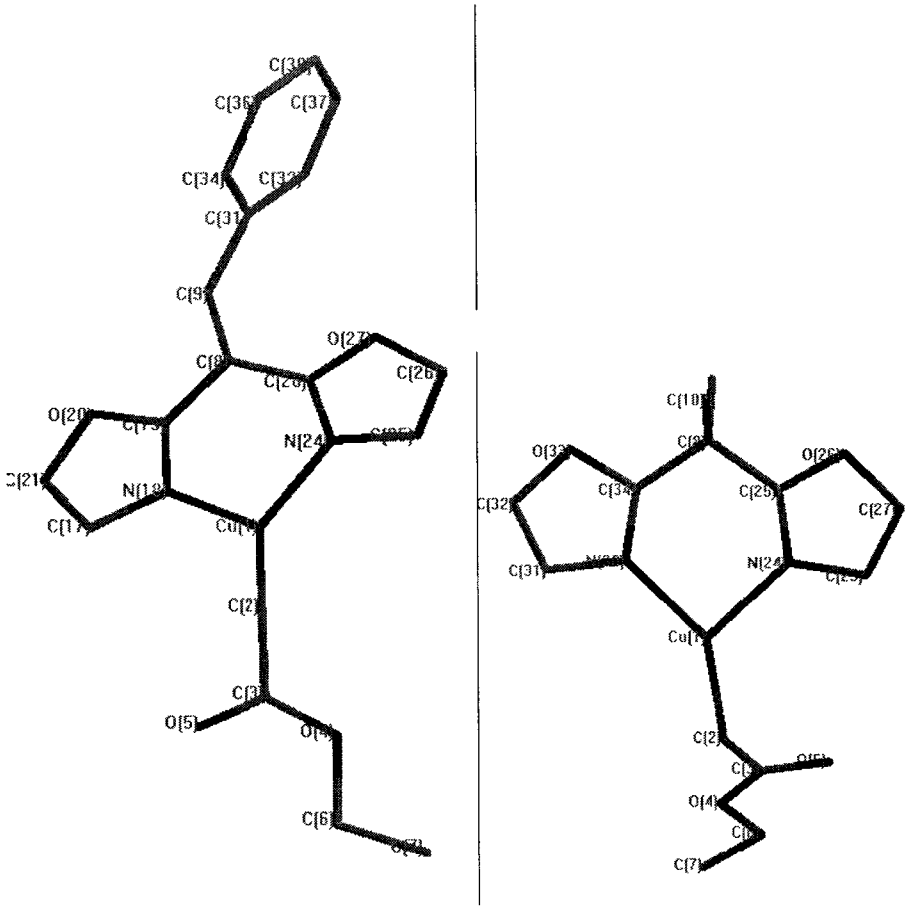
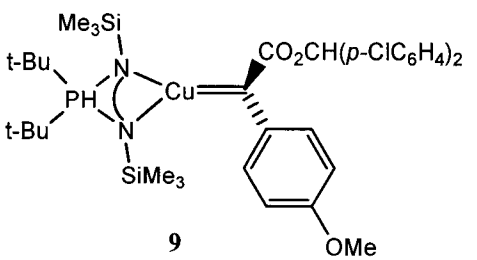


Figure 4. Chem-3D representations (with the Hs omitted for clarity) of the Cu(I)-metallocarbene complexes **7** (left) and **8** (right) model complexes whose optimized structure was determined using DFT. Selected bond lengths (Å) and bond angles (◦): For complex **7**: Cu-N18, 2.005; Cu-N24, 1.982; Cu-C2, 1.813; C19-C8-C28, 116.3, N18-Cu-C2, 128.7; N24-Cu-C2, 140.5; N18-Cu-N24, 90.8; N18-Cu-C2-C3, 74.2. For complex **8**: Cu-N30, 2.000; Cu-N24, 2.009; Cu-C2, 1.818; C32-C8-C25, 112.0; N30-Cu-C2, 144; N24-Cu-C2, 124.3; N30-Cu-N24, 91.6; N24-Cu1-C2-C3, 67.9.[2]

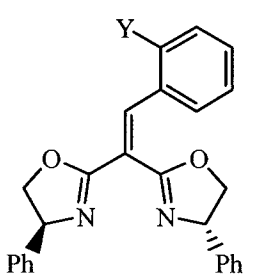
The results obtained from this calculation (Figure 4) revealed that **7** was more rigid and thus probably more stable than **8** (Cu-C2 of **7**< Cu-C of **8**). The carbonyl group for both **7** and **8** was calculated to be roughly perpendicular with the Cu-C bond, with **7** having the greater dihedral angle of 74.2° as opposed to 67.9° for **8**. This result would imply that the carbenoid carbon of **7**, should be the harder acid centre. On the basis of Pearson's HSAB theory[13] if one considers styrene a soft base then **7** should be the more reactive of the two. Another considerable and interesting difference was the observation that there were significant differences in the N-Cu-C bond angle for both **7** (128.7° and 140.5°) and **8** (124.3° and 144°) meaning that the Cu-Carbenoid carbon bond deviates away from the symmetry axis of the metallocarbene complex. This might suggest the higher ee's obtained with **8**, were due to the closer proximity of the carbenoid carbon to one of the sterogenic centres.[2]

Recently, several research groups conducted theoretical studies on the mechanism of Copper(I)-catalyzed diazo ester decomposition.[12] Shishkov *et al.*[14] reported the remarkable synthesis of a stable copper(I) α-carbonyl carbene. The Cu(I) carbene **9** was isolated in analytically pure, crystalline form as the first stable representative of this important class of compounds. Its solid-state X-ray crystal structure revealed that the carbene unit had an orthogonal orientation relative to both the ligand plane and the ester C=O group and a remarkably short Cu-$C_{carbene}$ distance of 1.822(4) Å. This value is very consistent with that obtained by Burke *et al.* [2] The solid-state structure of carbene **9** is in agreement with the Pfaltz sterochemical model for cyclopropanation and with predictions from quantum chemistry. Compound **9** is the first stable structurally characterized *R*-carbonyl copper carbene. Reaction of this carbene with styrene proceeds stereoselectively and affords *trans*-cyclopropane and a copper styrene complex in *ca.* 1:1 ratio. Kinetic experiments with pure **9** and previously characterized diaryl carbene[12g] are fully consistent with an associative mechanism.



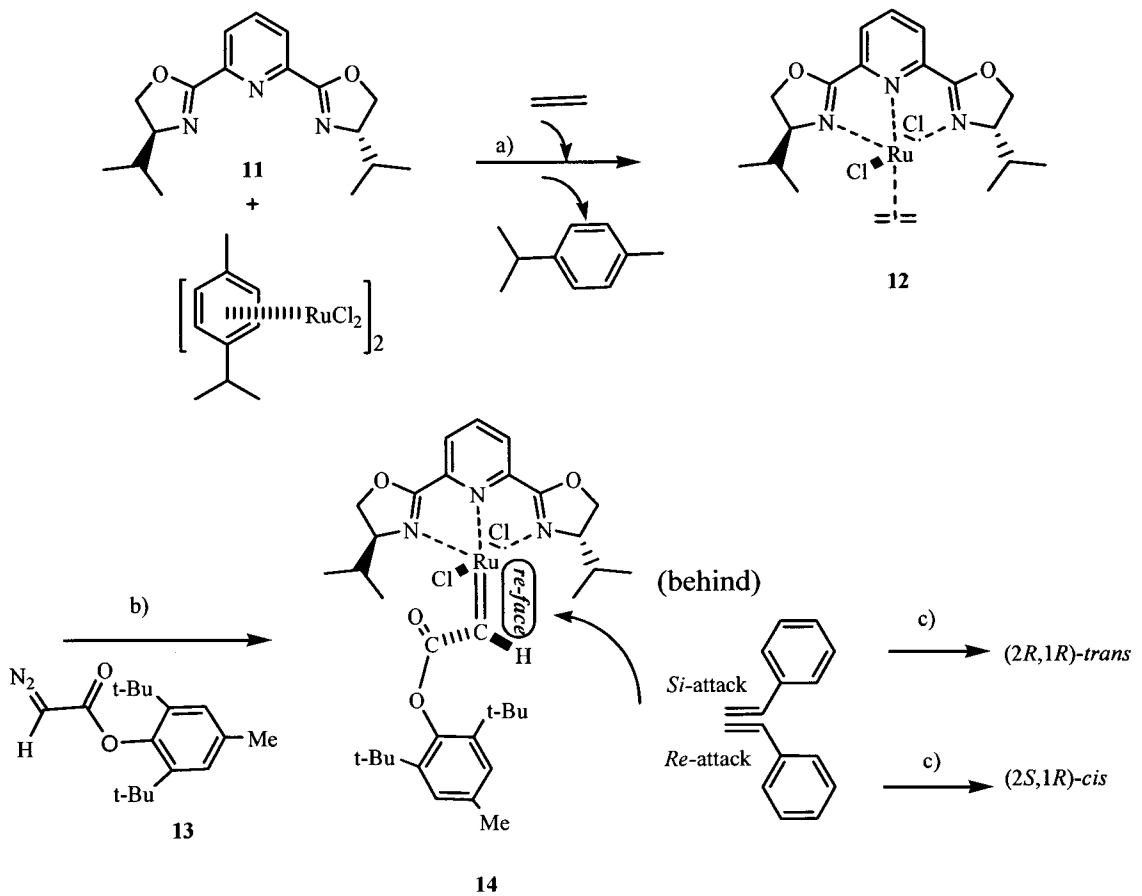
9

The enantioselectivity results obtained in the CACP with Arylid-BOX **1** containing *t*-Bu substituints were very satisfactory. As the yields were low, efforts were made to increase the yield in the CACP, with the introduction of *ortho*-methoxyl and *ortho*-chloro groups in the phenyl ring. As these groups are nearer the oxazoline ring then greater inductive effects were expected. These *ortho*-sustituted-Arylid-BOXs (**10a-10b**) were synthesized and evaluated in the CACP catalyzed by both Cu(I) and Ru(II).



10a Y=Cl
10b Y=OMe

Nishiyama group's[15] were the first to report the CACP with ruthenium and bis(oxazolinyl)pyridine **11** (PyBOX) ligands, the results revealed extremely high *trans* selectivities with high enantioselectivities at relatively low reaction temperatures (around 20-50°C). In Scheme 2 the formation of Nishiyama's catalyst **12** and the formation of metallocarbene **14** are depicted. The cyclopropane products obtained in this reaction may be the result of either a concerted or step-wise cationic process of carbene transfer from the Ru-Carbene **14** intermediate to the olefin.[15a] A working stereochemical model where *Re*-face attack of the metallocarbene is preferred is shown in Scheme 2.[15a]



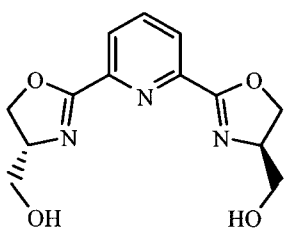
Scheme 2. a) Formation of Nishiyama's catalyst **12**;[15a] b) synthesis of the metallocarbene **14**;[16] c) hypothetic stereochemical approach for formation of the *trans*-cyclopropane.[15a]

Few examples are known where there is high *cis* stereoselectivity,[17] particularly with bis(oxazoline) ligands. Baratta's and Hermann's groups[17a] found that the complex $[(\eta^5\text{-}C_5H_5)Ru(PPh_3)_2Cl]$ and other derivatives, efficiently catalyzed the cyclopropanation of styrene and other electron-rich alkenes in the presence of EDA with

uncommonly high *cis* stereoselectivity. Their preliminary mechanistic studies have indicated the possibility of the intermediacy of a metallocyclobutane The groups of Demonceau and Viñas[17b] also showed that *cis* stereoselectivity was preferred. However the mechanism remains unkown.

Nishiyama and coworkers[18] in 2000 introduced a new type of PyBOX, PyBOX-*hm* **15**, having a hydroxymethyl group on the oxazoline rings. It was found that the ruthenium chloride complex containing **15** was very soluble in water and alcohols, consequently application of the *in situ* ruthenium complex to CACP in protic media, was investigated.[19] Since then, there have been no further reports of effective catalytic cyclopropanation systems in aqueous or protic solvents with cobalt catalysts.[20] Some Rh catalysts can decompose diazo compounds in the presence of water or alcohols giving alcohols or ethers.[21] In the case of copper catalysts, the free hydroxy groups on the ligands do not seem to interfere with the cyclopropanation reactions.[22]

The CACP using Ru and PyBOX-*hm* **15** were very low yielding with low enantioselectivity in organic solvents, like toluene and tetrahydrofuran (THF). However, when water was added to these solvents, the reaction proceeded smoothly, improved by the increased solubility of the Ru(PyBOX-*hm*)Cl_2 complex. The CACP carried out in toluene/water biphasic media resulted in a 94% ee for the *trans* isomer.[19a-b]



PyBOX-*hm* **15**

Immobilization of Arylid-BOX-copper Catalysts

Another, goal of this project was to immobilize the catalysts derived from these promising Arylid-BOX ligands on inorganic supports. The immobilization of Arylid-BOX-Cu(I)PF_6 and Arylid-BOX-Cu(II)$(OTf)_2$ complexes through ionic exchange on anionic supports, like: Montmorillonite K10, was investigated. Montmorillonite is a

member of the smectite group of clay minerals which has a 2:1 type layer structure. It is comprised of negatively charged silica sheets held together by charge-balanced counter-ions such as Mg^{2+}, Na^{+} and Ca^{2+}.[23] Montmorillonite's application is a consequence of its characteristics, like plasticity, swelling, ion exchange, density etc.[23] These properties are mainly governed by the interaction of the inter-layer materials with the environment.

A number of chiral catalysts, including bis(oxazoline)-copper complexes, have been successfully immobilized to clays.[24] For instance, Mayoral's group has extensively studied Laponite to immobilize bis(oxazoline)-copper complexes for asymmetric catalytic cyclopropanation reactions.[24d, 25b-d] Montmorillonite has also been used as a support. Fraile *et al.* have pointed out that the surface around the chiral catalyst might be considered a two-dimensional nano-reactor that is able to condition the approach of the reagents and consequently the transition state energies.[24d]

In 1997 Mayoral and co-workers immobilized non-covalently some of Evans' BOX-copper complexes through ion-exchange on anionic laponite and bentonite supports (Figure 5).[26] When they were tested in the catalytic asymmetric cyclopropanation, the selectivity and enantioselectivity were low.

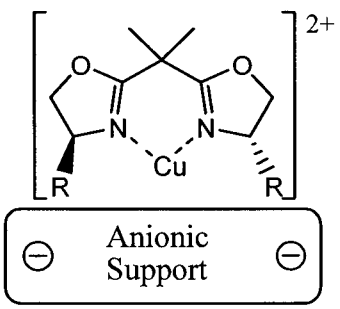
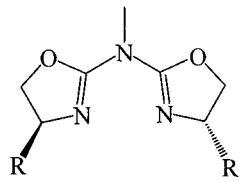


Figure 5. Immobilization of bis(oxazoline)-copper(II) complexes utilizing ionic exchange.

Mayoral and Reiser in 2004 immobilized AzaBOX **16** copper complexes on laponite and Nafion-Silica supports, and they were used for the catalytic asymmetric cyclopropanation reaction.[27] Three cycles were conducted, but both the yield and the enantioselectivity dropped considerably from the first cycle to the third.



AZABOX 16

R=*i*Pr, Bn, Ph, *t*Bu

BOX-Copper complexes can be immobilized via electrostatic non-covalent attachment was realized *via* hydrogen-bonding between silanols on a silica surface and the triflate anions of a chiral bis(oxazoline) complex as it is illustrated in Figure 6. This method was introduced by Van Koten's group[28] and it was employed in the heterogeneous catalytic Diels-Alder reaction by the same group and in the carbonyl-ene reaction by McDonagh and O'Leary.[29] The catalyst showed activity and enantioselectivity similar to that observed in the homogeneous phase for both reactions. However, a reversal of selectivity was observed due to a change in the conformation of the catalyst on immobilization.

In this thesis, we report for the first time our efforts on the non-covalent immobilization of Arylid-BOX-Cu(I)PF_6 and Arylid-BOX-Cu(II)$(OTf)_2$ catalysts to Montmorillonite and silica-gel.

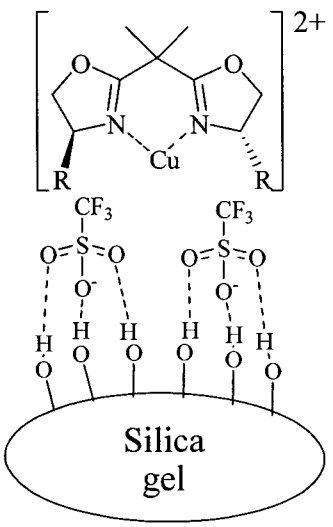
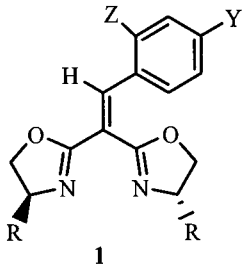


Figure 6. Immobilization *via* hydrogen bond formation.

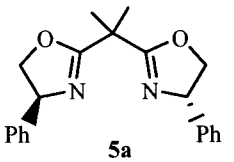
2. Results and Discussion

2.1 Theoretical Study



1

1c Y=Z=H, R=Ph
1d Y=Cl, Z=H, R=Ph
1e Y=OMe, Z=H, R=Ph
10a Y=H, Z=Cl, R=Ph
10b Y=H, Z=OMe, R=Ph



5a
***Ph*BOX**

An important computational study was then undertaken with Arylid-BOX ligands **1c-1e**, **10a** (synthesis, section 2.2), **10b** (synthesis, section 2.2), and Evans' *Ph*BOX **5a**. This was undertaken to gain a better insight into this mechanism and the issue of alkene attack on the metallocarbene intermediate, and if the electrodonating groups (Cl, OMe) and their positions (*ortho* or *para*) in the phenyl ring had some inductive and resonance effects in the metallocarbene intermediate. This study could give some information about the mechanism and the issue of alkene attack on the metallocarbene intermediate. We carried out calculations of the fukui function (FF) at the DFT and Hartree Fock (HF) level of theory. The FF is one of the most common descriptors widely used to predict relative site reactivities[31,32] and in fact, has been used to provide a more solid theoretical base for the local HSAB principle.[13] The FF has been defined as the electron density derivative with respect to the electron number, at constant external potential v(r) generated by the nuclei acting on the electrons,

$$f(r)=\left[\partial\rho(r)/\partial N\right]_{v(r)} \quad (1)$$

where $\rho(\mathbf{r})$ is the ground state electronic density of the system at point r, and N is the total electron number.

Lee *et al.*[33] proposed the condensed FF indices,

$$f_k^+ \approx q_k(N+1)-q_k(N)$$
$$f_k^- \approx q_k(N)-q_k(N-1) \quad (2)$$
$$f_k^0 \approx q_k(N+1)-q_k(N-1)$$

where, the FF is condensed in the individual atoms. Here $q_k(N+1)$, $q_k(N-1)$ and $q_k(N)$ are the atomic populations of atom k in the $N+1$, N and $N-1$ electron systems. The

indice f_k^+ reflects the capacity of atom k to accommodate an extra electron and is the indice most suited for studies on nucleophilic attack. Lee *et al.* proposed that the higher FF values are related to increased reactivity at that site,

$$f_k^\alpha = \sum_{\mu \in k} f_\mu^\alpha \quad (3)$$

having

$$f_\mu^\alpha = \left|c_{\mu\alpha}\right|^2 + c_{\mu\alpha} \sum_{\nu \neq \mu} c_{\nu\alpha} S_{\mu\nu} \quad (4)$$

where $c_{\mu\alpha}$ is the frontier molecular orbital coefficients and $S_{\mu\nu}$ is the overlap integral between the atomic basis functions $\chi_\mu(r)$ and $\chi_\upsilon(r)$. Equation 3 gives the condensed FFs for electrophilic $(\alpha = -)$ and for nucleophilic $(\alpha = +)$ attack, whilst an average is considered for radical attack. With regard to the mechanism of the cyclopropanation reaction, based on the literature, the metallocarbene is an electrophilic intermediate, for this reason the f_k^+ values of the carbenoid carbons were calculated in order to try and correlate the reactivity, or even stereoselectivity with the f_k^+ value.

Table 1. Condensed Fukui f_k^+ functions for the C11 or C12 carbenoid carbon of the metallocarbenes **17-22** and results for CACP of styrene.[a]

Entry	Ligand (mol%)	Metallo-carbene	Atom	FF (f_k^+)	Yield (%)	ee (*cis*) (%) (1*R*, 2*S*)[b]	ee (*trans*) (%) (1*R*, 2*R*)[b]
1[1]	**1c** (2.2)	**17**	**C12**	0,654	76	54	60
2[1]	**1e** (2.2)	**18**	**C12**	0,644	75	43	48
3	**10a** (2.2)	**19**	**C12**	0,657	60	50	56
4[1]	**1d** (2.2)	**20**	**C12**	0,655	45	55	61
5	**10b** (2.2)	**21**	**C12**	0,644	100	41	50
6[36]	**5a**[c] (0.8)	**22**	**C11**	0,657	98	54	66

[a] $CuPF_6$ (2 mol%)

[b] The major isomer is indicated in parenthesis;

[c] Cu(OTf)(I) (0.4 mol%)

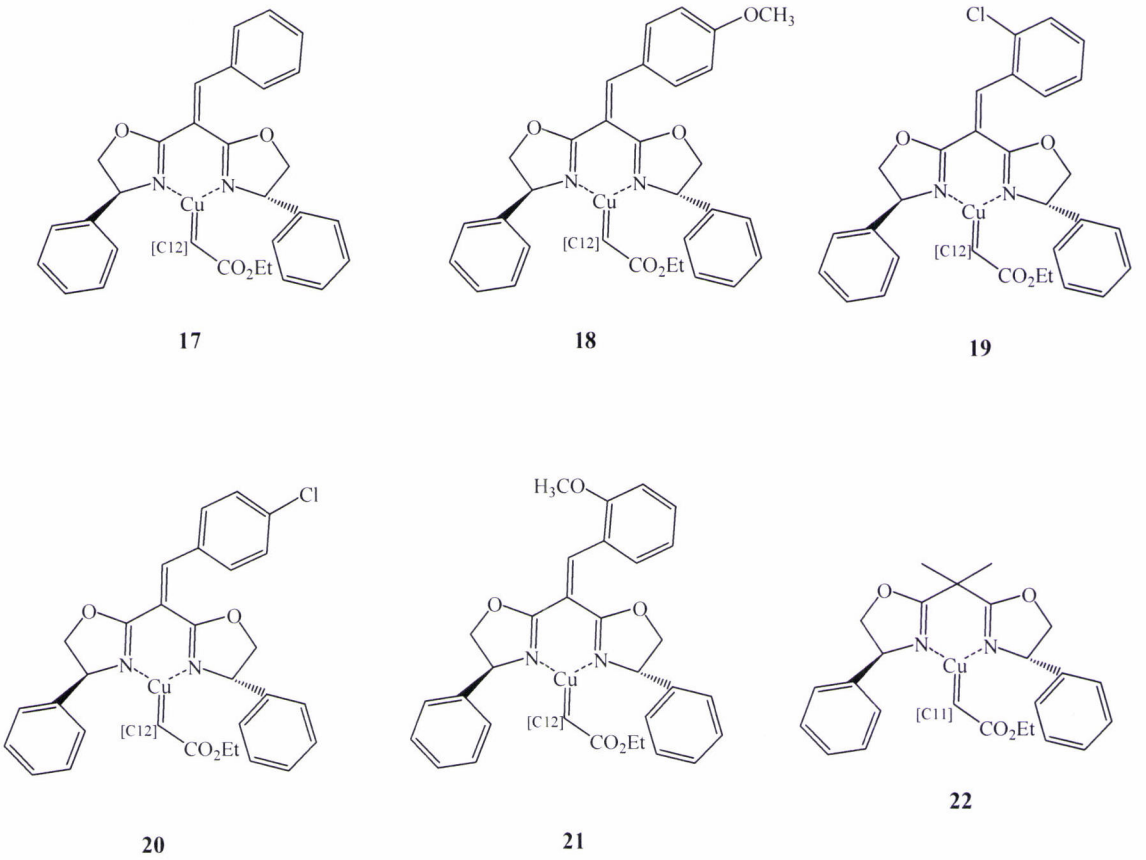


Figure 7. Arylid-BOX metallocarbenes **17-22**.

We were particularly interested in clarifying where the preferential (if any) site of nucleophilic attack by the alkene (electron rich) on the metallocarbene **17-22** intermediate would occur (Figure 7) and therefore have calculated the FF values for these molecules knowing that nucleophilic addition should preferentially occur at the carbon atom with the highest f_k^+ value. The calculated f_k^+ values are shown in Table 1, for the electrophilic carbenoid carbon (C11 or C12) of all metallocarbenes **17-22**.

The geometries of the molecules **17-22** have been fully optimized with both at HF and DFT calculations (Figure 8). The stationary points were subsequently confirmed to be minima by frequency calculations carried out at those levels. For the initial geometry optimization was used the PM6 method, DFT calculation were carried out on all metallocarbenes. The B3LYP[34,35] exchange correlation functional has been used. The Lan12DZ effective core basis set was employed for the metal atom while the 6-31G** basis-set was used for all the other atoms.

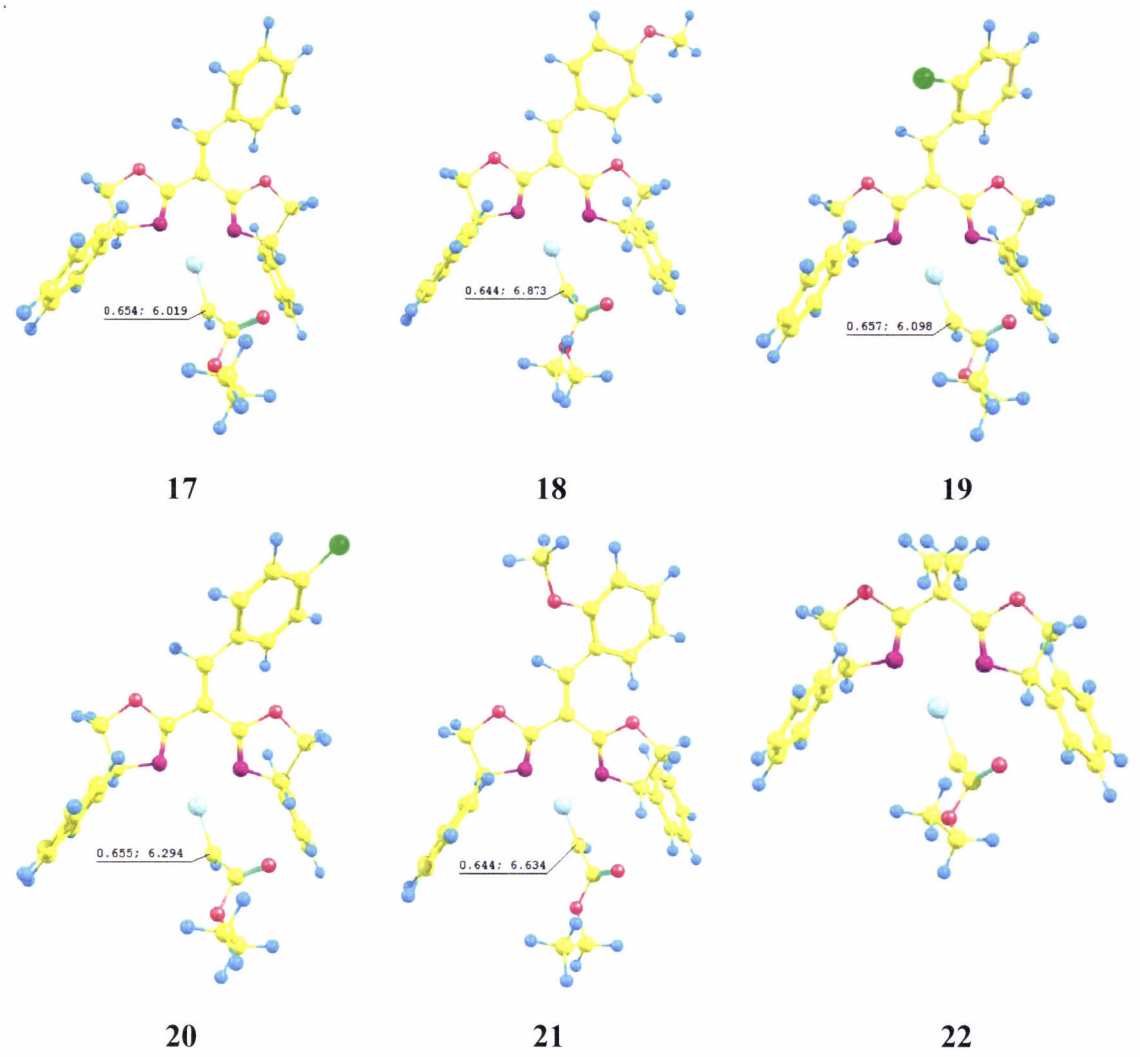
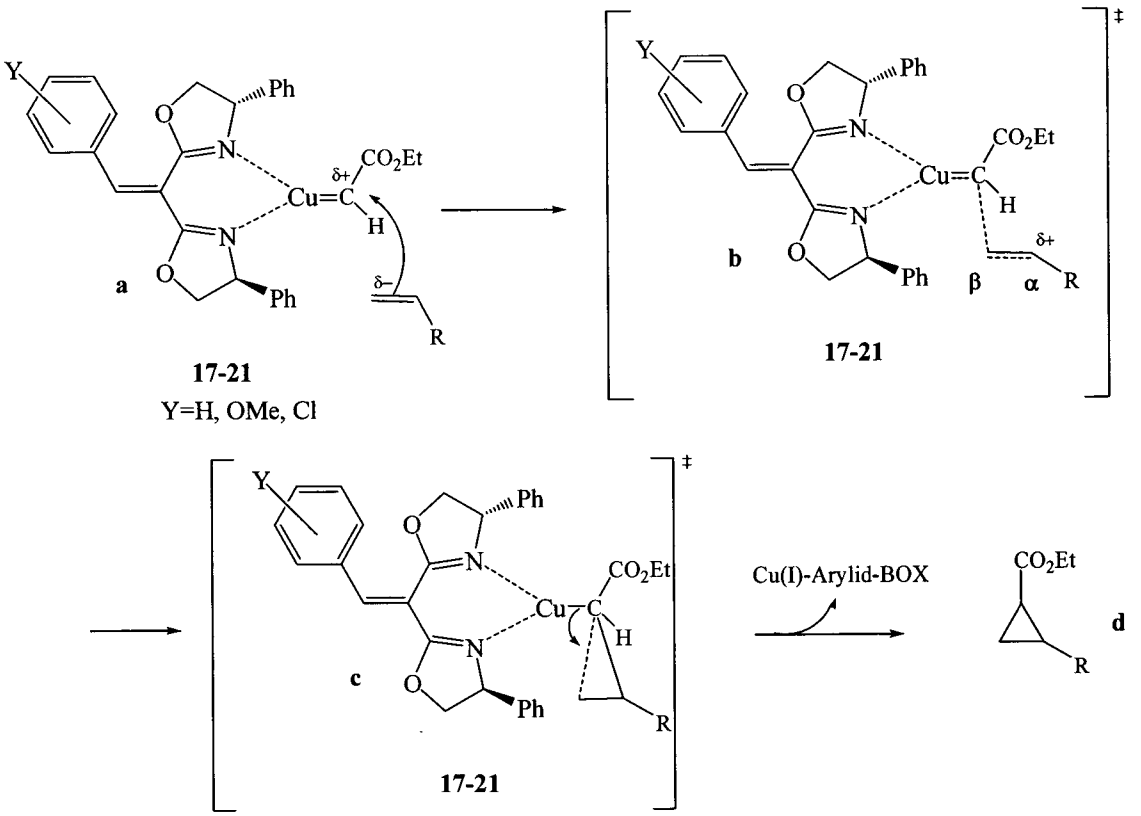


Figure 8. Calculated structures for the metallocarbenes **17**-**22**.

By analyzing these computational calculations, it can be seen that the f_k^+ values for the C11 or C12 carbenoid atom of all the metallocarbenes are very similar, and the differences are very small. This is in fact, in agreement with the experimental results that were obtained (see Section 2.3 for the full experimental conditions, Table 2). In conclusion, these calculations seem to show that the electrodonating group does not show any inductive and resonance effects in the metallocarbene intermediates.

In Scheme 3 a proposed mechanism is depicted. Species **a** is formed by the nucleophilic attack of the Cu(I)-Arylid-BOX catalyst on the α-diazo ester affording the metallocarebene intermediates (**17-21**). On the basis of the theoretical study undertaken by Rasmussen *et al.*[8] we have considered that the transition state **b** should result from an open addition, and the covalent bond to the β-carbon is formed before the covalent bond to the α-carbon (greater cationic character). This in turn leads to the second

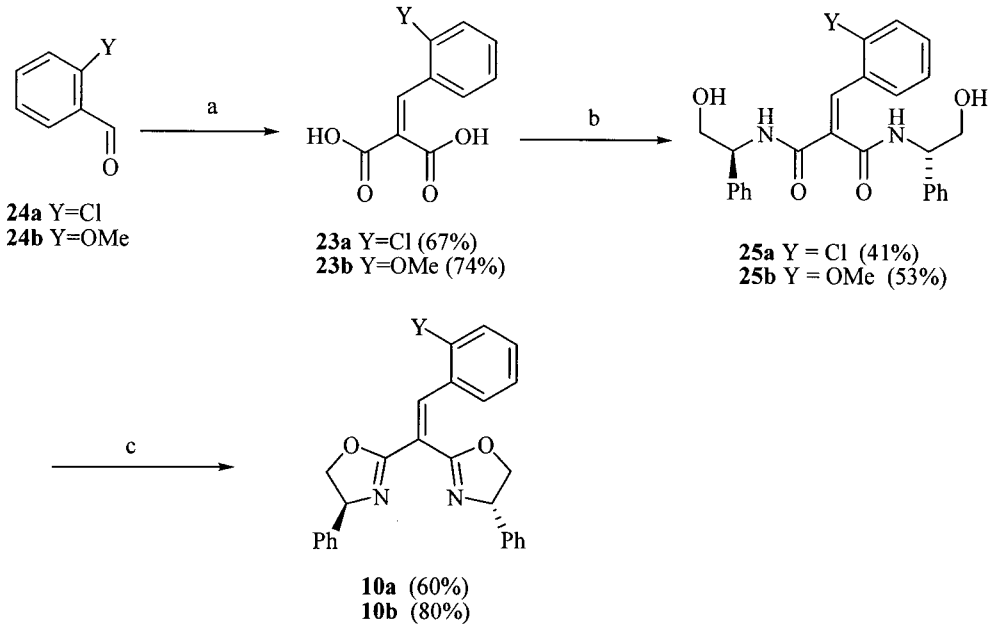


Scheme 3. Proposed reaction mechanism based on literature precedent.[8]

transition state, c which soon afterwards dissociates to give the cyclopropane **d**. Rasmussen *et al.*[8] described this mechanism by the following phrase: *"concerted but very asynchronous addition of the metallocarbene to the alkene"*.

2.2 Syntheses of Arylid-BOX ligands 10a and 10b

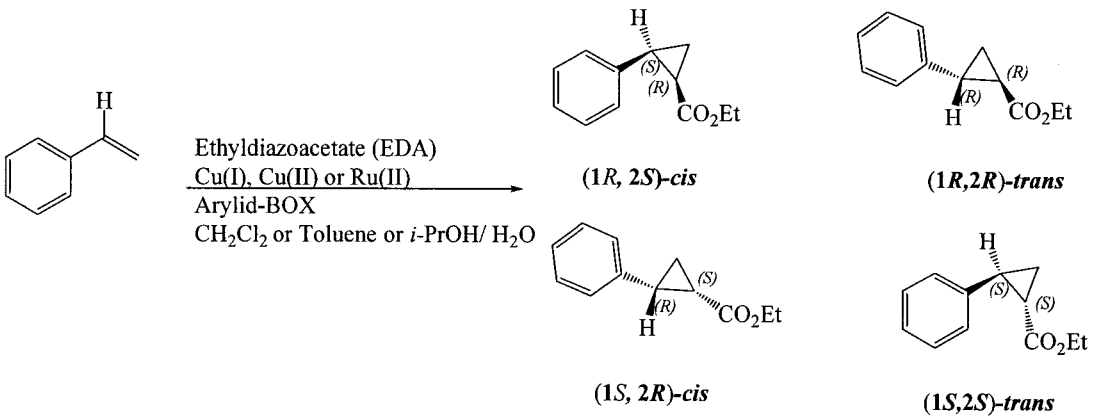
The Arylid-BOX ligands **10a** and **10b** were prepared in very good yields using the synthetic pathways shown in Scheme 4. For the synthesis of the Arylid-BOXs **10a** and **10b** arylidene malonic acids **23a** and **23b** were used (Scheme 4). These were obtained via the procedure of Neustadt *et al.*[30] using a simple Knoevenagel condensation with malonic acid and the respective aldehyde **24a** and **24b**. Our standard synthetic procedure[2,4] was subsequently used to transform the acids to the corresponding ligands. Satisfactory yields could be obtained in all cases.



Scheme 4. *Reagents and Conditions:* (a) Malonic acid, 70 °C (b) $(COCl)_2$, DMF, CH_2Cl_2, 0°C; (*S*)-(+)-Phenylglycinol, NEt_3, CH_2Cl_2, (c) CH_3SO_2Cl, NEt_3, CH_2Cl_2.

2.3 Catalytic Asymmetric Cyclopropanation

The Arylid-BOXs **10a** and **10b** were evaluated in the CACP of styrene with EDA and three different pre-catalyst, such as: Cu(I)OTf, Cu(I)PF_6 and $[RuCl_2(p\text{-cymene})]_2$ (Scheme 5).



Scheme 5. Catalytic asymmetric cyclopropanation of styrene – benchmark reaction.

2.3.1 Cu(I)-Bis-Arylid-BOX Catalysis

Arylid-BOXs **10a** and **10b** were tested in catalytic asymmetric cyclopropanations with Cu(I) (Table 2). Ligand **10a** gave the highest ee using $[Cu(MeCN)_4]PF_6$ as the pre-catalyst (Table 2, entry 2, 56% *trans*-isomer), but it was the catalyst formed from **10b** which gave the better yields. This is most likely due to the presence of the electron donating group in the *ortho* position. The des were only moderate, a maximum of 40% being obtained with both **10a** and **10b**. We tested ligand **10b** with toluene, using $[Cu(MeCN)_4]PF_6$ (Table 2, entry 5), but there was only a slight increase in the ee for the *cis* isomers. The chemical yield had greatly decreased in relation to using CH_2Cl_2 (24% as opposed to 100 % with CH_2Cl_2). On comparing the results obtained using both **10a** and **10b** with those found for their *para*-substituted counter-parts[1] ($[Cu(MeCN)_4]PF_6$ as the pre-catalyst) it can be seen that the ees are better for the *para*-substituted ligands (53 and 61% for both the *cis* and *trans* isomers - *para*-chloro substituted ligand, and 41 and 48% - *para*-methoxy substituted ligand). The des obtained with **10a** and **10b** were slightly higher than those of their *para*-substituted counterparts, which were about 30%. In the case of the *ortho*-substituted ligands the des were between 30 and 40%. However, the yields using the *ortho*-substituted ligands were better.

In most cases the quantity of maleate/fumerate side products (dimers) was less than that encountered with the Arylid-OX based Cu(I) catalysts (Chapter 2).

Table 2. Catalytic asymmetric cyclopropanation of styrene using Cu(I)-**10a** and Cu(I)-**10b**[a]

Entry	Ligand (mol%)	Pre-catalyst (mol%)	Yield[b] (%)	*cis:trans*[c]	*cis* (ee %)[c,d] (1*R*, 2*S*)	*trans* (ee %)[c,d] (1*R*, 2*R*)	Ratio Cyclopropanes: dimers[c]
1	**10a**(2.2)	Cu(I)OTf(2)	19	32:68	38	49	81:19
2	**10a**(2.2)	$CuPF_6$(2)	60	30:70	50	56	95:5
3	**10b**(2.2)	Cu(I)OTf(2)	100	34:66	10	10	99.5:0.5
4	**10b**(2.2)	$CuPF_6$(2)	100	31:69	41	50	95:5
5[e]	**10b**(2.2)	$CuPF_6$(2)	24	30:70	48	35	97:3

[a]Styrene (4 eq), chiral ligand, Cu(I) pre-catalyst, ethyl diazoacetate (1eq), CH_2Cl_2, rt, 24h.

[b]Determined by gas chromatography using di-n-buthylether as the internal standard.

[c]The %ee was determined by GC.

[d]The major isomer is indicated in parenthesis.

[e]Solvent was toluene, 40°C.

2.3.2 Ru(II)-catalyzed asymmetric cyclopropanation in aprotic, protic and biphasic media

Some CACPs of styrene with ligand **10b**, $[RuCl_2(p\text{-cymene})]_2$, EDA and either DCM or Toluene, including biphasic media (toluene with *i*-PrOH or water) were carried out. The results are shown in Table 3. The complexation was made *in situ*, following the method of Nishiyama *et al.*[19a,b], but, two important changes were made; Nishiyama *et al.* used (+ and -)-menthyl diazoacetate with PyBOX as the ligand!

Table 3. Asymmetric cyclopropanation of styrene with ethyl diazoacetate (EDA) using Arylid-BOX **10b** and $[RuCl_2(p\text{-cymene})]_2$[a]

Entry	Initial solvent (mL)	EDA Solvent (mL)	t (h)	Yield[b] (%)	*cis:trans*[c]	*cis* (ee %)[c,d] (1*S*, 2*R*)	*trans* (ee %)[c,d] (1*S*, 2*S*)	Ratio Cyclopropanes: dimers[c]
1	CH_2Cl_2 (3)	CH_2Cl_2 (1)	47	10	56:44	61	0	22:78
2	Toluene (3)	Toluene (1)	37	2	56:44	51	12	24:76
3	Toluene (1.5) + *i*PrOH (1)	Toluene (1)	47	9	67:33	80	5	48:52
4	Toluene (1.5) + H_2O (1)	Toluene (1)	47	11	79:21	89	26	65:35

[a]Styrene (5 eq), Chiral ligand **10b** (7 mol%), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol% of Ru), solvent, 40 °C, EDA (1 eq).

[b]Determined by gas chromatography using di-n-buthylether as the internal standard.

[c]The %ee was determined by chiral GC analysis.

[d]The major isomer is indicated in parenthesis.

The results obtained with this catalyst were very surprising, in that in the homogeneous phase, a 61% ee was achieved for the (1*S*, 2*R*)-*cis*-cyclopropane whilst the *trans*-cyclpropane was obtained as a racemic mixture using CH_2Cl_2 (Table 3, entry 1) but the de, yield and selectivity were very poor. The CACP with toluene gave similar results.

The reactions in aqueous biphasic media were conducted on the basis that it should have been possible to recover and recycle the catalyst, as it would remain in the aqueous phase.[19a] Catalyst recovery was not investigated because of the low yields. Gratifyingly an ee as high as 89% for the *cis*-cyclopropane was obtained with toluene/H_2O, a highest de of 58% was also obtained, but, unfortunately the yield and selectivity were poor. The CACP with toluene/*i*-PrOH, gave a slightly lower ee for the *cis*-cyclopropane product and a much lower ee for the *trans*-cyclopropane. The de was only 34% and the yield and selectivity were quite poor in comparison to the reaction in

toluene/water. The production of dimers (fumarate/maleate) decreased in the biphasic reaction media.

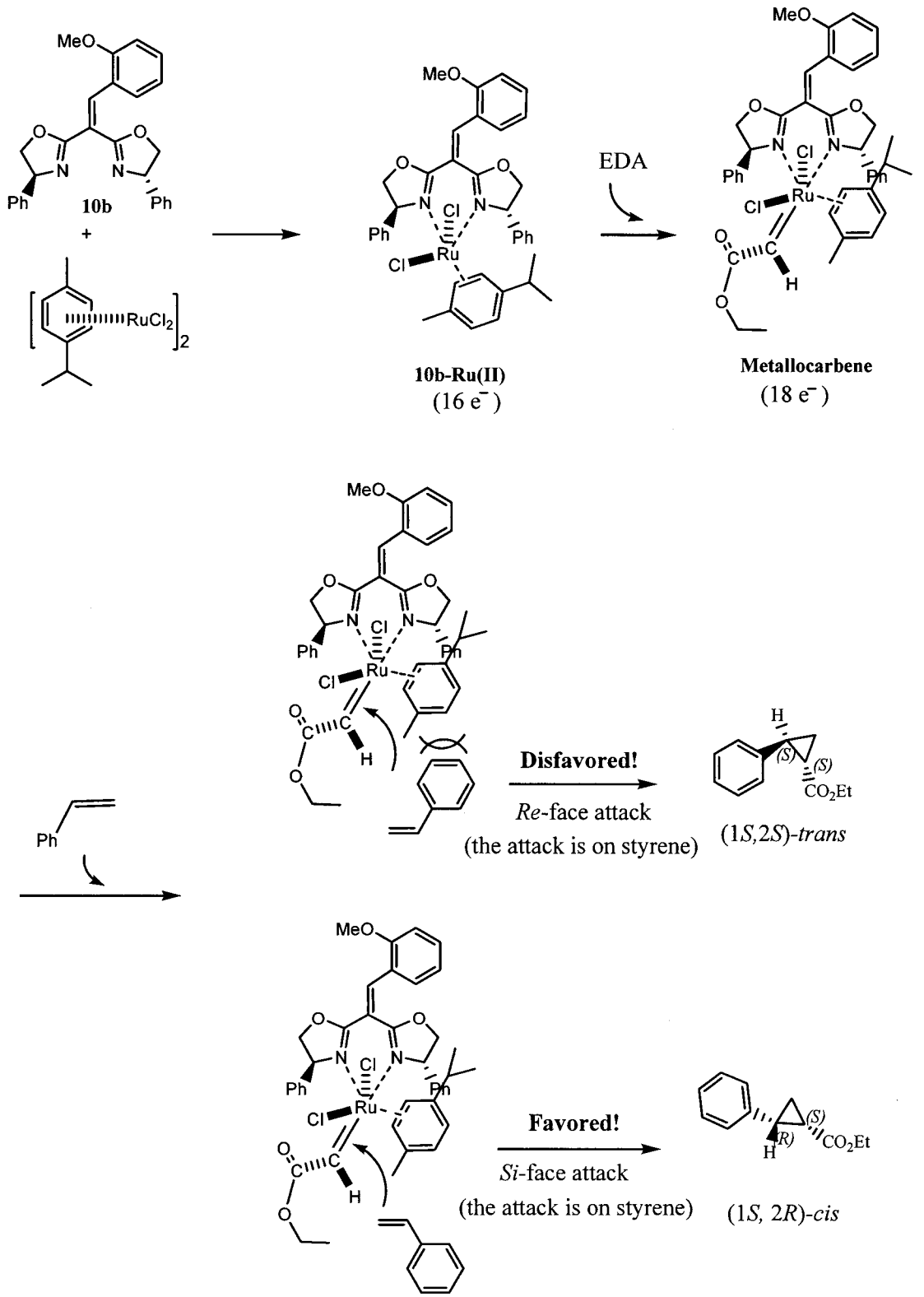
The results obtained in CH_2Cl_2 were inferior to those results obtained by Nishiyama *et al.*,[16] however, what was gratifying was the change to the *cis*-cyclopropane as the major diasteroisomer. In the case of toluene, Nishiyama *et al.*[19a] obtained a better ee (28%) for the *cis*-cyclopropane (with *d*-menthyl diazoacetate), like in this work. Our enantioselectivity was better; although the yield was poorer.

The best results were obtained when some water was present, there are two possible explanations for this effect: 1) carbene transfer is more rapid in water and/or 2) the reaction occurs under micellar or hydrophobic conditions forcing the metallocarbene to react with the styrene.[35]

Some authors have reported a decrease in the enantioselectivity in the cyclopropanation reaction in water.[36] The results obtained in this PhD project should prompt further research with these Ru(II)-bis(oxazoline) bidentate catalysts in biphasic aqueous media and other reaction media, in the future.

Regarding the mechanism, based on the work of Nishiyama *et al.*[15a] *Si*-face attack of alkene to the metallocarbene on its *Re*-face was preferred (Scheme 2) favoring the *trans*-cyclopropane product with configuration (1*R*, 2*R*). However, in our case it was the *cis*-cyclopropane with the (1*S*, 2*R*) configuration that was favored. A working model to explain the selective formation of the cyclopropane is shown in Scheme 6. It is postulated that due to the geometry of the metallocarbene complex formed using the Arylid-BOX ligand, and due to steric hindrance on the approach of the styrene, *Si*-face attack of the metallocarbene on styrene is preferred (Scheme 6). The cymene ligand also could block the *Re*-face of the metallocarbene. On looking at Nishiyama (Scheme 2) and our (Scheme 6) working models, it was noticed that the [Ru(II)Cl_2cymene**10b**] complex could be formed with 16 electrons, considering the cymene ligand was coordinated by one double bond. In the case of Nishiyama this situation didn't happen because they had tridentate ligand and also they introduced a ethene ligand (η^2) in solution. This ligand has less steric hindrance that the cymene ligand. Consequently, our complex should be rather accessible for forming the metallocarbene during the reaction, and this could explain the lower yields that were obtained. Nishiyama *et al.*[15a] didn't have this problem, because they had a more accessible complex for forming quickly the metallocarbene, this could explain their better yields. Some authors obtained preferentially *cis*-cyclopropanes with half-sandwich Ru(II) catalysts, and they

considered the mechanism should proceed via a metallocyclobutane intermediate.[17] However, there has only been reported a few examples on the isolation and characterization of metallocyclobutanes intermediates as they are very unstable species and thus mechanistic pathway is probably unlikely.[17]

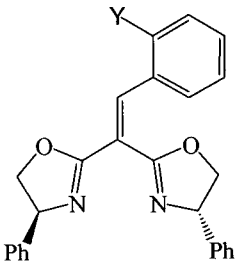


Scheme 6. Working model proposed for the formation of the *cis*-cyclopropane (1*S*, 2*R*).

2.4 Noncovalent Immobilization of Arylid-BOX-Copper Catalysts

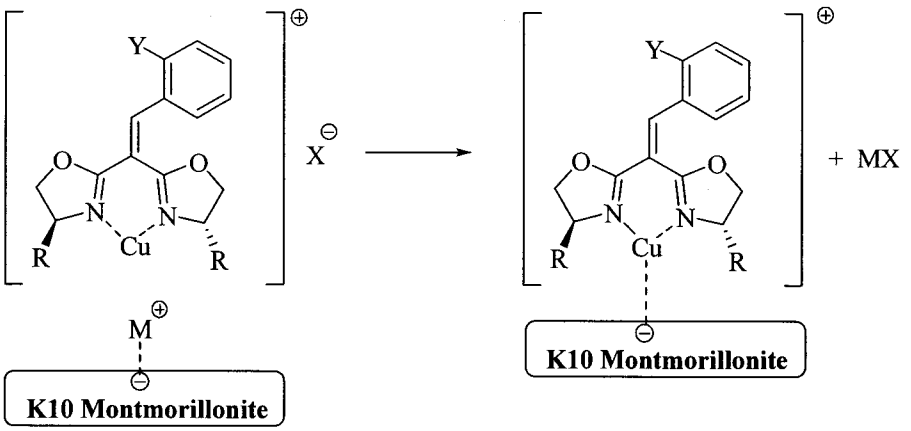
2.4.1 Electrostatic Interactions

Arylid-BOX-Copper complexes immobilized by ion exchange on MK10



1c Y=H
10b Y=OMe

Arylid-BOX **1c** was prepared following our procedure.[2,4] The chiral complex was obtained using an equimolecular amount of $Cu(OTf)_2$ and the ligand **1c** in dry dichloromethane. The ion exchange was carried out by stirring a suspension of the non-activated MK10 (MK10 was used without any acid treatment) in dichloromethane (Scheme 7). The quantity of Cu and ligand (mmol of N) immobilized on the MK10 was analyzed by both ICP-OES and EA, respectively. In the case of ligand **10b**, it was complexed with $CuPF_6$ in dry dichloromethane. The ion exchange was carried out with MK10 (Scheme 7). Based on the analysis of the immobilized Cu on the MK10 support, the immobilization of **10b**-Cu(I)PF_6 **27** was more effective than for the **1c**-$Cu(OTf)_2$ **26** complex, despite the fact, that the same amount of complex was immobilized in 50 mg less MK10 support in the case of the latter complex and that the copper bore a +2 charge. Both **1c**-$Cu(OTf)_2$ MK10 and **10b**-$CuPF_6$ MK10 were screened in the heterogeneous benchmark cyclopropanation of styrene with EDA (Scheme 4 and Table 4).



M = Na, Mg, Ca
Y= H, OMe

Scheme 7. Ion-exchange of the Cu-complexes on MK10.

Table 4. Catalytic asymmetric cyclopropanation of styrene with **1c**-Cu(OTf)$_2$ **26** on MK10 and **10b**-$CuPF_6$ **27** on MK10

Catalyst type	cycle	Complex	Cu (mmol/g)	t(h)	Yield[a] (%)	ee[b] *cis* (%)	ee[b] *trans* (%)	*cis:trans*[b] (%)	Selectivity[b] (%)
Homogeneous	N/A	**26**	-	20	5	53	63	27:73	ND
Heterogeneous	1st		0.133[d,f]	45	31	65	62	32:68	88
Heterogeneous	2nd		-	45	18	47	46	38:62	74
Heterogeneous	3rd		-	47	6	42	38	49:51	48
Heterogeneous	4th		0.087[e,g]	47	3	42	39	42:58	16
Homogeneous[2]	N/A	**27**	-	24	100	41	50	31:69	90
Heterogeneous	1st		0.171[d,h]	45	22	39	45	34:66	66
Heterogeneous	2nd		-	45	14	26	37	40:60	64
Heterogeneous	3rd		-	47	5	19	22	38:62	42
Heterogeneous	4th		0.060[e,i]	47	7	16	18	45:55	34

[a] Determined by GC using di-n-buthylether as the internal standard.

[b] Determined by chiral GC analysis.

[c] Toluene was used as solvent.

[d] Determined by ICP-OES analysis before the 1st run.

[e] Determined by ICP-OES analysis after the 4th run.

[f] 0.296 mmol N/g determined by EA before the 1st run.

[g] 0.269 mmol N/g determined by EA after the 4th run.

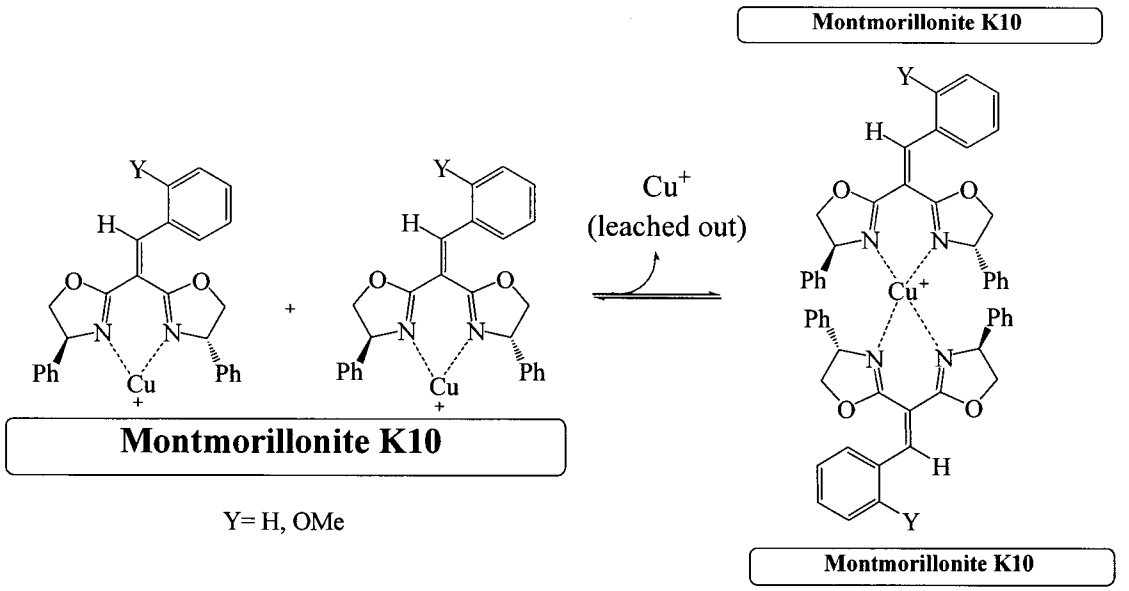
[h] 0.419 mmol N/g determined by EA before the 1st run.

[i] 0.289 mmol N/g determined by EA after the 4th run.

N/A (not applied)

Our goal was to compare the activity and selectivities of each immobilized catalyst with the same catalyst in the homogeneous phase. One should note that selectivity refers to the difference between cyclopropane products and maleate/fumarate

side-products. In terms of the enantioselectivity, it is obvious from these results that immobilized **26** gave slightly superior results to those obtained in the homogeneous phase. On going from the 1st cycle to the 2nd cycle there was a significant drop in both the enantioselectivities and yield. However, there was a significant deterioration in the results in the 3rd and 4th cycles. This we believe is a consequence of both (i) leaching of the catalyst from the support, as ICP analysis of the recovered support after the 4th cycle, revealed a 35% loss of catalyst and (ii) the fact that the loading of the catalyst used in the latter two cycles was less than the 1.6 mol% originally used. The quantity of nitrogen was determined in the MK10 immobilized **27** recovered after the 4th cycle by elemental analysis and this seemed to indicate that it was only the Cu that was being leached out and not the full catalyst, as the quantity of nitrogen remained more or less constant. This unexpected result might be a consequence of the formation of a putative tetra-complex, which would be expected to be less active furnishing low yields (see Scheme 8). In fact, a recent paper by Reiser's group has also suggested the inactivity of certain tetra-complexes.[37]It is not known for sure the reason for the formation of this putative complex, but perhaps subtle surface effects might have a role in its formation. Besides this, and although no study was conducted to confirm the actual positioning (location) of the Cu-catalyst on the solid support, perhaps the catalysts were immobilized in the pores of the support and only the smaller Cu ions could be leached out whilst the ligand remained trapped. The *cis*-cyclopropane increased relative to the *trans*-isomer on going from the 1st to the 3rd cycle, but from the 3rd to 4th it decreased by 7%. Curiously, the *cis*-cyclopropane had a better ee than the *trans*-cyclopropane in these reactions. Mayoral's group have reported a similar result in the case of analogous BOX derived Cu catalysts on other Clay supports.[38] Mayoral and co-workers have proposed a working model to explain this phenomenon, which involves key stereochemical interactions between the catalyst and the reagents.[39] It was hypothesized that potentially important steric effects between the surface and the incoming alkene enable the transition state leading to the *cis*-cyclopropane product to be freer from steric interactions.



Scheme 8. Putative equilibrium between the di-coordinate and the tetra-coordinated copper complexes due to possible surface effects.

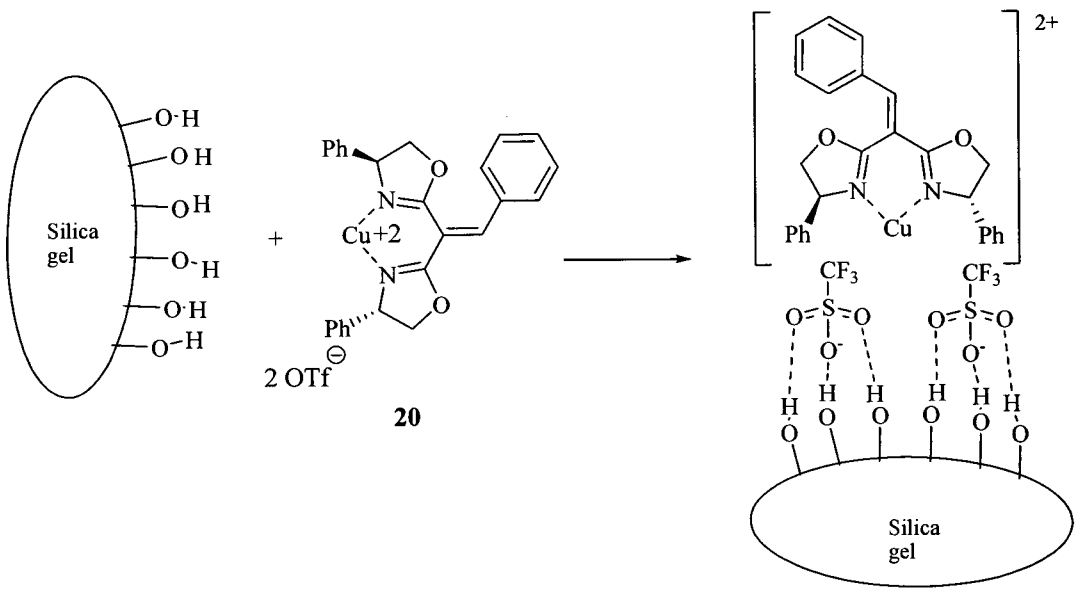
In the case of immobilized catalyst **27** the ees are similar but quite inferior in the 1st cycle in relation the homogeneous catalyst, and decreased in the 2nd cycle. Two more cycles was carried out, but the yields were mediocre and the ees decreased. This is perhaps more a consequence of the type of counter-ion used and its effect on the positioning of the catalyst within the clay layers. However, there was more leaching of the catalyst during the four cycles using **27** which might imply that the catalyst remains nearer the solid-liquid interface. The catalytic asymmetric cyclopropanation with heterogeneous catalyst **27** using styrene was carried out with 2.05 mol% of catalyst, practically, the same amount that was used in the original homogeneous catalysis (2 mol%). The enantioselectivity was lower using this immobilized catalyst than for the latter homogeneous catalytic system. The results obtained for the 1st cycle were very close to those obtained in the homogeneous reaction, the main difference was the higher yield obtained in the heterogeneous phase, this is accounted for on the basis of the reduced level of maleate/fumarate side-product synthesis in the case of the heterogeneous reaction. With this immobilized catalyst we observed once again, that the yield and the stereoselectivities drop from one cycle to the next. The most likely reason for this, is catalyst leaching from the support as there was a 65% loss of catalyst on going from the first cycle to the 4th. There was also a gradual increase in the proportion of *cis*-cyclopropane produced on going from the first to the 2nd cycle.

The elemental analysis of the recovered support after the 4th cycle, revealed the proportion: Cu:ligand was 1:2.4, obviously implying the existence of a tetra-coordinated complex which should be less active than the original di-cordinated complex (Scheme 8).

2.4.2 Immobilization *via* Hydrogen Bonding

Arylid-BOX-Cu(II) complex immobilization by hydrogen bonding on SiO_2

1c-Cu(OTf)$_2$ **26** in dicloromethane was immobilized onto silica-gel using the expeditious method introduced by Van Koten[28] (Scheme 9). The electrostatically immobilized catalyst was tested in the benchmark catalytic asymmetric cyclopropanation (Scheme 4) using both dichloromethane and toluene as solvents (Table 5).



Scheme 9. Schematic representation for the immobilization of **1c**-Cu(OTf)$_2$ **26** on silica-gel.

Table 5. Catalytic asymmetric cyclopropanation of styrene with complex **26** immobilized on SiO_2.

Catalyst type	Cycle	Solvent	Cu[a] (mmol/g)	Yield[b] (%)	ee[c] *cis* (%)	ee[c] *trans* (%)	*cis:trans*[c] (%)	Selectivity[c] (%)
Homogeneous	N/A	CH_2Cl_2	-	5	53	63	27:73	ND
Heterogeneous	1st		-	19	46	38	34:66	60
Heterogeneous	2nd		-	30	45	46	36:64	74
Heterogeneous	3rd		0.053	37	35	23	40:60	82
Homogeneous[d][1,2]	N/A	Toluene	-	25	39	47	35:65	ND
Heterogeneous[d]	1st		-	25	43	50	41:59	72
Heterogeneous[d]	2nd		0.045	11	43	19	39:61	70

[a] Determined by ICP-OES analysis after the respective run;

[b] Determined by mass quantification;

[c] Determined by chiral GC analysis;

[d] The temperature was 40 °C.

N/A (not applied)

In the case of the reactions run in dichloromethane, the enantioselectivity was lower in the case of the supported reactions, although the yields increased from the first to the third cycle. There was also a gradual increase in the amount of *cis*-cyclopropane produced on going from the homogeneous phase to the last cycle. In this case, the quantity of maleate/fumarate side-product increased on going from the first cycle to the third cycle. There was significant leaching in this case, as can be seen from the 81% reduction in immobilized Cu from the first cycle to the third (it was estimated that there was initially 0.28 mmol of Cu immobilized on the support).

When toluene was used, the enantioselectivity obtained in the first run was slightly better than that obtained in the homogeneous phase. Although, the enantioselectivity and the yield of the *cis*-cyclopropane were constant in the first and second cycles, the enantioselectivity of the *trans*-cyclopropane and its yield dropped drastically in the second cycle. There was an increase in the formation of the *cis*-cyclopropane using this support. Once again there was significant leaching in the order of 84%. Unfortunately, no analysis of the ligand by elemental analysis was conducted in order to determine if tetra-complex formation may have occurred.

3. Conclusions

The Arylid-BOX ligands **10a** and **10c**, were evaluated in the CACP reaction using Cu(I) and Ru(II). Ru(II) gave better ees than Cu(I), but lower yields and high

levels of fumarate/maleate formation. However, this was the first time that Ru(II) was coupled with bis(oxazoline) ligands (bidentate ligands), protic solvents and biphasic systems. Some surprising results were obtained in that an ee as high as 89% could be obtained for the *cis*-isomer, which is contrary to the literature reports using PyBOX-Ru(II) catalysts.

Some Fukuii Function values were calculated for the metallocarbenes **17-22** in order to try and correlate the electronic structure of the catalyst with catalytic reactivity and stereoselectivity. No significant correlations were observed and this was probably due to the operation of very weak inductive and resonance effects.

The immobilization of **26** by cationic exchange on MK10 was more effective than the immobilization of the same via electrostatic interactions on SiO_2.

On comparing MK10 immobilized **1c**-Cu(OTf)$_2$ **26** with the respective homogeneous catalyst it was the former that gave the better results in terms of enantioselectivity in the first cycle. The MK10 immobilized **10c**-Cu(I)PF_6 **27** gave lower ees than the homogeneous catalyst in the first cycle. However the two immobilized catalysts both suffered leaching from the support. The yields dropped off significantly in the third and fourth cycles, undoubtedly due to leaching and probably due to the formation of a putative tetra-coordinated complex, which was less active. There was a gradual increase in the production of the *cis*-cyclopropane as the number of cycles advanced, this was probably due to steric interactions with the solid support.

In the case of the electrostatically immobilized **1c**-Cu(OTf)$_2$ **26** complex on silica gel there was very significant leaching of the catalyst, particularly, when toluene was used as the solvent. However, the ees remained constant throughout despite there being once again a preference for the *cis*-cyclopropane.

4. Experimental Procedure

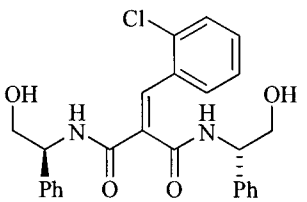
General remarks

(+)-Bis[(*S*)-4-phenyloxazoline-2-yl]-2-phenylethene **1c** was prepared following the previously described methods.[2,4] Solvents were dried using common laboratory methods.[40] All reagents were obtained from Aldrich, Fluka, Alfa Aesar or Acros. Column chromatography was carried out on silica gel (sds, 70–200 μm) and flash column chromatography (Merck, 40–63 μm and sds, 40-63 μm). TLC was carried out

on aluminium-backed Kisel-gel 60 F254 plates (Merck). Plates were visualized either by UV light or by phosphomolybdic acid in ethanol. The melting point was recorded on a Barnstead Electrothermal 9100 apparatus and was uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. The NMR spectra were recorded on either a Bruker AMX300 or a Bruker Avance 400 instrument. Mass spectra were recorded on a VG Autospec M(Waters-Micromass) spectrometer using the FAB technique and Waters-Micromass GC-TOF and MicroTOF Focus (Bruker Daltonics) using the TOF technique. Infra-red spectra were measured with a Perkin Elmer Paragon 1000 model. Gas chromatographic (GC) analyses of the products were performed on a Hewlett Packard (HP) 6890 series instrument equipped with a flame ionization detector (FID). The chromatograph was fitted with a cyclosil-B capillary column (30 m, 250 μm, 0.25 μm) (Agilent 112-2532). ICP-OES analysis was performed on a Perkin Elmer Optima 4300 DV at CACTI, Universidad de Vigo. EA analysis was performed on a EA 1108 CHNS-O Fisons instrument.

4.1 Synthesis of Arylid-BOX Ligands

(+)-(*S,S*)-*N,N'*-Bis(2-hydroxy-1-phenylethyl)-2-(2-chlorobenzylidene)malonamide 25a



25a

General Procedure for the synthesis of malonamides (25a, 25b): A dry two-necked round bottom flask (50 mL) equipped with a magnetic stir bar was charged with 2-(2-chlorobenzylidene)malonic acid **23a** (4.8 g, 21.0 mmol), dimethylformamide (0.23 mL, 2.94 mmol) and CH_2Cl_2 (30 mL). The solution was cooled to 0 °C, and oxalyl chloride (4.6 mL, 53 mmol) was added dropwise over 30 min and the solution was stirred at room temperature until the evolution of gas ended. The solution was evaporated in *vacuo* to give 2-(2-chlorobenzylidene)malonyl chloride as an yellow semi-solid (due to the unstable nature of this compound it was stored in the freezer at –10°C). Yield: 5.14 g (100%). A two necked round bottom flask (50 mL) fitted with a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (1.0 g, 7.30 mmol) and dry CH_2Cl_2

(20 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (1.27 mL, 9.13 mmol) was added via syringe. A solution of 2-(2-chlorobenzylidene)malonyl chloride (0.96 g, 3.6 mmol) in CH_2Cl_2 (5 mL) was slowly added via syringe to the vigorously stirred reaction mixture over 30 min. The ice bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was washed with 2M HCl (12 mL), saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (15 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give (*S,S*)-*N,N'*-bis(2-hydroxy-1-phenylethyl)-2-(2-chlorobenzylidene)malonamide **25a** as an yellow solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford the *title compound* **25a** as a white solid. Yield: 0.69 g (41%); mp 79 – 80 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, 1H, *J*= 8.1 Hz, N*H*), 7.88 (s, 1H, RC*H*=CR_2), 7.41 (d, 1H, *J*= 8.1 Hz, N*H*), 7.32 – 7.12 (m, 10H, C*H*(Ar)), 7.02 – 7.00 (m, 3H, C*H*(Ar)), 6.90 – 6.85 (m, 2H, C*H*(Ar)), 5.22 – 5.12 (m, 2H, C*H*), 3.93 – 3.62 (m, 4H, CH_2) ppm.

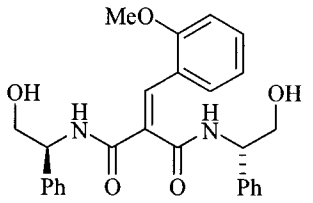
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.66, 164.43, 138.39, 137.59, 136.57, 134.35, 133.10, 131.78, 130.49, 129.83, 129.50, 128.80, 128.68, 128.56, 127.80, 127.70, 126.88, 126.72, 66.03, 66.43, 56.42, 55.98 ppm.

IR (KBr) υ_{max}: 3271, 3061, 3031, 2929, 2875, 1665, 1529, 1454, 1373, 1263, 1205, 1054, 1035, 951, 911, 839, 804, 756, 700, 637, 531 cm^{-1}.

$[\alpha]^{20}_D$ = + 62.23 (*c* = 1.03, $CHCl_3$).

TOF-MS *m/z*: 465.16 $[M+H]^+$; **HRMS** (TOF) found 465.15756, $C_{26}H_{26}N_2O_4Cl$ requires 465.15029.

(+)-(*S*,*S*)-*N*,*N'*-Bis(2-hydroxy-1-phenylethyl)-2-(2-ethoxybenzylidene)malonamide 25b



25b

The same procedure as described previously was used in the reaction of 2-(2-methoxy-benzylidene)malonyl chloride (0.95 g, 3.65 mmol) with (*S*)-phenylglycinol (1.0 g, 7.3 mmol) and dry triethylamine (1.27 mL, 9.13 mmol) to give (+)-(*S*,*S*)-*N*,*N'*-bis(2-hydroxy-1-phenylethyl)-2-(2-methoxybenzylidene)malonamide **25b** as a white solid after purification by column chromatography (silica gel, EtOAc); Yield: 0.884 g (53%). mp 130.2 – 131.7 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.4 (d, 1H, *J*= 7.8 Hz, N*H*), 7.95 (s, 1H, RC*H*=CR_2), 7.32 – 7.17 (m, 11H, C*H*(Ar)), 7.03 – 7.01 (m, 2H, N*H*, C*H*(Ar)), 6.72 – 6.66 (m, 2H, C*H*(Ar)), 5.20 – 5.13 (m, 2H, C*H*), 3.87 – 3.63 (m, 4H, CH_2), 3.55 (s, 3H, -OCH_3), 3.32 (sb, 1H, -O*H*), 2.06 (sb, 1H, -O*H*) ppm.

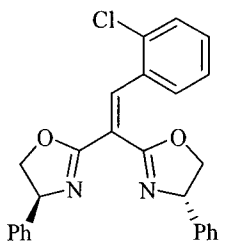
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.50, 164.77, 157.47, 138.65, 137.92, 136.51, 131.04, 130.70, 129.88, 128.65, 127.69, 127.63, 126.88, 126.71, 122.42, 120.50, 110.68, 66.46, 65.61, 56.37, 55.88, 55.14 ppm.

IR (KBr) υ_{max}: 3333, 32478, 3061, 2939, 2939, 2879, 2837, 1657, 1602, 1534, 1490, 1462, 1437, 1373, 1283, 1248, 1196, 1128, 1051, 1027, 901, 851, 753, 701, 637, 527 cm^{-1}.

$[\alpha]^{22}_D$ = +62.24 (*c* = 0.85, $CHCl_3$).

FAB-MS *m/z*: 461.27 $[M+H]^+$.

(+)-Bis[(*S*)-4-phenyloxazoline-2-yl]-2-(2-chlorophenyl)ethane 10a



10a

General Procedure for the synthesis of Arylid Box (10a, 10b): A solution of methanesulfonyl chloride (0.15 g, 1.3 mmol) in dry dichloromethane (1 mL) was added dropwise over 20 min to a solution of malonamide **25a** (0.2 g, 0.43 mmol) and dry triethylamine (0.36 mL, 2.58 mmol) in dry dichloromethane (10 mL) and the solution was stirred between −5 and −10°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude product. The crude product was purified by column chromatography (silica gel, EtOAc:Hex (1:2)) giving the (+)-bis[(*S*)-4-phenyloxazoline-2-yl]-2-(2-chlorophenyl)ethene**10a** as a white semi-solid. Yield: 0.11 g (60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1H, R_2C=C*H*R), 7.65 (d, *J*= 7.2 Hz, C*H*(Ar)), 7.45 – 7.18 (m, 12H, C*H*(Ar)), 5.47 (t, 1H, *J*= 9.3 Hz, C*H*), 5.35 – 5.29 (m, 1H, C*H*), 4.84 – 4.69 (m, 2H, CH_2), 4.27 – 4.18 (m, 2H, CH_2) ppm.

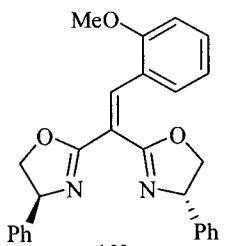
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.02, 161.36, 141.97, 141.70, 138.80, 132.83, 128.68, 128.54, 126.91, 126.73, 126.66, 120.82, 74.92, 70.33 ppm.

IR (NaCl, $CHCl_3$): υ_{max} 3031, 3017, 3011, 1672, 1639, 1494, 1473, 1455, 1409, 1356, 1261.55, 1230, 1210, 1182, 1021, 936, 790, 756, 666 cm^{-1}.

$[\alpha]_D^{20} = +50.26\,(c = 1.89, CHCl_3)$.

TOF-MS *m/z*: 429.13 [*M*+H]$^+$; **HRMS (TOF)** found 429.2073; $C_{26}H_{22}N_2O_2Cl$ requires 429.12916.

(+)-Bis[(*S*)-4-phenyloxazoline-2-yl]-2-(2-methoxyphenyl)ethene 10b



10b

Using the same procedure as described previously, malonamide **25b** (0.40 g, 0.87 mmol) was reacted with methanesulfonyl chloride (0.25 g, 2.17 mmol) and dry triethylamine (0.73 mL, 5.21 mmol) to give the (+)-bis[(*S*)-4-phenyloxazoline-2-yl]-2-

(2-methoxyphenyl)ethene **10b** as a white solid after crystallization with CH_2Cl_2/EtOAc/Hex. Yield: 0.29 g (80%); mp 167.0 – 168.0°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1H, R_2C=C*H*R), 7.60 (d, 1H, *J*= 6.6 Hz, C*H*(Ar)), 7.36 – 7.27 (m, 8H, C*H*(Ar)), 7.25 – 7.22 (m, 3H, C*H*(Ar)), 6.89 (t, 2H, *J*= 6.9 Hz, C*H*(Ar)), 5.48 - 5.32 (m, 2H, C*H*), 4.81 – 4.72 (m, 2H, CH_2), 4.26 – 4.18 (m, 2H, CH_2), 3.85 (s, 3H, -OCH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.63, 162.22, 156.81, 142.29, 142.00, 137.72, 129.41, 128.61, 128.49, 126.98, 126.74, 123.30, 120.35, 118.17, 110.68, 74.84, 74.81, 70.20, 70.10, 55.49 ppm.

IR (KBr) υ_{max}: 3057, 3025, 3002, 2973, 2941, 2908, 2853, 2605, 2496, 1677, 1633, 1597, 1577, 1489, 1468, 1450, 1403, 1355, 1318, 1300, 1251, 1201, 1176, 1114, 1018, 962.11, 937, 910, 757, 702, 642, 597, 526 cm^{-1}.

$[\alpha]^{20}_D$ = + 137.76 (*c* =0.94, $CHCl_3$).

TOF-MS *m/z*: 425.18 $[M+H]^+$.

HRMS (TOF) found, 425.18597; $C_{27}H_{25}N_2O_3$ requires 425.17869.

4.2 Homogeneous CACP

4.2.1 Cyclopropanations using $[Cu(OTf)]_2.(C_6H_6)$ and $[Cu(MeCN)_4]PF_6$ pre-catalysts

Pre-catalyst (0.014 mmol, 1 mol%) or (0.028 mmol, 2 mol%) was added to a two-necked round-bottomed flask containing the chiral ligand (2.1 – 6.3 mol%) in CH_2Cl_2 (1 ml) and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Alkene (14 mmol) and a solution of ethyl diazoacetate (0.159 g, 1.4 mmol) in CH_2Cl_2 (1 ml) or toluene (1 ml) was then added to the reaction mixture over a period of 16 h using a syringe pump. After the addition of ethyl diazoacetate, the mixture was stirred for 16 h. The reaction mixture was firstly passed through a short pad of silica gel (washed with CH_2Cl_2) to remove the catalyst complex, the products were then isolated by column chromatography (hexane/EtOAc 9:1). All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers, the ratio was determined using GC analysis. Isolated yields, diastereoselectivities, and enantioselectives are given in Table 2.

4.2.2 Cyclopropanations using Ru(II) Catalysts

$[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol, 2.5 mol%) was added to a two-neck round-bottomed flask containing the chiral ligand **10b** (0.035 mmol, 7 mol%) in solvent and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Styrene (2.5 mmol, 5 eq) and a solution of ethyl diazoacetate (0.057 g, 0.5 mmol) in solvent (1 ml) was then added to the reaction mixture over a period of 6 h using a syringe pump at 40°C. After the addition of ethyl diazoacetate, the mixture was stirred for several hours. Yields were determined by gas chromatography using di-n-butyl ether as the internal standard. All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers. Yields, diastereoselectivities, and enantioselectives are given in Table 3.

Heterogenization of Arylid-BOX-Copper(I) and Arylid-BOX-Copper(II) Catalysts

4.3 Immobilization of Arylid-BOX based catalysts on MK10

4.3.1. Immobilization of the Arylid-BOX-Copper Catalysts on MK10

Immobilization of (1)-$Cu(OTf)_2$ 26:

Arylid-BOX **1c** (20 mg, 0.05 mmol), $Cu(OTf)_2$ (18 mg, 0.05 mmol) and dry CH_2Cl_2 (3 mL) were added to a flask under nitrogen. The mixture was stirred for 2 h. The solvent was removed. Montmorillonite K10 (300 mg) was added to the complex (38 mg, 0.05 mmol) and dry CH_2Cl_2 (5 mL). The resulting suspension was stirred for 24h at room temperature. The solid was filtered, washed with CH_2Cl_2, and dried under vacuum. 279 mg of immobilized catalyst was obtained, which was calculated (ICP-OES analysis) to contain 0.133 mmol of Cu /g support or 0.296 mmol N/g support (as determined by EA).

Immobilization of 10b-$CuPF_6$ 27:

Using the same procedure as described previously, Arylid-BOX **10b** (25.5 mg, 0.06 mmol), $[Cu(MeCN)_4]PF_6$ (22.51 mg, 0.06 mmol) were dissolved in CH_2Cl_2 (3 mL). The resulting complex (36 mg, 0.05 mmol) was immobilized on MK10 (250 mg), after washing the immobilized catalyst with CH_2Cl_2 and dried thoroughly affording a final

dry weight of 227 mg. It was calculated to contain 0.171 mmol Cu/g support or 0.419 mmol N/g support (as determined by EA).

4.3.2. Heterogeneous Catalytic Asymmetric Cyclopropanation with the MK10 Supported Catalysts:

Application of 1c-Cu(OTf)$_2$ 26 immobilized on MK10

Ethyl diazoacetate (EDA) (0.032 mg, 0.28 mmol) was added to a mixture containing the immobilized (**1c**)-Cu(OTf)$_2$ catalyst (0.172 g, 0.0228 mmol, 1.6 mol %) under nitrogen in dry CH_2Cl_2 (4 mL). This was followed by the addition of styrene (580 mg, 5.6 mmol). The reaction mixture was stirred for 15 min followed by the addition of EDA (0.159 mg, 1.4 mmol) in CH_2Cl_2 (1 mL) via syringe pump over 6 h. The reaction was stirred for 45 to 47 h under nitrogen. The solid was filtered and washed with CH_2Cl_2 and EtOAc, the volatiles were then removed *in vacuo*. The crude product was analyzed by GC using di-n-butyl ether as the internal standard (Table 4). For the other runs the same procedure was used, however, due to the powdery nature of the supported catalyst, some catalyst was inevitably lost, however, although the quantity of supported catalyst used in the subsequent cycles was reduced, the proportions were always the same. In order to rapidly conduct these catalytic reactions it was assumed that there was negligible catalyst leaching.

Application of 10b-Cu(I)PF$_6$ 27 immobilized on MK10

To a mixture containing the immobilized **10b**-CuPF$_6$ catalyst (0.168 g, 0.0287 mmol, 2.05 mol %) under nitrogen in dry CH_2Cl_2 (4 mL) was added styrene (580 mg, 5.6 mmol). The reaction mixture was stirred for 15 min followed by the addition of EDA (0.159 mg, 1.4 mmol) in CH_2Cl_2 (1 mL) via syringe pump over 6 h. The reaction was stirred for 45 to 47 h under nitrogen. The solid was filtered and washed with CH_2Cl_2 and EtOAc, the volatiles were removed *in vacuo*. The crude product was analyzed by GC using di-n-butyl ether as the internal standard (Table 4). For the other cycles the same procedure was used.

4.3.3 Immobilization *via* Hydrogen bonding

Heterogeneous Catalytic Asymmetric Cyclopropanation with Silica-Gel Supported Arylid-BOX –Copper Catalysts:

A mixture of Arylid-BOX **1c** (11.8 mg, 0.03 mmol) and $Cu(OTf)_2$ (10.1 mg, 0.028 mmol) were dissolved in dry dichloromethane (2 ml) in a Schlenk tube under nitrogen and stirred for 30 min at rt. The catalyst complex solution was filtered and the filtrate was added to pre-dried silica gel (100 mg, 63-20 μm, dried for 1 h under vacuum at 70 °C) in a dry Schlenk tube under nitrogen. The mixture was stirred until the green colour had disappeared from the solution. The silica gel (which was coloured at this point), was allowed to settle and washed with dry dichloromethane (2 ml) then left under the appropriate dry reaction solvent (2 mL) and nitrogen. EDA (0.032 mg, 0.28 mmol) was added to the mixture containing the immobilized catalyst complex under nitrogen along with more dry solvent (1 mL), followed by styrene (580 mg, 5.6 mmol). The reaction mixture was stirred for 15 min followed by the addition of EDA (0.159 mg, 1.4 mmol) in an appropriate dry reaction solvent (1 mL) via syringe pump over 6 h. The reaction was stirred for over 91.5 h under nitrogen. The solvent layer was removed with a pasteur pipette and filtered through Celite, the remaining solid was then washed with dry solvent (2 x 5 ml) and the washings filtered under vacuum through Celite. The silica gel catalyst was left under a dry solvent (1 ml) and nitrogen for subsequent catalytic runs. The combined extracts were evaporated under reduced pressure to give the crude product as a colorless oil, which was purified by silica gel chromatography, (9:1, Hexane:EtOAc). The product mixture was analyzed by GC.

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Chapter 4

Synthesis and Immobilization of Arylid-BOX-Derivatives on Wang Resin: Catalytic Asymmetric Cyclopropanation

Abstract

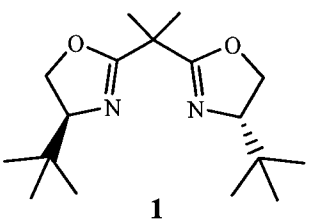
The aim of this work was to immobilize Arylid-BOX **18** on to a Br-Wang resin and use it in the catalytic asymmetric cyclopropanation of styrene with different Cu(I) and Cu(II) pre-catalysts and solvents, in order to find the optimal reaction conditions. The synthetic pathway furnished a novel Arylid-BOX-derivative **34** instead of the desired functionalized Arylid-BOX **19**. The evaluation of ligand **34** in the catalytic asymmetric cyclopropanation of styrene using Cu(I) gave a highest ee of 68%, a better result than that obtained for the Arylid-BOX **18a**. The ligand **34** was grafted to Wang resin, a loading of 0.321 mmol of ligand/g polymer could be obtained. $[Cu(MeCN)_4]PF_6$ or $Cu(OTf)_2$ were used in the CACP of styrene with CH_2Cl_2 or toluene as solvent. A highest ee of 71% was obtained and the catalyst was recycled and re-used up to 4 times. In the case of the heterogeneous CACP using $[Cu(MeCN)_4]PF_6$ and toluene, the yield, ees, des and selectivity were maintained over the four cycles. This heterogeneous catalyst was shown to be very similar to the homogeneous catalyst.

1. Introduction

The heterogenisation of chiral ligands by covalent bond formation is the most effective immobilization strategy overall. This strategy requires the functionalization of the ligand without changing the stereochemical configuration of the ligand. Two main classes of support are usually employed, (i) organic (polymeric) and (ii) inorganic (e.g. silica gel) supports. Over the last decade several research groups have developed a wide range of strategies for the immobilization of bis(oxazoline) ligands via covalent bond formation.[1,2] Immobilizations on organic polymer supports are more versatile and ligand polymerization

strategies are more practical thus leading to a large variety of immobilized catalysts based on the same chiral ligand motif.[2]

With regard to bis(oxazolines) an important goal was to immobilize Evans' *t*BuBOX[3] **1** ligand to a solid support and compare the heterogeneous version of the reaction with it's homogeneous counter-part.[4] Only a few examples of the covalent immobilization of these ligands using polymers, and their application in CACP were given. The first strategy for the immobilization of bis(oxazolines) on insoluble organic polymers was developed by Burguete *et al.*[5,6] The method consisted in functionalizing of the BOX **2** ligand with polymerizable groups (vinylbenzyl) with subsequent polymerization, either; homopolymerization or copolymerization with styrene and divinylbenzene (Scheme 1). They also introduced another method, by grafting onto a commercially available resin, like Merrifield resin.



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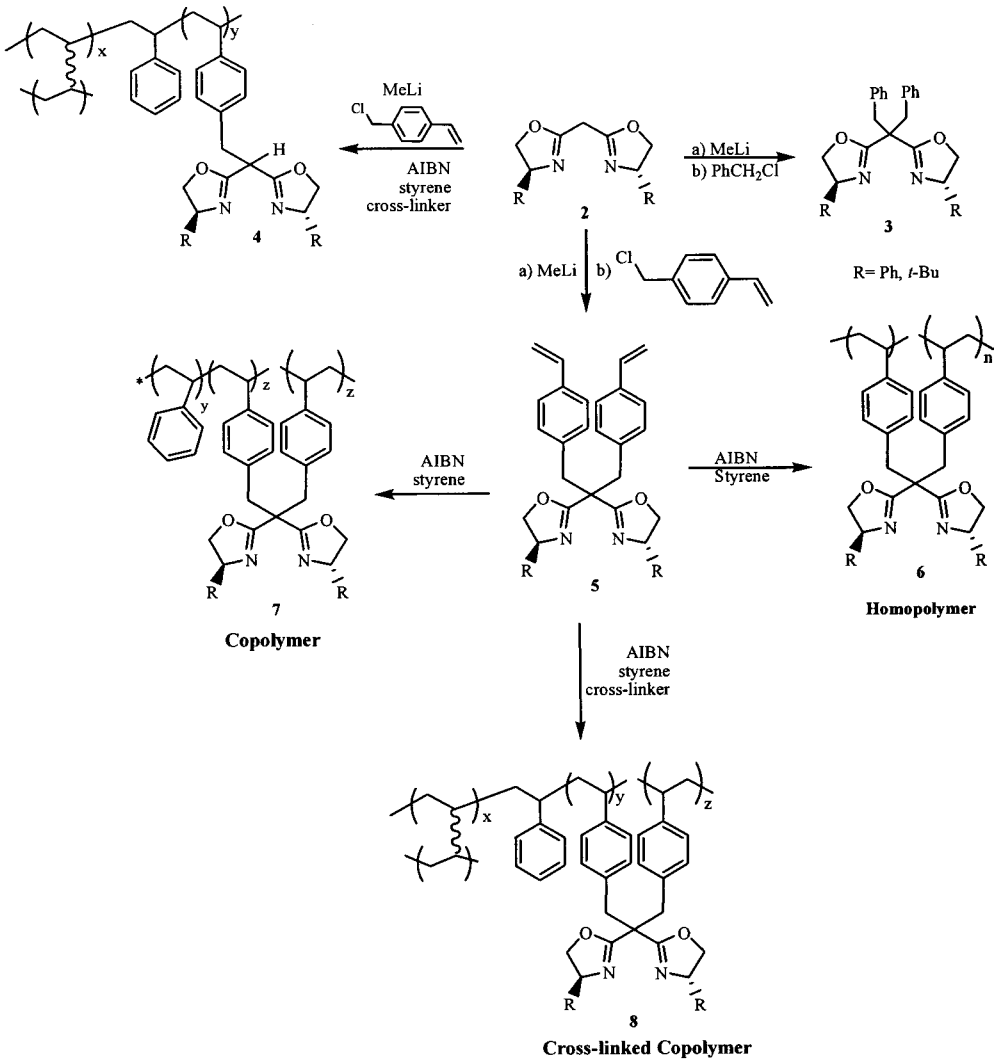
The best result obtained for the CACP of styrene was 70% ee for the homopolymer of the *t*BuBOX monomer **6**. This system could be reused up to five times without loss of enantioselectivity.[6] The homogeneous CACP of dibenzylated *t*BuBOX **3** (Scheme 1) gave the same enantioselectivity results. One of the problems of these BOX-containing polymers, even with copolymers present, was that most of the chiral ligand remains in the non-accessible core of the polymer, and does not participate in the catalysis. Thus, the catalytic activity of homopolymers and copolymers using different crosslinkers, and different proportions of the different monomers was investigated in the benchmark reaction using PhBOX-derived monomers.[7] Enantioselectivities similar to those found in the homogeneous phase were described for most of the polymers prepared, but more interesting, the ligand economy was much higher when using a dendrimeric cross-linker.



Scheme 1. Polymerization strategy for BOX immobilization.

As already mentioned, one of the drawbacks of the polymerization strategy is that the best ligand for enantioselective cyclopropanation reactions, i.e. the *t*BuBOX **1**, gives significantly lower selectivities when it is dibenzylated in the methylene bridge.[5] Another possible problem is that difunctionalized BOX monomers act as cross-linkers within the polymer, and this may affect the conformational preferences of the catalyst and hence its stereodirecting ability. One solution to these drawbacks was the monofunctionalization of the BOX monomer by other types of linker different from the benzyl group. However, Burguete *et al.*[6] synthesized monofunctionalized BOX **4** and evaluated it in the CACP of styrene, but the results were quite disappointing, only 11% yield and a maximum ee of only 33%. Salvadori's group[8] designed the immobilized BOX **10** with minimal steric hindrance at the methylene carbon, compared with the *t*BuBOX **1** used in homogeneous phase CACP. Excellent results were obtained in several cyclopropanation reactions with

several alkenes (like styrene, 2-methylpropene and 1,1-diphenylethylene) and ethyl diazoacetate using a highly cross-linked material (obtained from styrene and divinylbenzene co-monomers). Enantioselectivities of over 90% ee, identical to those found in the homogeneous phase were obtained. Furthermore, the catalyst was recoverable up to four cycles without loss of selectivity.

Regarding grafting strategies, modification of BOX **2** (Scheme 2) in the methylene bridge allows attachment through a single linker. Knight and Belcher[9] developed a synthesis for the immobilized BOX **17** starting from the diester **13** (Scheme 2). This compound was transformed into the dihydroxyamide **14** which was cyclized to give the bis(oxazoline) **15**. Desilylation of **15** furnished the respective alcohol **16**. This ligand was grafted to a Wang resin, giving **17**, and the corresponding immobilized catalysts were tested in the benchmark styrene cyclopropanation reaction. Only modest enantioselectivities (*ca.* 60% ee) were obtained with the *t*BuBOX **17** immobilized ligand. These results were inferior to those obtained in the homogeneous phase, even with a structurally related ligand.

Regarding solid phase asymmetric catalysis with BOXs: AzaBOX ligands **11** and **12** present some attractive advantages over BOX ligands **9-11** (Figure 1) and **17** (Scheme 2). Firstly, they have a very good attachment point in the bridge between the rings, and secondly, their copper complexes are more stable, which is desirable for a better recoverability.

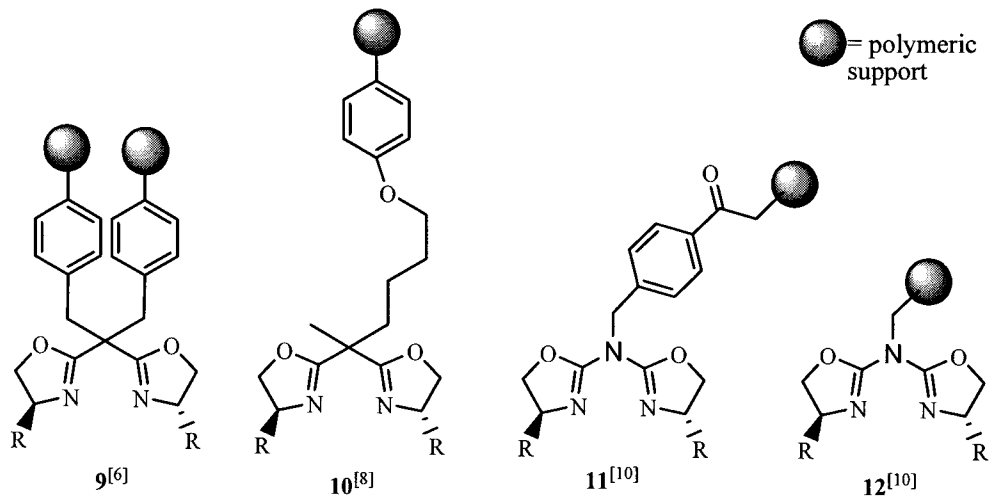
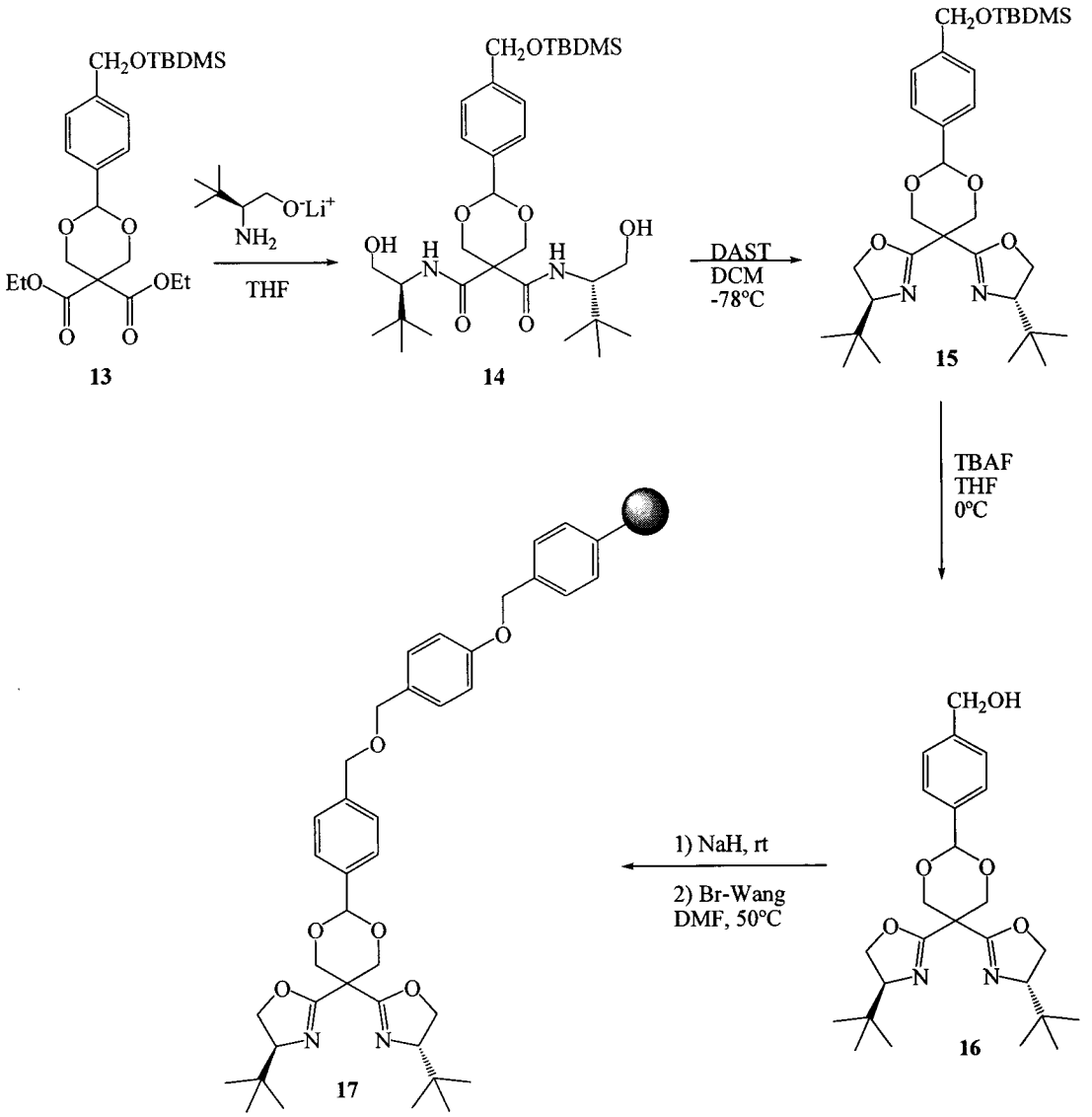


Figure 1. Different strategies for grafting BOX ligands to polymeric supports using a single linker.



Scheme 2. Strategy for grafting Knight's BOX **16** to Wang resin.[9]

Thus, Mayoral, Reiser and coworkers[10] have recently described Tentagel™ and polystyrene immobilized AzaBOX ligands. These immobilized catalysts were used in some benchmark cyclopropanation reactions, as well as in the cyclopropanation of 1,1-diphenylethylene with ethyl diazoacetate. Polystyrene gave better results than Tentagel™ as the support. After optimizing the catalyst preparation, increasing the degree of functionalization of the resin, an excellent catalyst was obtained, which could give high chemoselectivities (up to 94%) without excess alkene, and excellent enantioselectivities (up to 99% ee with styrene). Furthermore, the catalyst was recovered and reused with different alkenes in each run (styrene, 1,1-diphenylethylene, α-methylstyrene and 1-hexene), giving good chemoselectivities and enantioselectivities up to the fourth cycle. The immobilized aza*t*BuBOX ligand is the first example of a *multitask* immobilized catalyst,

since it could be used in the Mukaiyama-aldol reaction, reused in the same reaction, and then used in the benchmark cyclopropanation reaction. Under these conditions, 99% chemoselectivity (without excess of alkene), 97% ee for the *trans*-cyclopropanes and 92% ee for the *cis*-cyclopropanes were obtained.[11] These results are in fact better than those obtained in the homogeneous phase.

We decided to immobilize the Arylid-BOX family of ligands **18**[12,13] onto a Wang resin as the presence of the C=C bond should lead to less conformational freedom of the ligand within the support giving a more rigid catalyst.

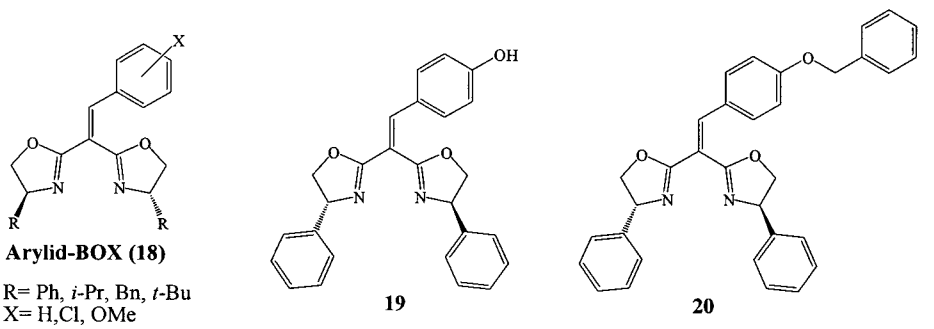
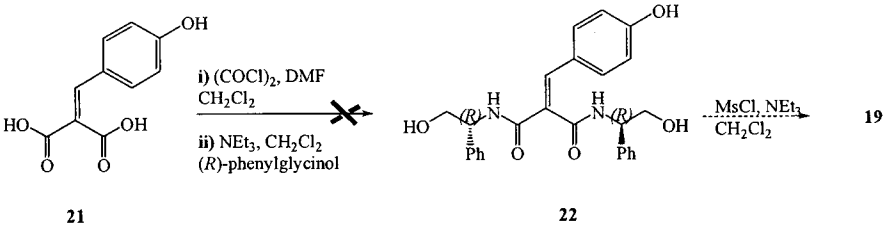


Figure 2. Structures of Arylid-BOX and derivatives.

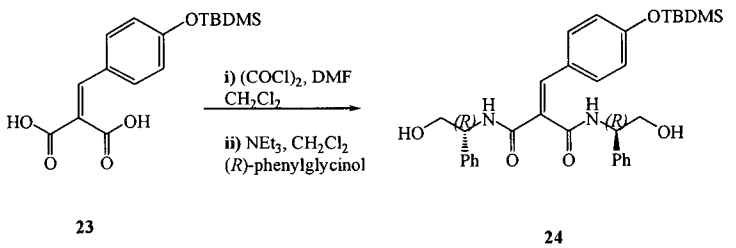
To achieve this objective the plan was to synthesize the BOX **19** (Figure 2) and immobilize it to the support via the *para*-hydroxyl group. Many unsuccessful attempts were made in our group at doing this. The first strategy that was looked at (Scheme 3), involved a cyclization of the diamidoalcohol **22,** however, it was not possible to obtain this compound. It was believed that the phenol unit was interfering with the cyclization process.[14] Assuming that this was case, the TBDMS protected diamidoalcohol **24** was synthesized and subjected to a cyclization reaction. Unfortunately this reaction failed to work (Scheme 3).[15] The third approach involved the synthesis of the Arylid-BOX ligands **26** *para*-substitued with chloro and bromo groups which were then investigated in a Suzuki-Miyaura coupling reaction with phenyl boronic acid. As immobilized phenylboronic acid is known and available, this model reaction was crucial to determine the viability of this approach for getting **28**. Unfortunately, after much investigation with many Pd catalysts it was impossible to obtain the phenyl BOX **27**. (Scheme 3).[15] Our strategy was to obtain ligand **19** from its benzyloxy protected precursor **20** and attach it to a suitable polymeric support via the hydroxyl group.

1st Attempt

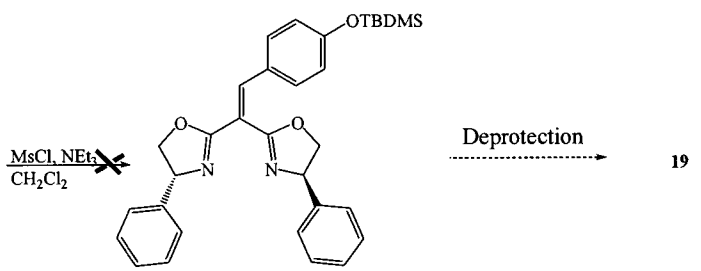


21 22

2nd Attempt



23 24



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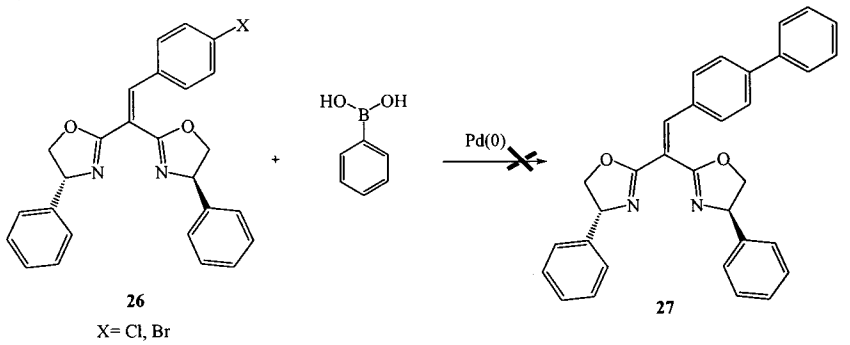
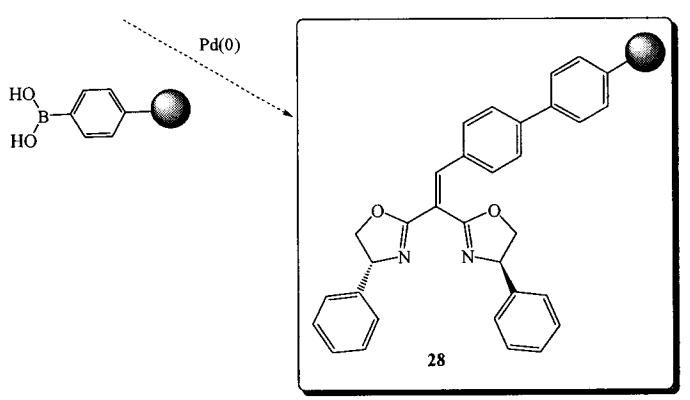
3rd Attempt



26
X= Cl, Br

27



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Scheme 3. Methods for the immobilization of the Arylid-BOX ligand.

2. Results and Discussion

2.1 Synthesis and Immobilization of Derivatives of Arylid-BOX on Wang Resin

The Arylid-BOX **20** was prepared in good yields using the established method for the synthesis of Isbut-BOX[15] and Arylid-BOX **18**[12,13] ligands (Figure 3).

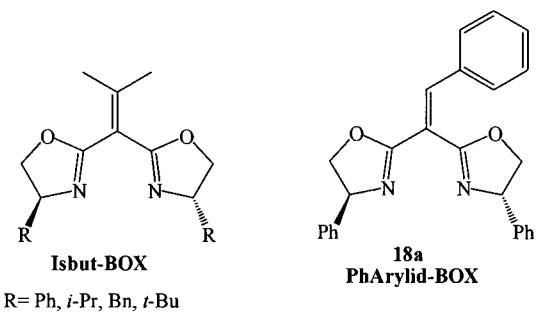
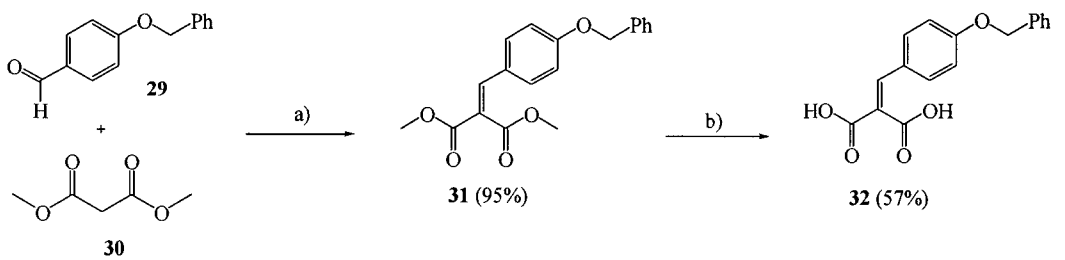


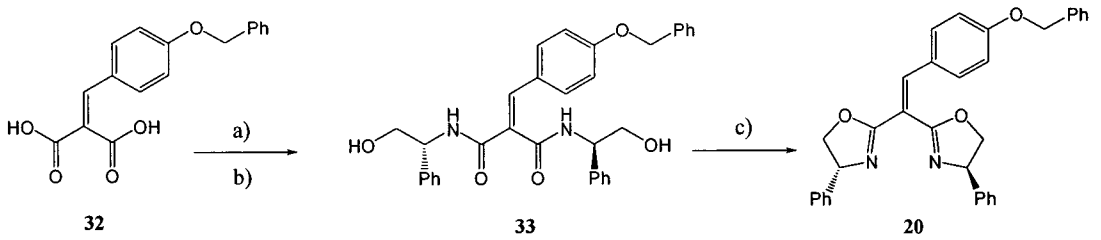
Figure 3. Isbut-BOX and PhArylid-BOX ligands.

The synthesis and mechanism were outlined in the Chapter 2. The dimethyl malonate **31**, its carboxylic acid derivative **33** (Scheme 4) and the α-amino alcohol (Scheme 5) were synthesized using the literature methods. **31** was obtained via the procedure reported by Evans *et al.*[16] using a simple Knoevenagel condensation with dimethyl malonate **30** and 4-benzyloxybenzaldehyde **29**. The hydrolysis of **31** with NaOH in EtOH furnished **32** (Scheme 4). The α-amino alcohol (*R*)-phenylglycinol was obtained using the method of Mckennon *et al.*[17]

The synthesis of ligand **20** was achieved via two important steps: formation of the malonamide **33** and subsequent cyclization to afford the bis(oxazoline) **20** (Scheme 5).



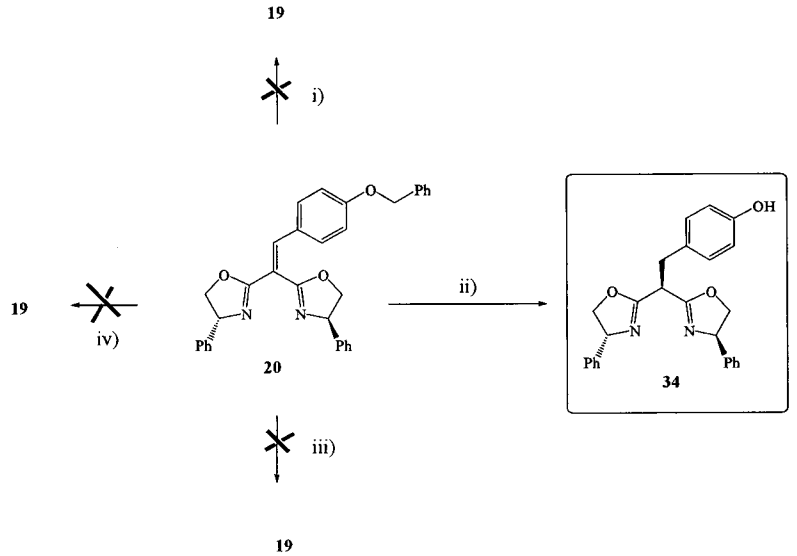
Scheme 4. *Reaction conditions:* a) piperidine (5 mol%), acetic acid (5 mol%), benzene, Δ; b) NaOH (2.5 eq), EtOH, 0°C.



32 33 20

Scheme 5. *Reaction conditions:* a) $(COCl)_2$, DMF, CH_2Cl_2; b) (*R*)-Phenylglycinol, NEt_3, CH_2Cl_2; c) MsCl, NEt_3, CH_2Cl_2.

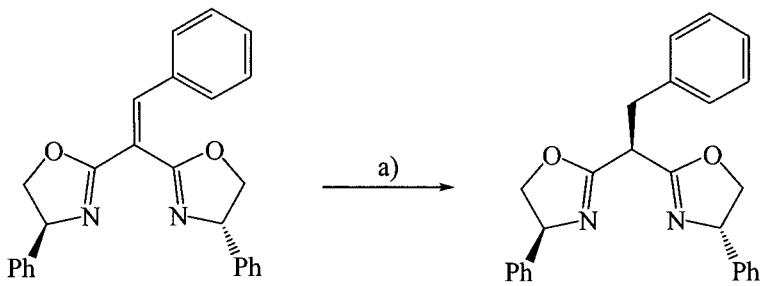
The next step consisted in the debenzylation of ligand **20** using the common method of Pd on activated carbon H_2[18] (balloon pressure) at room temperature during several hours (Scheme 6). It was assumed that since the double bond was extremely conjugated and had two oxazoline rings attached, it would remain intact under these conditions. However, only starting material was recovered as indicated by ^1H NMR. The reaction was repeated with heating at 50°C, but, only the hydrogenated product **34** was obtained. Efforts to obtain ligand **19** (Scheme 6) continued, these efforts included reducing the reaction time, and using the method of Felix *et al.*[19] This method was more suitable than the common method with H_2 (balloon pressure), it consists in the catalytic transfer hydrogenation with 1,4-cyclohexadiene, as a donor of hydrogen, at room temperature (25°C) with 10% Pd/C. However, the initial Arylid-BOX **20** was obtained in all cases (Scheme 6).



Scheme 6. *Reaction conditions:* i) Pd/C (10%), H_2 (balloon pressure), EtOH at room temp., 24h; ii) Pd/C (10%), H_2 (balloon pressure), EtOH at 50°C, 24h; iii) Pd/C (10%), H_2 (balloon pressure), EtOH at 50°C, 8h; iv) Pd/C (5%), 1,4-cyclohexadiene (10 eq), EtOH at room temp., 5 days;

Looking on the bright side, a new method for the synthesis of BOX ligands of the type **34** has been developed!

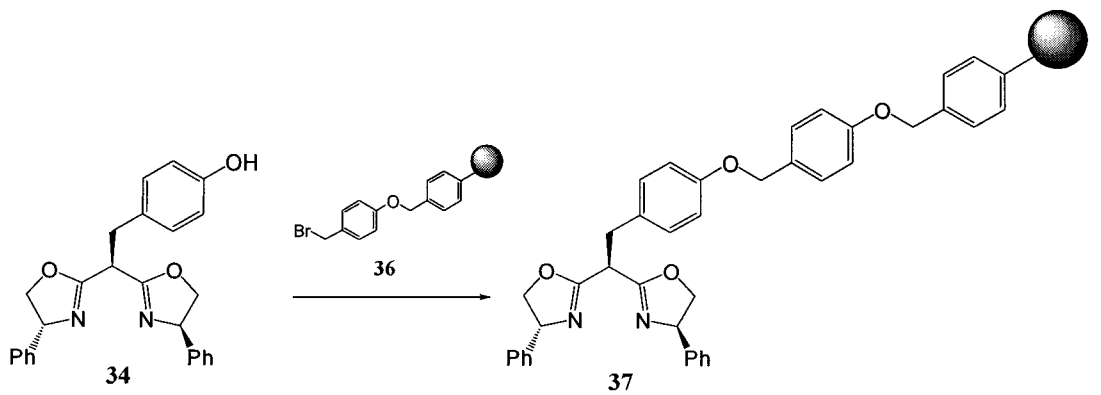
Ligand **18a** was prepared following the previously described method.[12-14] It was then transformed to the hydrogenated BOX derivative **35** (Scheme 7) in satisfactory yield.



18a **35** (49%)

Scheme 7. *Reaction conditions:* a) Pd/C, H_2, EtOH, 50°C.

The immobilization of **34** onto Wang resin (benzyloxybenzyl bromide, 0.5 – 1 mmol Br/g resin) **36** was carried out with NaH in DMF to furnish the corresponding alkoxide intermediate followed by the addition of Br-Wang resin to give the immobilized ligand **37** (Scheme 8). Micro-analysis of **37** indicated a loading of 0.321 mmol of ligand/g of resin. This method was used by Knight and Belcher.[9]



34 **37**

Scheme 8. *Reaction conditions:* NaH, DMF, 50°C.

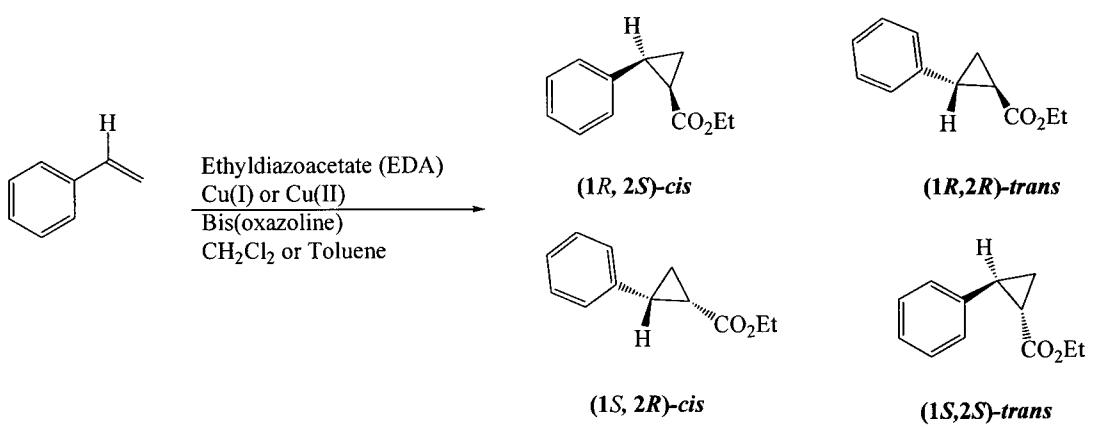
We chose grafting of ligand **34** on to Wang resin **36**, because Wang resin **36** is a well defined polymeric resin, and the active sites in the resin will be more accessible during the reaction.

2.2 Catalytic Asymmetric Cyclopropanation of Styrene using supported Arylid-BOX 37

The polymer supported Arylid-BOX-derivative **37** was evaluated in the benchmark CACP of styrene, three studies were carried out with $[Cu(MeCN)_4]PF_6$ and two different solvents, CH_2Cl_2 and toluene, and $Cu(OTf)_2$ with CH_2Cl_2 (Scheme 9 and Table 1). The objective was to compare these reactions with the homogeneous reaction.

Both of the non-immobilized Arylid-BOX-derivatives **34** and **35** were also evaluated in the CACP of styrene (Scheme 9). The best ees were obtained using ligand **34**, 68% ee for *cis*-cyclopropane and 64% for the *trans*-cyclopropane, but the yield and de were inferior to those obtained with ligand **35**. The ees were slightly higher for the *cis*-cyclopropane (68% ee) than for the *trans*-cyclopropane (64% ee). An opposite result to that obtained with the Arylid-BOX ligand.[12,13] The CACP with ligand **35** gave similar ees to that obtained with the PhArylid-BOX **18a** ligand (Figure 2). These results seem to indicate some inductive effect by the hydroxyl group in ligand **34**. Another less likely hypothesis is that the hydroxyl group of ligand **34** may coordinate to the Cu metal, thus activating the catalyst.

The polymeric-ligand **37** was complexed with both Cu(I) and Cu(II) pre-catalysts. The results obtained in the heterogeneous CACP of styrene with $[Cu(MeCN]_4PF_6$ using EDA and CH_2Cl_2 showed that the ee of the *cis*-cyclopropane decreased, but the ee of the *trans*-cyclopropane remained the same as that obtained in the homogeneous CACP (Table 1, entries 3 and 4). The des increased in the heterogeneous system.



Scheme 9. Asymmetric cyclopropanation of styrene — the benchmark reaction for this study.

Table 1. Catalytic Asymmetric Cyclopropanation of styrene.[a]

Entry	Catalyst	ligand	Solvent	Cycle	Yield[b] (%)	*cis*:*trans*[c]	ee[c] *cis* (%)	ee[c] *trans* (%)	Products :dimers[c]
1	$CuPF_6$	18a	CH_2Cl_2	-	30	35:65	45	57	Nd
2		35[e]	CH_2Cl_2	-	63	29:71	52	59	92:8
3		34	CH_2Cl_2	-	31	37:63	68	64	93:7
4		37	CH_2Cl_2	1st	61	32:68	45	68	99:1
5			CH_2Cl_2	2nd	38	30:70	50	67	89:11
6			CH_2Cl_2	3rd	57	32:68	44	69	97:3
7[f]			CH_2Cl_2	4th	44	32:68	36	47	97:3
8		37	Toluene[d]	1st	30	33:67	62	71	98:2
9			Toluene[d]	2nd	26	33:67	61	71	91:9
10			Toluene[d]	3rd	36	36:64	58	66	91:9
11[g]			Toluene[d]	4th	33	36:64	57	64	90:10
12	$Cu(OTf)_2$	37	CH_2Cl_2	1st	5	32:68	52	68	76:24
13			CH_2Cl_2	2nd	47	31:69	47	70	95:5
14			CH_2Cl_2	3rd	19	28:72	13	36	72:28
15[h]			CH_2Cl_2	4th	24	30:70	17	22	81:19

[a] Styrene (4 equiv), $[Cu(MeCN)_4]PF_6$ or $Cu(OTf)_2$ (0.027 mmol, 2 mol%), **37** (2.2 mol%), EDA (1 equiv), solvent (5 mL), rt, 48h.

[b] Calculated by determining the product weight.

[c] Determination by chiral GC analysis.

[d] Temperature was 40 °C.

[e] Determination by using an internal standard

[f] ICP-OES 0.204 mmol Cu/g after the 4th cycle (before the 1st cycle 0.265 mmol Cu/g)

[g] ICP-OES 0.137 mmol Cu/g after the 4th cycle (before the 1st cycle 0.265 mmol Cu/g)

[h] ICP-OES 0.109 mmol Cu/g after the 4th cycle (before the 1st cycle 0.266 mmol Cu/g)

In the 2nd cycle the ee of the *cis*-cyclopropane increased as well as the de, but the yield decreased, due to the decrease in the selectivity, i.e. the amount of maleate/fumerate side-products increased due to increased dimerization under these conditions. This behavior might imply reduced or no free copper in the reaction. In the 3rd cycle the ee of the *cis*-cyclopropane decreased 6% and the de 2%, but the yield and selectivity increased, these results were very similar to those encountered in the 1st cycle. In the 4th cycle both the ees and the yield decreased, particularly for the *trans*-cyclopropane. The de and selectivity remained constant. After the last cycle the supported-ligand **37**-$[Cu(MeCN)_4]PF_6$ complex was analyzed by ICP-OES, and it was determined to have a loading of 0.204 mmol Cu/g, this result indicated only 23% leaching of Cu(I) over the 4 reaction cycles.

Toluene was used as the solvent in the CACP of styrene using $[Cu(MeCN)_4]PF_6$-polymer supported ligand **37** and the reactions were carried out at 50°C. Heating was necessary to activate the catalyst.[15] The results obtained for 1st and 2nd cycles (*cis*-isomer 61% ee and *trans*-isomer 71% ee) were very similar although there was a slight

decrease in the yield and the selectivity. In the 3rd cycle there was a slight decrease in the ees and the de, but the yield increased by 10%. The results obtained in the 4th cycle were closer to the 3rd cycle. The supported Cu(I)-complex isolated after the 4th cycle was analyzed by ICP-OES and a loading of 0.137 mmol Cu/g was determined. 48% of the Cu(I) had leached out over the 4 cycles.

The results obtained for the CACP with toluene were better than for CH_2Cl_2, but surprisingly, the ICP-OES analysis revealed more leaching with toluene. This was probably due to the higher temperature.

For the CACP of styrene with **37**-$Cu(OTf)_2$, EDA and CH_2Cl_2 the ees and des remained almost constant between the 1st (*cis*-isomer 52% ee and *trans*-isomer 68% ee) and the 2nd cycle (*cis*-isomer 47% ee and *trans*-isomer 70% ee), but the yield and the selectivity had significantly increased. After the 2nd cycle the ees, yield and selectivity decreased more than half. Obviously, these results were a consequence of the high level of leaching of the copper from the supported ligand, as ICP-OES analysis of the isolated polymer-ligand showed that 59% of the Cu(II) had leached out over the 4 cycles.

Comparing the results obtained for the non-covalent immobilized Arylid-BOX catalysts (Chapter 3, section 2.4) with the covalent immobilized catalyst, the latter was superior in all aspects: activity, selectivity and recycling. It must be noted that leaching of the catalyst was less than that observed in the non-covalent immobilization.

3. Conclusions

The immobilization method developed in this PhD project has many advantages over the grafting technique by polymerization previously documented in the literature.[6] Burguete *et al.*[6] could only obtain a highest ee of 33% with their immobilized ligand **4** (Scheme 1), in this reaction we have obtained a much better ee of 71%. For one thing, it is a very simple method, grafting by a polar displacement reaction. The immobilized catalyst gave similar results to that of the non-immobilized catalyst in the CACP of styrene with $[Cu(MeCN)_4]PF_6$.

In this reaction the supported-Arylid-BOX-derivative **37** with $[Cu(MeCN)_4]PF_6$ and toluene gave similar results to those obtained in the homogenous phase, and the catalyst could be recycled and reused up to 4 times without loss of selectivity and activity, which is a significant achievement.

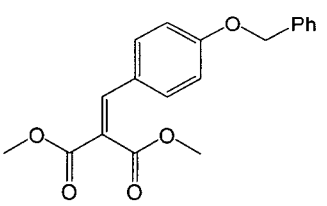
4. Experimental Procedure

General Remarks

(+)-Bis[(*S*)-4-phenyloxazoline-2-yl]-2-phenylethene (**18a**) was prepared following previously described methods.[13-14] Solvents were dried using common laboratory methods.[20] All reagents were obtained from Aldrich, Fluka, Alfa Aesar or Acros. Column chromatography was carried out on silica gel (sds, 70–200 μm) and flash column chromatography (Merck, 40–63 μm and sds, 40-63 μm). TLC was carried out on aluminium-backed Kisel-gel 60 F254 plates (Merck). Plates were visualized either by UV light or by phosphomolybdic acid in ethanol. The melting point was recorded on a Barnstead Electrothermal 9100 apparatus and was uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. The NMR spectra were recorded on either a Bruker AMX300 or a Bruker Avance 400 instrument. Mass spectra were recorded on a VG Autospec M(Waters-Micromass) spectrometer using the FAB technique. Infra-red spectra were measured with a Perkin Elmer Paragon 1000 model. Gas chromatographic (GC) analyses of the products were performed on a Hewlett Packard (HP) 6890 series instrument equipped with a flame ionization detector (FID). The chromatograph was fitted with a cyclosil-B capillary column (30 m, 250 μm, 0.25 μm) (Agilent 112-2532). ICP-OES analyses were performed on a Perkin Elmer Optima 4300 DV at CACTI, Universidad de Vigo. EA analysis was performed on a EA 1108 CHNS-O Fisons instrument.

4.1 Synthesis and Immobilization of Arylid-BOX derivatives on Wang-Resin

Synthesis of dimethyl 2-(4-(benzyloxy)benzylidene)malonate 31:



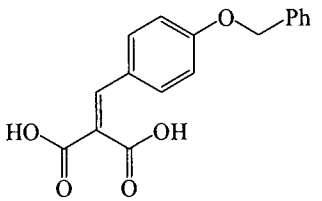
31

A dry round-bottom flask equipped with a Dean-Stark trap, was charged with acetic acid (0.068 mL, 1.2 mmol, 5 mol%), piperidine (0.11 mL, 1.2 mmol, 5 mol%), dimethyl malonate **30** (2.7 mL, 0.024 mol) and 4-benzyloxylbenzaldehyde **29** (5 g, 0.024 mol)

and benzene (60 mL). The solution was stirred at reflux until 0.43 mL of H_2O was removed. The cooled reaction was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* **31** as a pale yellow solid: Yield: 8.13 g (95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (s, 1H, ArC*H*=CR_2), 7.39 – 6.83 (m, 9H, C*H*(Ar)), 4.50 (s, 2H, OC*H*$_2$Ph), 3.87 (s, 3H, -CO_2C*H*$_3$), 3.84 (s, 3H, -CO_2C*H*$_3$) ppm.

Synthesis of 2-(4-benzyloxybenzylidene)malonic acid 32:



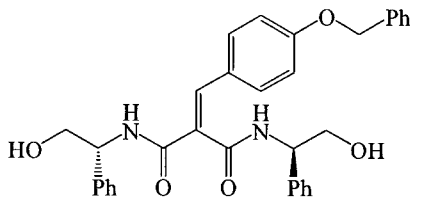
32

A solution of **31** (6.580 g, 0.020 mol) in ethanol (50 mL) was added to a solution of NaOH (2.016 g, 0.050 mol) in ethanol (150 mL) and stirred for 4 days at 0°C. The ethanol was removed under reduced pressure and the residue was dissolved in H_2O (until the solution became clear), cooled, and cautiously acidified with conc. HCl to a pH of 3.0, the acid was extracted with EtOAc (3 x 75 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated to afford the *title compound* **32** as a pale yellow solid: Yield: 3.410 g (57%). **mp**: 186°C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.56 (d, 2H, *J*=8.7 Hz, C*H*(Ar)), 7.47 – 7.33 (m, 6H, C*H*(Ar) and RC*H*=CR_2), 7.07 (d, 2H, *J*=8.4 Hz, C*H*(Ar)), 5.15 (s, 2H, O-C*H*$_2$Ph) ppm.

IR (KBr) υ_{max}: 3346, 2979, 1728, 1665, 1514, 1436, 1280, 1217, 1067, 1174, 837 cm^{-1}.

Synthesis of (*R,R*)-*N,N'*-bis(2-hydroxy-1-phenylethyl)-2-(4-benzyloxybenzylidene)malonamide 33:



33

A dry 25 mL two-necked round bottom flask equipped with a magnetic stir bar was charged with 2-(4-benzyloxy)malonic acid **32** (1 g, 3.35 mmol), dimethylformamide (0.03 mL, 0.44 mmol) and CH_2Cl_2 (10 mL). The solution was cooled to 0 °C, and oxalyl chloride (0.73 mL, 8.38 mmol) was added dropwise over 30 min and the solution was stirred at room temperature until the evolution of gas ended. The solution was evaporated in *vacuo* to give 4-benzyloxybenzylidenemalonyl chloride as a yellow semi-solid (due to the unstable nature of this compound it was stored in the freezer at –10°C). A 25 mL two necked round bottom flask fitted with a magnetic stirring bar was charged with a solution of (*R*)-phenylglycinol (1.22 g, 8.88 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C using an ice bath. Dry triethylamine (1.24 mL, 8.88 mmol) was added via syringe. A solution of crude 2-(4-benzyloxybenzylidene)malonyl chloride (1.28 g, 3.35 mmol) in CH_2Cl_2 (5 mL) was slowly added via syringe to the vigorously stirred reaction mixture over 30 min. The ice bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was washed with 2M HCl (12 mL), saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (15 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give (*R,R*)-*N,N'*-bis(2-hydroxy-1-phenylethyl)-2-(4-benzyloxybenzylidene)malonamide **33** as a yellow solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford the amide **33** as a white solid: Yield: 0.955 g (53%). **mp** 90 - 91 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, 1H, *J*= 8.9 Hz, N*H*), 7.84 (d, 1H, N*H*), 7.41 – 7.30 (m, 6H, C*H*(Ar)), 7.26 – 7.18 (m, 10H, C*H*(Ar)), 7.03 (d, 2H, *J*=8.8 Hz, C*H*(Ar)), 6.52 (d, 2H, *J*=8.8 Hz, C*H*(Ar)), 5.39 – 5.37 (m, 1H, C*H*), 5.23 – 5.22 (m, 1H, C*H*),

4.91 (s, 2H, -OCH_2Ph), 3.86 – 3.79 (m, 2H, CH_2), 3.66 (dd, 2H, J=9.7, 11.6 Hz, CH_2) ppm.

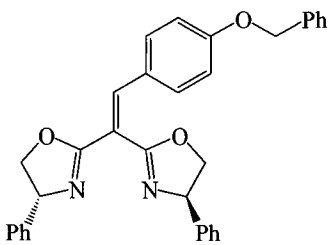
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.82, 165.25, 159.82, 139.29, 138.26, 137.57, 136.26, 131.70, 128.68, 128.61, 128.14, 128.08, 127.72, 127.66, 127.40, 127.26, 126.52, 125.35, 114.54, 69.74, 65.71, 65.53, 56.10 ppm.

IR (KBr) υ_{max}: 3274, 3061, 3031, 2930, 2872, 1736, 1659, 1601, 1511, 1454, 1424, 1380, 1251, 1177, 1057, 1026, 914, 829, 753, 699, 635, 524 cm^{-1}.

$[\alpha]^{20}_D$ = + 62.23 (c = 1.03, $CHCl_3$).

FAB-MS *m/z*: 537.20 $[M+H]^+$.

Synthesis of bis[(*R*)-4-phenyloxazoline-2-yl]-2-(4-benzyloxyphenyl)ethene 20:



20

A solution of methanesulfonyl chloride (0.166 g, 1.45 mmol) in dry dichloromethane (1 mL) was added dropwise over 20 min to a solution of malonamide **33** (0.354 g, 0.66 mmol) and dry triethylamine (0.55 mL, 3.96 mmol) in dry dichloromethane (20 mL) and the solution was stirred between −5 and −10°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 days. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude product. The crude product was purified by column chromatography (silica gel, EtOAc:Hex (1:1)) giving the (+)-bis[(*R*)-4-phenyloxazoline-2-yl]-2-(4-benzyloxyphenyl)ethene **20** as a white solid: Yield: 0.11 g (60%). **mp:** 68°C (decomposition).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1H, R_2C=C*H*R), 7.50 (d, J= 8.8 Hz, C*H*(Ar)), 7.42 – 7.23 (m, 15H, C*H*(Ar)), 6.93 (d, 2H, J= 8.7 Hz, C*H*(Ar)), 5.43 (dd, 2H, J=9 Hz,

CH_2), 5.08 (s, 2H, -OCH_2Ph), 4.88 (dd, 1H, *J*=9, 10 Hz, C*H*H), 4.81(dd, *J*=9, 12 Hz, CH*H*), 4.31 (t, 1H, *J*=8.4 Hz, C*H*), 4.20 (t, 1H, *J*=8.2 Hz, C*H*) ppm.

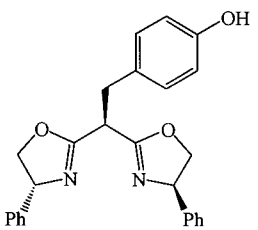
^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.73, 162.22, 160.19, 142.25, 141.85, 141.36, 136.43, 131.49, 128.66, 128.61, 128.57, 128.15, 127.47, 126.98, 126.77, 126.72, 74.85, 74.81, 70.17, 70.05, 70.02 ppm.

IR(KBr): υ_{max} 3291, 3060, 3030, 2958, 2899, 1739, 1670, 1633, 1601, 1494, 1454, 1409, 1382, 1356, 1304, 1250, 1173, 1119, 1080, 1014, 959, 934, 910, 876, 828, 741, 698, 627, 612, 527 cm^{-1}.

$[\alpha]^{20}_D$ = + 50.26 (*c* = 1.89, $CHCl_3$).

FAB-MS *m/z*: 501.18 $[M+H]^+$.

Synthesis of bis[(*R*)-4-phenyloxazoline-2-yl]-2-(4-hydroxyphenyl)ethane 34:



34

Attempt i:

A dry 50 mL round bottom flask equipped with a magnetic stir bar was charged with Arylid-BOX **20** (0.05g, 0.1 mmol), dry ethanol (25 mL) and Pd on activated carbon (0.023 g, 0.5 eq). The mixture was stirred at room temperature and a balloon filled with hydrogen was placed on top of to the flask and the reaction was stirred for 24h. The mixture was filtered through a celite filter and washed with CH_2Cl_2 (30 mL) and the solvent was removed under vacuum. The crude product was purified by column chromatography (silica gel, EtOAc:Hex (1:1)) giving the *starting compound* **20** as a white solid.

Attempt ii:

A dry 50 mL round bottom flask equipped with a magnetic stir bar was charged with Arylid-BOX **20** (0.371g, 0.74 mmol), dry ethanol (25 mL) and Pd on activated carbon (0.186 g, 0.5 eq). The mixture was warmed to 50 °C and a balloon filled with hydrogen

was placed on top of the flask. The reaction was stirred for 24h. It was cooled to room temp., the mixture was filtered through a celite filter and washed with CH_2Cl_2 (30 mL) and the solvent was removed under vacuum. The crude product was purified by column chromatography (silica gel, EtOAc:Hex (1:9)) giving the *title compound* **34** as a colorless semi-solid: Yield: 0.058 g (46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 – 7.23 (m, 10H, C*H*(Ar)), 6.98 – 6.93 (m, 2H, C*H*(Ar)), 6.29 (d, *J*= 8.3 Hz, C*H*(Ar)), 5.21 (dd, 2H, *J*= 9, 18 Hz, CH_2), 4.7 (dd, 2H, *J*=8.6, 10 Hz, C*H*), 4.24 (t, 1H, *J*=8 Hz, C*H*), 4.17 – 4.09 (m, 2H, CH_2), 3.34 – 3.28 (m, 1H, C*H*H), 3.27 – 3.22 (m, 2H, CH*H*) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.06, 165.93, 155.93, 141.56, 141.37, 129.71, 128.71, 127.79, 127.74, 127.68, 126.89, 126.55, 126.41, 115.64, 75.53, 75.36, 69.29, 68.94, 41.85, 34.86 ppm.

IR (KBr): υ_{max} = 3062, 3029, 2963, 2925, 2684, 2606, 1736, 1657, 1616, 1516, 1494, 1454, 1363, 1271, 1239, 1174, 1103, 994, 930, 823, 761, 700, 539 cm^{-1}.

FAB-MS *m/z*: 413.04 $[M+H]^+$.

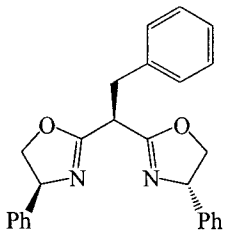
Attempt iii:

A dry 50 mL round bottom flask equipped with a magnetic stir bar was charged with Arylid-BOX **20** (0.05g, 0.10 mmol), dry ethanol (10 mL) and Pd on activated carbon (0.023 g, 0.5 eq). The mixture was warmed to 50 °C and a balloon filled with hydrogen was placed on top of the flask. The reaction was stirred for 8h. It was cooled to room temp., the mixture was filtered through a celite filter and washed with CH_2Cl_2 (30 mL) and the solvent was removed under vacuum. The crude product was purified by column chromatography (silica gel, EtOAc:Hex (1:1)) giving the *starting compound* **20** as a white solid.

Attempt iv:

The substrate **20** (0.05 g, 0.10 mmol) was dissolved in 10 mL of absolute ethanol placed in the 3 x 25-cm reaction vessel and immersed in a water bath at 25 °C. A gentle stream of nitrogen was passed through the reaction mixture and an equal weight of 10% palladium-carbon (100 mg) was added followed by the addition of 1,4-cyclohexadiene (0.095 mL, 1 mmol, 10 eq.). The reaction proceeded for 5 days and the mixture was filtered (celite), washed with solvent, and evaporated under reduced pressure. The crude product was analyzed by ^{1}H NMR which showed only the initial compound **20**.

Synthesis of bis[(*S*)-4-phenyloxazoline-2-yl]-2-phenylethane 35:

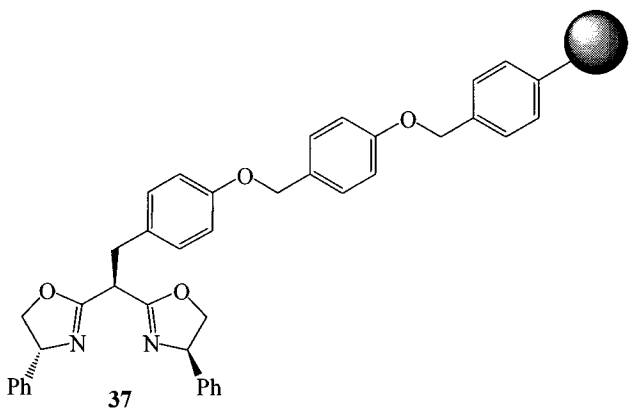


35

The same procedure as described previously Bis[(*S*)-4-phenyloxazoline-2-yl]-2-phenylethene **18a** (118 mg, 0.3 mmol), Pd/C 5% (64 mg, 50%) and dry EtOH were introduced into a 2-neeked flask. A balloon containing hydrogen was attached and the reaction stirred for 24h. The crude product was purified by column chromatography (silica gel, EtOAc:Hex (2:1)) giving the Bis[(*R*)-4-phenyloxazoline-2-yl]-2-(4-hydroxyphenyl)ethane **35** as a white semi-solid. Yield: 0.058 g (49%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 – 7.19 (m, 13H, C*H*(Ar)), 6.94 (s_{broad}, 2H, C*H*(Ar)), 5.19 (s_{broad}, 2H, CH_2), 4.66 (t, 2H, *J*=9 Hz, C*H*), 4.16 (t, 1H, *J*=8 Hz, C*H*), 4.06 (t, 2H, *J*=8 Hz, CH_2), 3.45 – 3.35 (m, 2H, CH_2) ppm.

Wang resin supported bis[(*R*)-4-phenyloxazoline-2-yl]-2-(4-hydroxyphenyl)ethane 37:



37

Bis(oxazoline) **34** (130 mg, 0.315 mmol) was dissolved in dry DMF (5 mL), NaH 60% (27 mg, 0.63 mmol) was added in one portion, the mixture became yellow, the suspension was then stirred for 30 min at room temp. Wang-Br resin **36** (0.5 – 1 mmol/g, 0.630 g, 0.315 mmol) was added to the reaction mixture, which was stirred overnight under a nitrogen atmosphere at 50°C. The resin was filtered off and washed

successively with MeOH (3 mL), THF:H_2O 1:1 (3 mL), H_2O (3 mL), CH_2Cl_2 (3mL) and MeOH (3 mL). The supported ligand **37** was dried at 40 °C under vacuum for several hours, giving a final mass of 0.598 g. It was determined by microanalysis (0.9% N) to have a loading of 0.321 mmol of ligand/g resin.

4.2 Homogeneous Catalytic Asymmetric Cyclopropanation of styrene:

Representative Cyclopropanation using $[Cu(MeCN)_4]PF_6$ pre-catalyst

$[Cu(MeCN)_4]PF_6$ (0.028 mmol, 2 mol%) was added to a two-neck round-bottomed flask containing the chiral bis(oxazoline) (2.2 mol%) in CH_2Cl_2 (1 ml) and the solution was stirred at room temperature for 15 min under a nitrogen atmosphere. Styrene (14 mmol) and a solution of ethyl diazoacetate (1.4 mmol) in CH_2Cl_2 (1 ml) was then added to the reaction mixture over a period of 8 h using a syringe pump. After the addition of ethyl diazoacetate, the mixture was stirred for 16 h. The reaction mixture was firstly passed through a short pad of silica gel (washed with CH_2Cl_2) to remove the catalyst complex, the products were then isolated by column chromatography (hexane/EtOAc 9:1). All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers, the ratio was determined using GC analysis. Isolated yields, diastereoselectivities, and enantioselectives are given in Table 1.

GC conditions:

CACP of styrene:

Oven temperature: 120°C

Split: 120:1

t_R ((1*S*,2*R*)-ethyl 2-phenylcyclopropanecarboxylate)= 47.803 min

t_R ((1*R*,2*S*)-ethyl 2-phenylcyclopropanecarboxylate)= 50.830 min

t_R ((1*R*,2*R*)-ethyl 2-phenylcyclopropanecarboxylate)= 62.416 min

t_R ((1*S*,2*S*)-ethyl 2-phenylcyclopropanecarboxylate)= 64.010 min

4.3 Heterogeneous Catalytic Asymmetric Cyclopropanation of styrene using: $[Cu(MeCN)_4]PF_6$ as the pre-catalyst:

Representative asymmetric cyclopropanation of styrene: To a suspension of $[Cu(MeCN)_4]PF_6$ (10 mg, 0.027 mmol, 2 mol%) in solvent (4 mL) was added the supported ligand **37** (92 mg, 0.029 mmol, 2.2 mol%). After 1 h, styrene (0.58 mL, 5.6 mmol, 4 equiv) was added to the green solution. This was followed by the addition of a solution of ethyl diazoacetate (159 mg, 1.4 mmol, 1.0 equiv) in solvent (1mL) to the reaction vessel via syringe pump over 8 h. The reaction mixture was stirred at room temperature for 40 h, and was filtered off and washed with CH_2Cl_2 to collect the products. The yellow polymer was dried under vacuum and could be used again in the catalytic reaction. The crude product was analyzed by GC. For the other runs the same procedure was used. All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers, the ratio was determined using GC analysis. Isolated yields, diastereoselectivities, and enantioselectives are given in Table 1.

$Cu(OTf)_2$ as the pre-catalyst:

Representative asymmetric cyclopropanation of styrene: Ethyl diazoacetate (EDA) (0.032 mg, 0.28 mmol) was added to a suspension of $Cu(OTf)_2$ (9.6 mg, 0.027 mmol, 2 mol%) in DCM (4 mL) was added polymer **37** (92 mg, 0.029 mmol, 2.2 mol%) under nitrogen in dry CH_2Cl_2 (4 mL). This was followed by the addition of styrene (580 mg, 5.6 mmol). The reaction mixture was stirred for 15 min followed by the addition of EDA (0.159 mg, 1.4 mmol) in CH_2Cl_2 (1 mL) via syringe pump over 6 h. The reaction was stirred for 48 h under nitrogen. The solid was filtered and washed with CH_2Cl_2, the volatiles were then removed *in vacuo*. The crude product was analyzed by GC. For the other runs the same procedure was used. All cyclopropane products were obtained as a mixture of *cis* and *trans* diastereomers, the ratio was determined using GC analysis. Isolated yields, diastereoselectivities, and enantioselectives are given in Table 1.

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Chapter 5

Immobilization of PYRPHOS Ligand on a PVA Support and Evaluation in the Catalytic Asymmetric Hydroformylation Reaction

Abstract

In this chapter a new method for the functionalization of the PYRPHOS ligand **3** is described and the obtained functionalized ligand was immobilized to a polyvinyl alcohol (PVA) support. After complexation of the functionalized PYRPHOS ligand **3** to a Rh(COD)-complex fragment its catalytic properties in the asymmetric hydroformylation of styrene were examined including the recycling of the catalyst over a sequence of consecutive experiments: in comparison to the model complexes that were studied, some hydrogenation products were produced in the first 6 cycles, and the ees and regioselectivities were lower.

The method for catalytic asymmetric hydroformylation (CAHF) was optimized using the DEGUPHOS ligand **4** and $Rh(CO)_2acac$, with different pressures and solvents. The best ee obtained was 42% with a regioselectivity of 96% at a conversion of 18% in THF, at 20 bar and 80 °C.

1. Introduction

Asymmetric hydroformylation is a key reaction in the fine-chemical production in industry. The development of more selective and active ligand systems, applicable for more than a single substrate is a very important challenge.

An industrial application of the catalytic asymmetric hydroformylation (CAHF) reaction, leading selectively to the branched aldehyde, still does not exist. The expected potential of the reaction is however illustrated by the interest shown by academia as

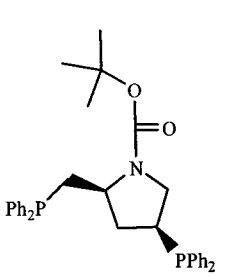
well as industry, resulting in many publications including reviews[1-5] and an excellent book by van Leeuwen and Claver[6] on the matter.

Phosphorus ligands have demonstrated a very important role in the CAHF.[1] However as in CAHF the ligands used are very expensive, thus it seems to be very reasonable that for these chiral ligands a general approach allowing an effective recycling of the catalyst should be implemented in the process development. Several immobilization methods have been developed for recycling the catalyst, these are: immobilization on a solid support,[7-9] and in a biphasic system[10] ($scCO_2$, aqueous, micellar, perfluorocarbon solvents, ionic liquids). Immobilized ligands for CAHF are known, for example, Stille[7] immobilized (-)-BPPM **1** on a polymer support and the resulting hydroformylation of styrene gave the product with >98% ee. Nozaki[9] hydroformylated styrene using 0.05 mol% of polystyrene polymer supported BINAPHOS **2**-Rh(I) and achieved 100% conversion and a very high ee for the branched aldehyde.

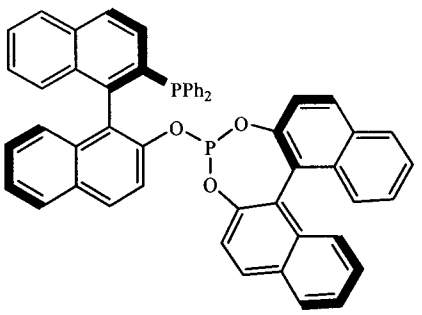
The PYRPHOS ligand **3**[11] (Chapter 1) is a versatile ligand and useful for catalytic asymmetric reactions. Therefore the immobilization of this ligand on polyvinyl alcohol (PVA) seemed to be promising and was investigated and evaluated in the CAHF.

Walter's group was the first to report the use of a PVA matrix for catalyst immobilization.[8] It could support various mono-phosphine groups (Scheme 1) that were after Rh-loading used as the catalysts in the hydroformylation of 1-octene. The immobilized catalyst could be used up to 6-7 times.

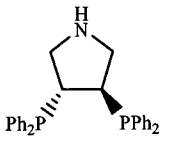
PVA is a polymer that exhibits free hydroxyl groups that contain a lot of reactive centers which might be functionalized with donor groups. The most obvious and common approach to functionalizing PVA is the transformation of two hydroxyl groups localized in 1- and 3-position of the PVA into cyclic acetals (Figure 1).[12] In the 2-position, these acetal units can potentially carry a spacer group to which a donor group can be connected that can bind to an active transition metal.



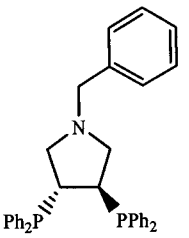
DPPM 1



(*R*,*S*)-BINAPHOS 2

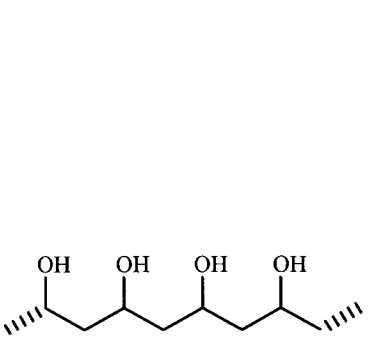


PYRPHOS 3

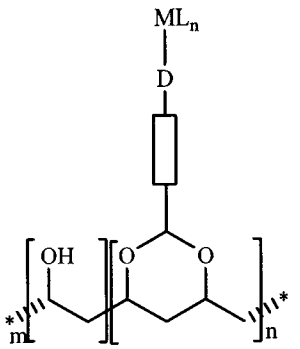


DEGUPHOS 4

By varying the degree of transformation of the hydroxyl groups into 1,3-dioxanes (ratio *n*/*m*, Figure 1), the polarity of the functionalized PVA can be adjusted. In this way, even apolar substrates, such as long-chain olefins, may enter the polymer material and be catalytically transformed. Adsorption of the modified PVA on an inorganic support can lead to an additional heterogenization step with layers of the modified PVA covering the surface of the inorganic support. Pre-catalysts prepared in this way could be applied in interfacial catalysis comparable to SAPCs,[13] SILPs,[14] or other supported systems (Figure 2).[15]



PVA



PL-MLn

Figure 1. Schematic view of a representative part of PVA (left) and of a polyvinyl alcohol functionalized by transacetalation (**PL-MLn**) (spacer, D: donor function, MLn: transition metal fragment).

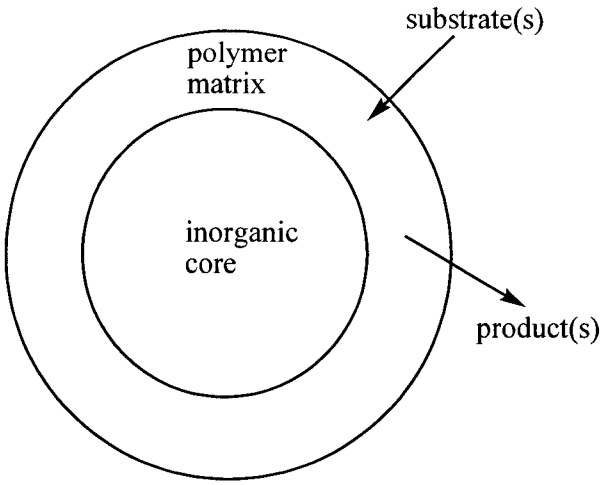
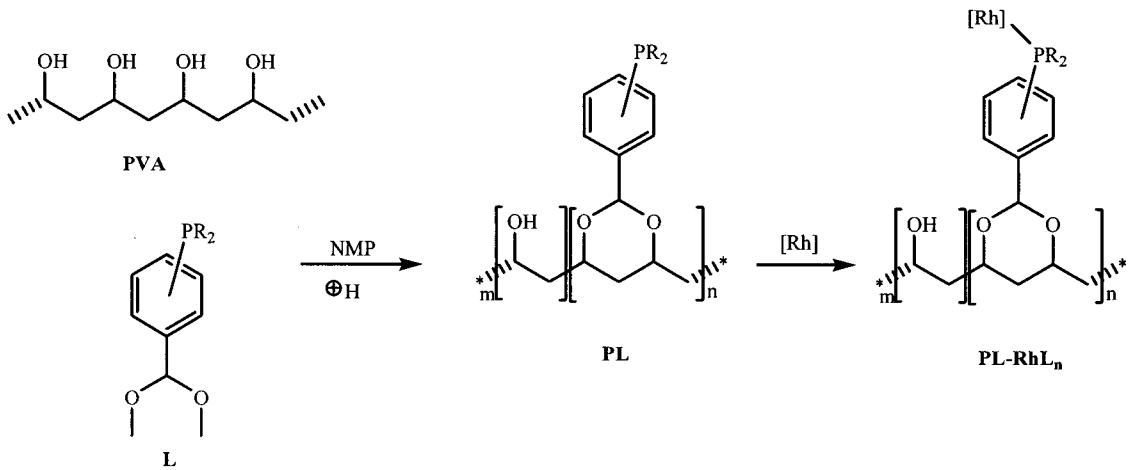


Figure 2. Schematic view of a PVA layer on the surface of an inorganic support with possible application as a support in interfacial catalysis, the catalyst being immobilized on the polymer matrix.



Scheme 1. Transacetalation of PVA, formation of the phosphino-functionalized **L** polymers **PL** and the corresponding [Rh]-modified PVAs **PL-RhL$_n$** ([Rh]: [(COD)RhCl]) by complexation.[8]

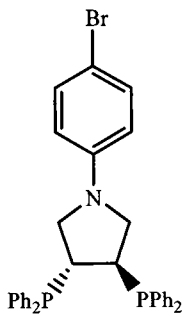
The transformation of the free hydroxyl groups of commercially available PVA into cyclic 1,3-dioxanes substituted at the 2-, 4-, and 6-positions can be performed via the transacetalation reaction in *N*-methyl-2-pyrrolidinone (NMP) under acidic catalysis (Scheme 1). The characterization of the modified polymers was accomplished by comparison of their spectroscopic data with those of the appropriate ligands equipped with functional units modeling the PVA backbone.[8]

The aim of this work was to study the immobilization of PYRPHOS **1** ligand[11] to a PVA support and to test it in the CAHF of styrene. For this, a PVA supported phosphino functionalized diethylacetal system had to be prepared as the pre-cursor.

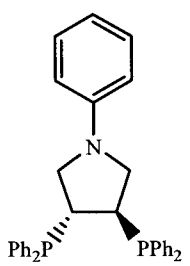
Several possible strategies were explored. One of which involved the synthesis of the bromo-functionalized ligand **5**:

In the first strategy replacement of the bromine by a formyl group through Li-Halogen exchange followed by formylation by treatment with DMF or CO_2[16] would enable the introduction of the desired acetal function.

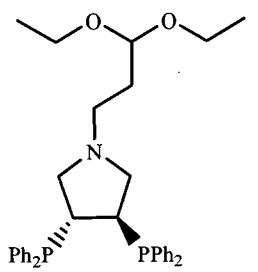
Suzuki coupling with 4-benzaldehydediphenylborane or the Heck reaction were other alternative approaches, (Scheme 2). The Suzuki reaction (the Pd-catalyzed cross-coupling of aryl boronic acids with aryl halides) is recognized as the most promising and versatile method for construction of biaryls, and is thus widely used in the synthesis of fine chemicals, agrochemicals, and active pharmaceutical intermediates.[17] The Heck reaction is a well-established method for the coupling of aryl halides with olefins.[18] PYRPHOS **3** is not readily available, so the strategy was aimed to alternative derivatives of this diphosphine, before addressing the synthesis of PYRPHOS **3**. Gonsalves *et al.*[19] synthesized the phenyl PYRPHOS analogue **6** and they had considerable problems making it.



5

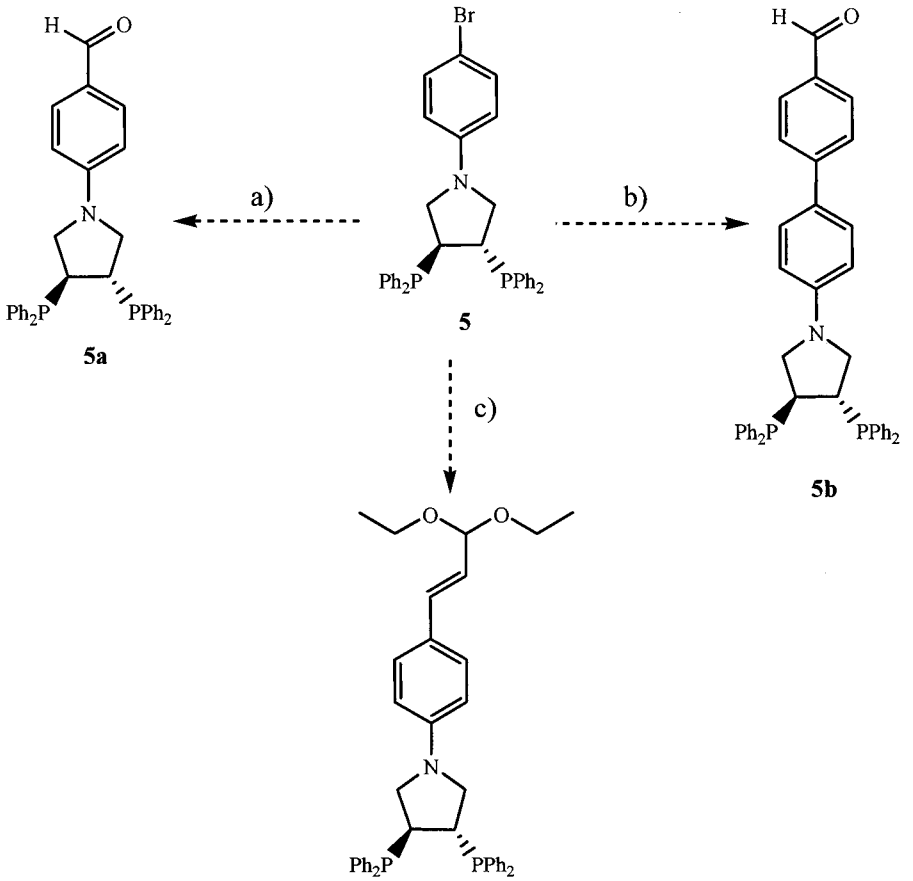


6



7

The second and third strategies were to attach an **7**. The alkyl diacetal linker to the PYRPHOS **3** to give the ligand **7**. In these strategies some steps were based on the Nagel method,[11e] as described in chapter 1. The second strategy consisted in transforming the dimesylate to the PYRPHOS derivative **5**. The final strategy consisted in obtaining the PYRPHOS.HCl salt, by using Nagel's method and coupling the halogenated alkyl diacetal reagent under basic conditions with this substrate to give the PYRPHOS diacetal **7**. The overall objective was to immobilize the PYRPHOS diacetal **7** to a PVA support using Walter's method[8] and to evaluate the corresponding immobilized catalyst in the CAHF. The reaction conditions of the CAHF were to be



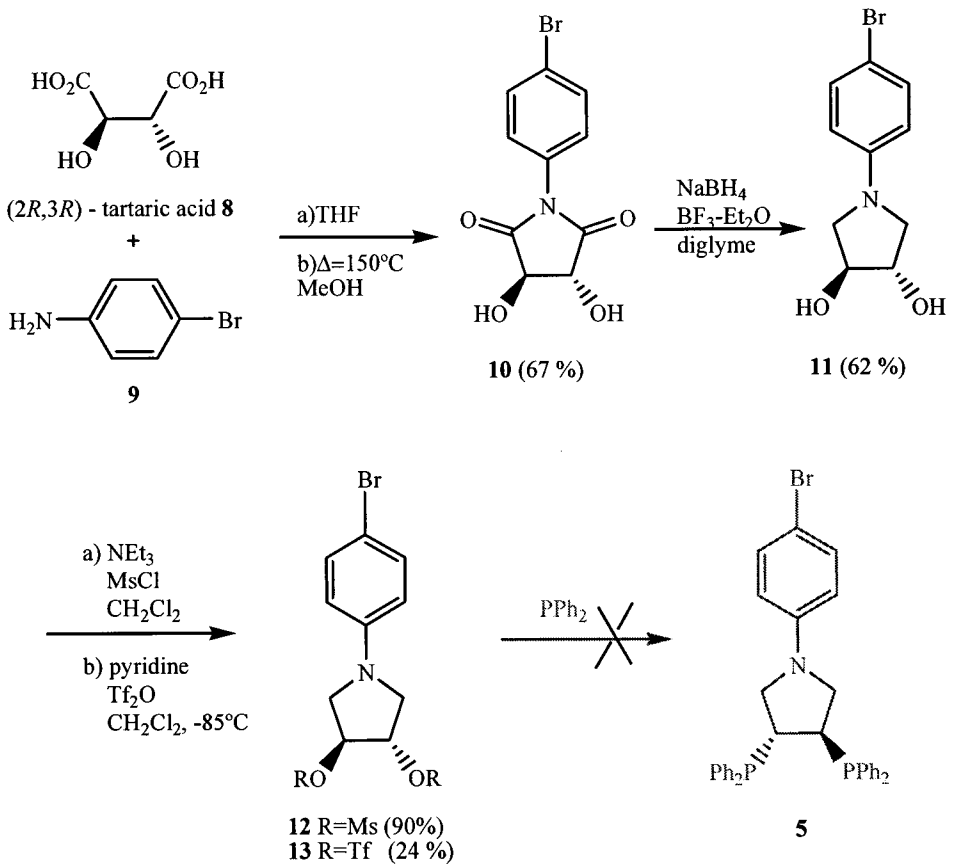
Scheme 2. Representative routes for the functionalisation of diphosphine ligand **5** with an acetal group: a) Halogen exchange;[16] b) Suzuki reaction;[17] c) Heck reaction.[18]

optimized with the homogenous catalyst using the DEGUPHOS ligand **4** with $Rh(CO)_2acac$ as the Rh pre-cursor. It was then of interest to compare the immobilized system with the homogenous system.

2. Results and Discussion

2.1 Synthesis of PYRPHOS derivatives

In order to functionalize PYRPHOS **3** with the diacetal group, three different strategies were investigated (as mentioned above). The first strategy consisted in the synthesis of the diphenylphosphine **5**, a PYRPHOS derivative, according to the method depicted in the Scheme 3.



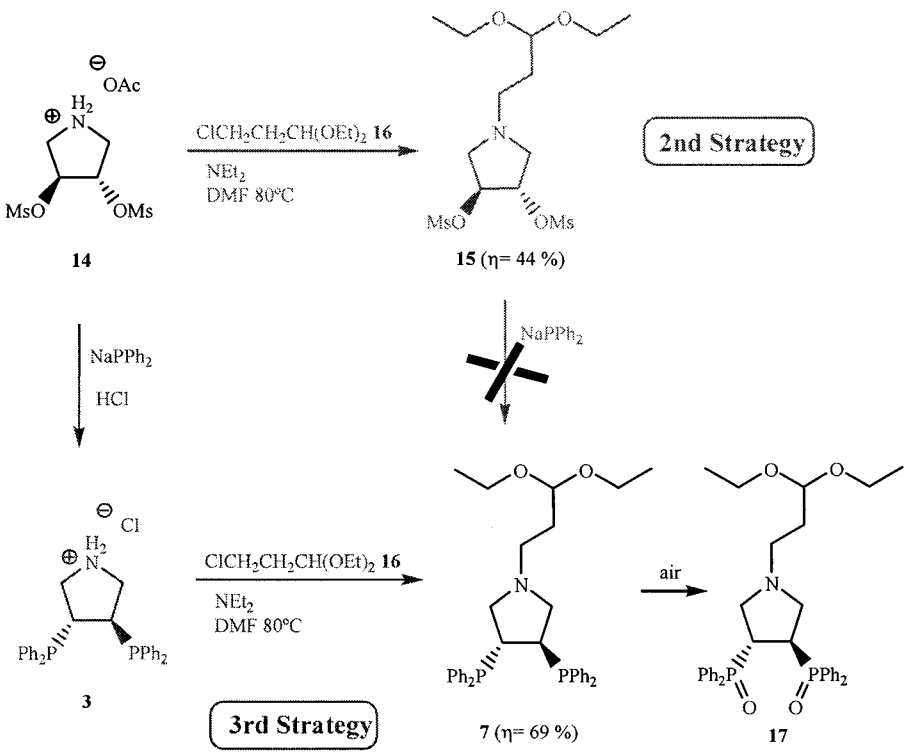
Scheme 3. Synthetic pathway to ligand **5**.

The synthetic pathway to the PYRPHOS derivative **5** (Scheme 3), can be divided into four key steps. The first step involved obtaining the tartranil product **10** using the procedure of Bourson.[20] This consisted in reacting cheap (2*R*,3*R*)-tartaric acid **8** and 4-bromoaniline **9** giving the tartranil **10** in 67% yield. In the second step, the pyrrolidine-diol **11** was obtained in good yield using Nagel's method,[11e] which consisted in the reduction of tartranil **10** using $NaBH_4/BF_3$-Et_2O. In the third step, the dimesylate **12** was obtained in a very good yield by reacting **11** with NEt_3 and methanesulfonylchloride. As an alternative activated intermediate, the ditriflate **13**, was synthesized using Marson's[21] procedure, but unfortunately the yield was low. The fourth step gave many problems and could not be successfully conducted. Several attempts were made to displace the mesylate groups of dimesylate **12**, using sodium, lithium and potassium diphenylphosphide, and different solvents like 1,3-dioxane, THF and DMF. None of these methods gave the diphosphine **5**. Another leaving group (triflate) was tested, the method used was that of Gonsalves *et al.*[19] and once again ligand **5** could not be obtained. It must be pointed out that Gonsalves *et al.*[19] obtained ligand **6** in 23% yield only. This was undoubtly due to the quality of the diphenylphosphides used, as they

were obtained from the corresponding chlorodiphenylphosphine precursor they probably contained impurities which could promote various side-reactions. Also of note was the fact that we naively failed to use the techniques used for handling air sensitive compounds at this stage.

The second strategy was, based on the Nagel method.[11] The pyrrolidine dimesylate salt **14** was obtained, and coupled with halogenated diacetal **16** using an excess of base (NEt_3) in DMF at 80°C, furnishing the respective dimesylate diacetal **15** in 44% yield (Scheme 4). This compound was reacted with $NaPPh_2$ and $KPPh_2$ in DMF, but ligand **7** could not be obtained: after purification the major compound obtained was the starting reagent **15**.

The third strategy involved the use of the well know PYRPHOS **3**.HCl salt (synthesized using Nagel's method) and coupled with halogenated alkyl diacetal **16** using excess base (NEt_3) in DMF at 80°C, furnishing the respective PYRPHOS diacetal **7** in 69% yield. This ligand is sensitive to air and had to be carefully protected from air, as it suffers oxidation very easy, giving the corresponding oxide **17.** Ligand **7** was characterized by ^{31}P NMR, showing a signal at -7.6 ppm whereas the DEGUPHOS ligand has its resonance at -5 ppm.[11e] The phosphinoxide **17** had a signal at 33 ppm in



Scheme 4. Second and third strategies.

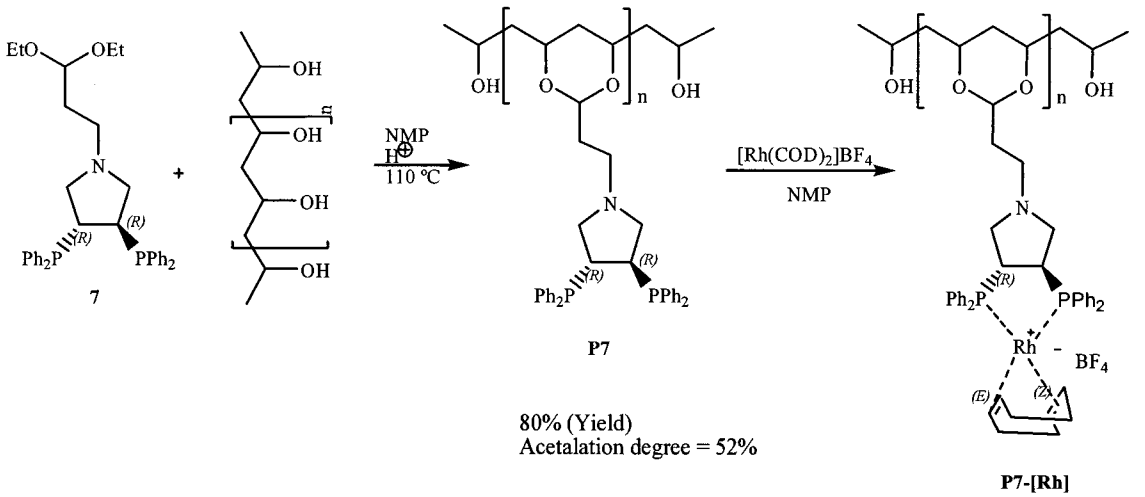
the ^{31}P NMR spectrum at lower field. Ligand **7** presented a ^{1}H NMR spectrum with the characteristic hydrogen of the acetal at 4.5 ppm, and the aromatic hydrogens around 7.41 – 7.10 ppm. In the case of ligand **17**, the difference was in the aromatic hydrogen region of around 7.69 – 7.10 ppm. These signals are more deshielded in the case of ligand **17**.

2.2. Immobilization of ligand 7 on PVA Support

Ligand **7** was immobilized to PVA via the transformation of the free diol groups of commercially available PVA into cyclic 1,3-dioxanes substituted at the 2-, 4-, and 6-positions via an acid catalyzed transacetalation reaction in NMP (Scheme 5). The ethanol released during the transacetalation reaction was distilled off during the reaction. The resulting polymers **P7** were characterized by spectroscopic methods. Characterization of the polymers via spectroscopic methods however, is somewhat ambiguous as the spectra could not be compared to those of suitable standards.

A comparison of the ^{1}H NMR spectra of **7** with **P7**, where the functionalisation on the PVA is confirmed by the absence of signals for the methyl groups of the ethyl units at 1.15 ppm. Furthermore, proton resonances of the aromatic protons (at 7.5 ppm) on the polymer **P7** overlapping with the proton resonance of the acetal showed the successful modification of the polymer. Accordingly the ^{31}P NMR spectrum of **P7** showed the same chemical shift for the P atom as for ligand **7**, which was -7.67 ppm. These findings confirm the successful modification of the PVA. The degree of acetalation was determined by making a comparative estimate between the initial weights of ligand **7** and PVA and the final weight of the **P7**. This calculation estimates that 52% ligand was immobilized on the polymer.

Complexing **P7** with the Rh complex was analogously performed using the procedure for the free ligand **7**: by reaction of $[Rh(COD)_2]BF_4$ in NMP solution in the same way as for the formation of pre-catalysts of the type [(COD)(phosphine)rhodium(I)]BF_4 (Schemes 5).[11e] The ^{31}P NMR spectrum of the **P7**-[Rh] complex showed a multiplet at 34.0 – 36.0 ppm, these signals are characteristic of the complex [(COD)(phosphine)rhodium(I)]BF_4, but not a pure complex was obtained, traces of phosphine oxide were present on the polymer.



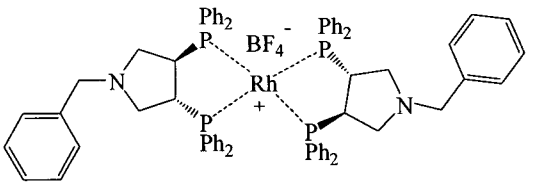
Scheme 5. Immobilization onto a PVA support.

The polymeric pre-catalysts were then adsorbed on an inorganic support, here cylindrical Al_2O_3 pellets with a size of 3.3 mm diameter and 3.9 mm length were employed. Therefore the Rh-modified polymer was dissolved in an organic solvent, such as NMP, and adsorption on the Al_2O_3 pellets (76 g, the maximum quantity introduced to the mechanical support of the reactor) proceeded by simple removal of the solvent in the presence of the support. It was expected that the polymeric layer was stable under the catalytic conditions of the CAHF reaction and suitable for interfacial catalysis.

In order to demonstrate that the immobilized catalyst Rh-**P7** was recyclable, a number of repetitive CAHF experiments of styrene were carried out.

It must be noted that immobilized ligand P7 was not spectroscopically 100% pure, it consisted of 90% ligand P7, the other 10% were identified as oxidized product. Nevertheless Rh-loading proceeded with this ligand in order to show the general capability of this approach for obtaining active Rh-catalysts in the CAHF.

2.3 Synthesis and characterization of bis[(3*R*,4*R*)-N-Benzyl-3,4-Bis(diphenylphosphino)pyrrolidin-P,P']rhodium-tetrafluoroborate 18

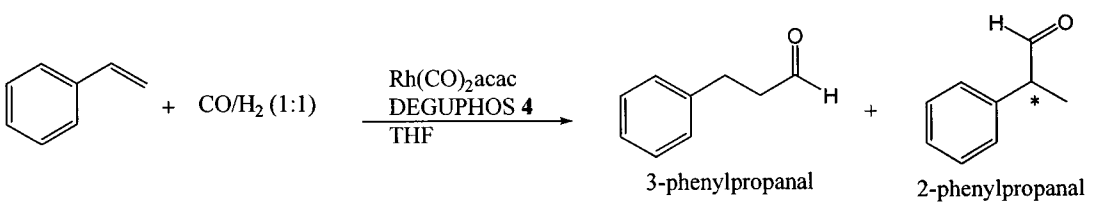


18

The rhodium complex **18** was synthesized with 1 equiv. of $[Rh(COD)_2]BF_4$ and 2 equiv. of DEGUPHOS **4** in dichloromethane, affording the complex in good yield. The ^{31}P NMR spectrum of **18** showed a doublet at 35 ppm with J=131 Hz, this coupling constant is characteristic for the tetra-coordinated Rh complex. This complex was evaluated in CAHF.

2.4. Asymmetric Hydroformylation catalyzed by Rh(I)

Hydroformylation is the reaction of alkenes with carbon monoxide and hydrogen to form aldehydes, and is a versatile method for functionalisation of C-C double bonds (Scheme 6, Figure 3).[1] Styrene, being a generally accepted and widely used benchmark substrate for the asymmetric hydroformylation reaction, was selected as the substrate (Scheme 6).[5]



Scheme 6. Catalytic asymmetric hydroformylation using a Rh-DEGUPHOS pre-catalyst.

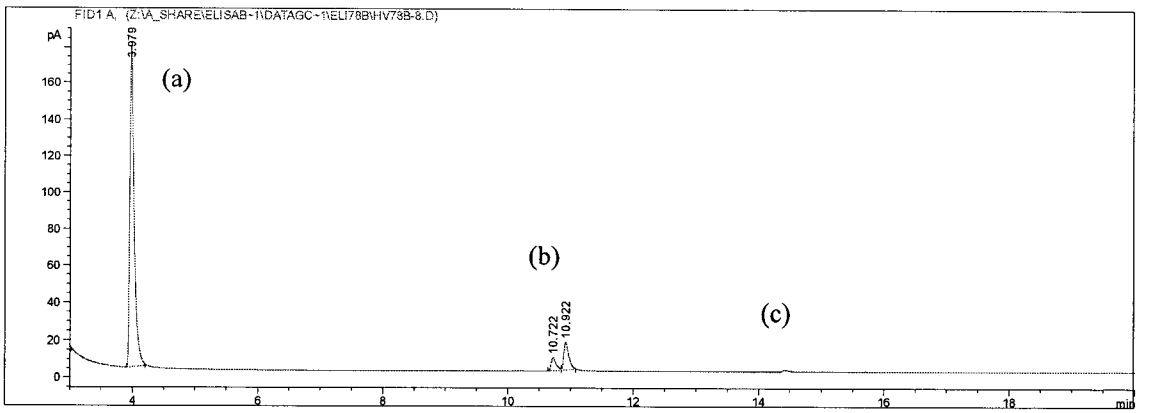


Figure 3. Chromatogram from a CAHF of styrene with the homogeneous catalyst **18**: (a) styrene; (b) branched aldehydes; (c) linear aldehyde.

2.4.1 CAHF of styrene with homogeneous catalyst

In order to determine the ideal reaction conditions for the CAHF of styrene with the immobilized pre-catalyst **P7**-[Rh] a series of CAHFs of styrene were performed using an *in situ* catalyst system with DEGUPHOS **4** or **17**. In this way, the activity and selectivity of these catalyst systems could be compared. In this approach, the catalysts were prepared *in situ* by mixing the substrate, ligand **4** or **17** with the catalyst precursor: $Rh(CO)_2acac$ in different ratios and different solvents. The reactor was pressurized and heated up with different pressure conditions (80°C, 20 or 10 bar (1:1 CO/H_2)), and the reagents were allowed to react under these conditions. The gas uptake was meticulously measured (Table 1, Figures 4 and 5) and the reaction progress monitored by sampling followed by GC-analysis.

By sampling the reaction values for the regioselectivity and enantioselectivity it was possible to evaluate the catalysts performance (Table 1, Figures 4 and 5). It turned out that a change of the ligand in the catalytic system from DEGUPHOS **4** to its related phosphinoxide **17** had a crucial impact on the selectivities of the CAHF of styrene: regioselectivity (the % of desired branched aldehyde) was diminished, favoring the linear product over the branched one, and the ee dropped considerably as well. Furthermore, regarding the activity, this was not positively influenced. So the phosphinoxide **17** was overall a very inadequate ligand. A representation of its concentration versus time curves is thus omitted from figures 4 and 5.

Table 1. Reagents and conditions for the CAHF of styrene[a]

Run	Ligand (mg, mmol)	$Rh(CO)_2acac$ /mg (mmol)	solvent (mL)	t (h)	p (bar)	Conversion (%)[d]	ee[b] (%)	Regio-selectivity[c] (%)
1	**4** (13.1, 0.024)	6.0 (0.023)	THF (195)	7 (20)[d]	10	11(62)	34(17)	87(74)
2	**4** (13, (0.024)	5.6 (0.022)	THF (195)	5.5	20	10	34	93
3	**4** (60.5, 0.114)	6.2 (0.024)	THF (195)	7.15	20	18	42	96
4	**4** (12.9, 0.024)	5.7 (0.022)	Toluene (195)	6.57	10	31	22	80
5	**4** (12.9, 0.024)	6.8 (0.026)	Toluene (190)	6.58	20	39	15	82
6	**17**(16.1, 0.027)	6.8 (0.026)	THF (195)	5.98	20	19	8	46
7	Complex **18** (0.023)		THF (190)	6(6)[e]	20(40)[e]	4(15)[e]	44 (42)[e]	95(95)[e]

[a] Reaction conditions: T = 80 °C; $CO/H_2$1= 1; 5 mL styrene.

[b] Enantiomeric excess determined by chiral GC after 7 h reaction time values in parentheses: after 20h reaction time.

[c] Regioselectivity = desired branched product after 7 h reaction time, values in parentheses: after 20h reaction time.

[d] Conversion after 7h reaction time, values in parentheses: after 20h reaction time.

[e] reaction at 90°C

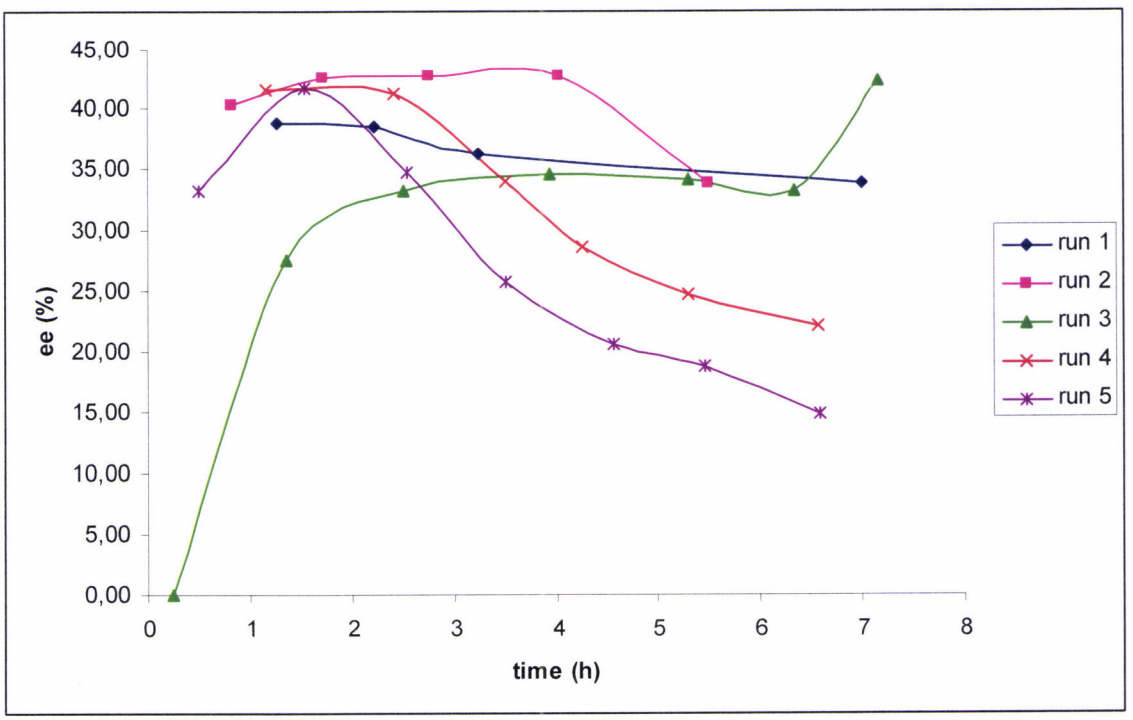


Figure 4. Representation of the ee (%) vs time.

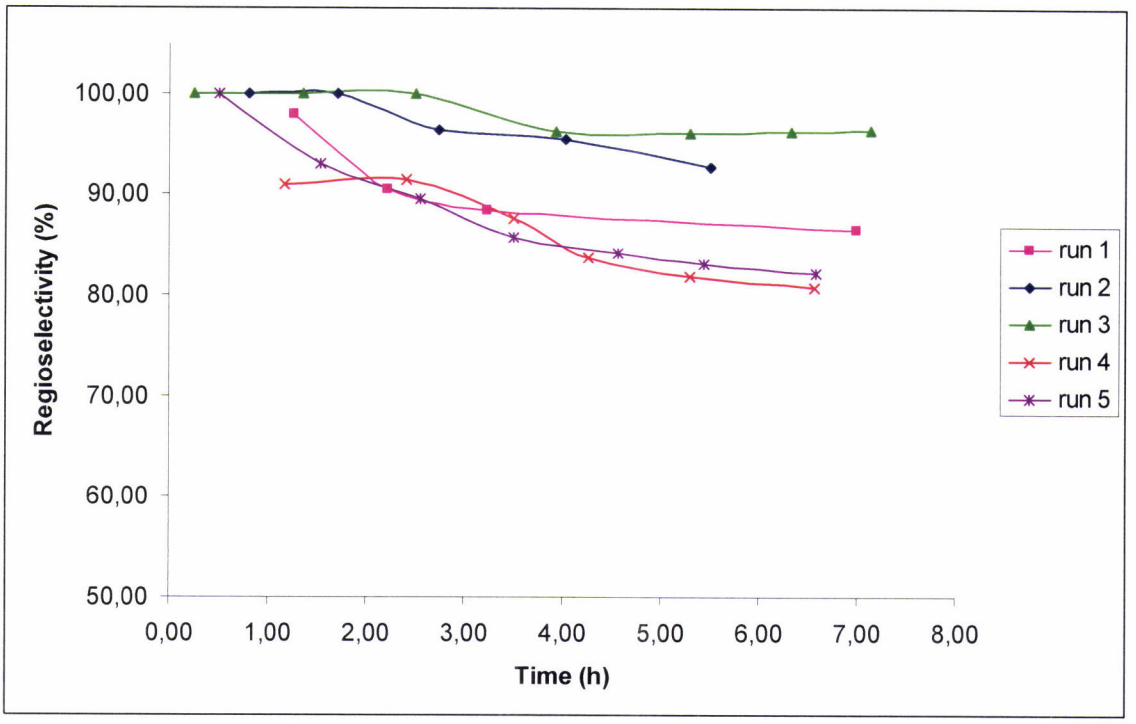


Figure 5. Representation of the regioselectivity (%) vs time.

The results represented in table 1 and figure 4 and 5 show that the run 4 and 5 where toluene was used, show higher activity than the experiments with THF as the solvent (runs 1-3) but suffer from lower selectivity in terms of regioselectivity and ee. This is furthermore confirmed by their corresponding concentration versus time curves where for these runs during the experiments a significant decrease in ee and regioselectivity is observed as well, which might be due to the lower potential of toluene to act as a stabilizing solvent for the highly reactive Rh-containing intermediate(s) that lead(s) to the branched product.

The experiments performed in THF show a somewhat lower activity, but a constant ee of *ca* 35% was obtained with a high regioselectivity of between 86 and 97%. Based on these two experiments, it seemed that the active catalyst could be decomposed via decomplexation of the ligand from the Rh metal, after the 4th hour (Figures 3 and 4). To maintain a sufficient quantity of the active catalyst during the catalytic reaction a slight excess of DEGUPHOS **4** (run 3) was introduced to the reaction mixture, the concentration versus time curves indicated an induction period for catalyst formation which could explain the increasing regioselectivity and ee during this experiment leading to the assumption that an already preformed catalyst might have shown better selectivities. An excess of ligand should lead to a better selectivity but

with lower activity according to analogous studies with analogous catalytic systems.[22]The experiment with complex **18** at 20 bar and 80°C (run 7), reached a constant and good ee of 44% and also gave a very good regioselectivity, (giving 95% of branched aldehyde), however, the activity of the catalyst was lower because, of the presence of a less active tetracoordinated complex. In order to get a better yield we decided to increase the pressure and temperature to 40 bar and 90°C, respectively. The results obtained for the ee and regioselectivity were maintained, but only a 15 % conversion was obtained. In conclusion, the results with complex **18** were similar to that obtained when an excess of ligand was used (run 3), which is not unexpected as this tetra-complex should be formed under *in situ* conditions. The tetracoodinate complex is stable for the CAHF, giving good selectivity but a lower activity.

2.4.2 CAHF of styrene with a heterogeneous catalyst

The CAHF of styrene was carried out in order to evaluate the activity and selectivity of the immobilized catalyst on the aforementioned support, [**Rh**]-**P7**. The reactions were conducted at 80°C and 20 bar in toluene. Toluene was used instead of THF as it gave better conversions, despite the fact, that toluene gave inferior ees and regioselectivities than THF. The better conversion was a more important aspect to consider because generally heterogeneous reactions are slower and give lower conversions. The higher conversion should enable a more detailed insight into the changes in the selectivity and product distribution caused by a change from the homogeneous to the immobilized catalyst system. The results obtained are shown in Table 2 and Figures 6 - 8.

The Experiments were performed in the following way: the immobilized catalyst was put in the autoclave in a cage, both toluene and styrene were added and the autoclave pre-pressurized to *ca.* 10 bar, the autoclave was heated to 80°C and the pressure was adjusted to 20 bar. This moment was taken as the starting point of the reaction, samples were taken and analyzed via GC (Figures 7 and 8). At the end of the reaction the autoclave content was released and collected and a new substrate and solvent were added and the procedure repeated. A sample was taken in order to determine the constitution of the mixture in the autoclave at the beginning, thus acting as the reference point.

Table 2. Catalytic asymmetric hydroformylation with [Rh]-**P7**.[a]

Cycle	t (h)	Conversion (%)	ee[b] (%)	Regioselectivity[c] (%)	Chemoselectivity[d] (%)
1	9.92	86	9	85	62
2	6.18	80	10	77	78
3	4.95	39	9	62	80
4	7.08	46	8	57	94
5	6.43	49	7	56	97
6	6.95	59	6	56	98
7	6.58	60	5	56	100
8	6.08	78	7	55	100
9	6.37	38	8	55	100
10	6.08	62	4	52	100

[a] Reaction conditions: T = 80 °C; p = 20 bar (1:1 CO/H_2); 195 mL toluene; 5 mL styrene, ~1.2 mmol (2.76 mol%) [Rh]-**P7**;

[b] Enantiomeric excess determined by chiral GC.

[c] Regioselectivity = value of the desired branched product.

[d] Chemoselectivity = value of the desired product.

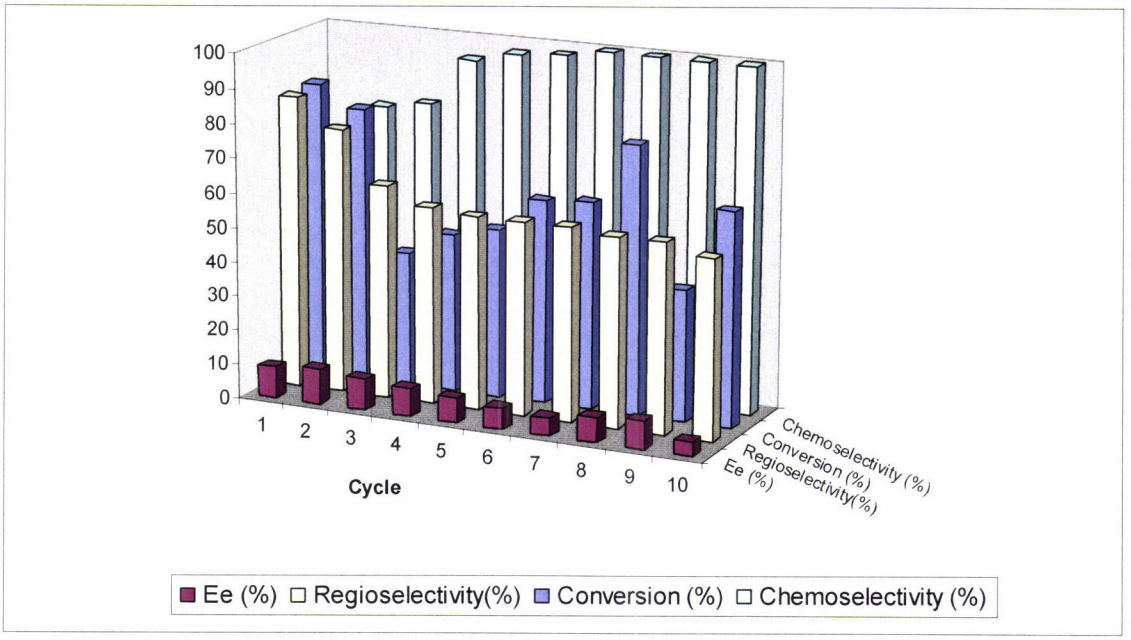


Figure 6. Representation of conversion, regioselectivity, chemoselectivity and ee in the different runs of hydroformylation with immobilized catalyst.

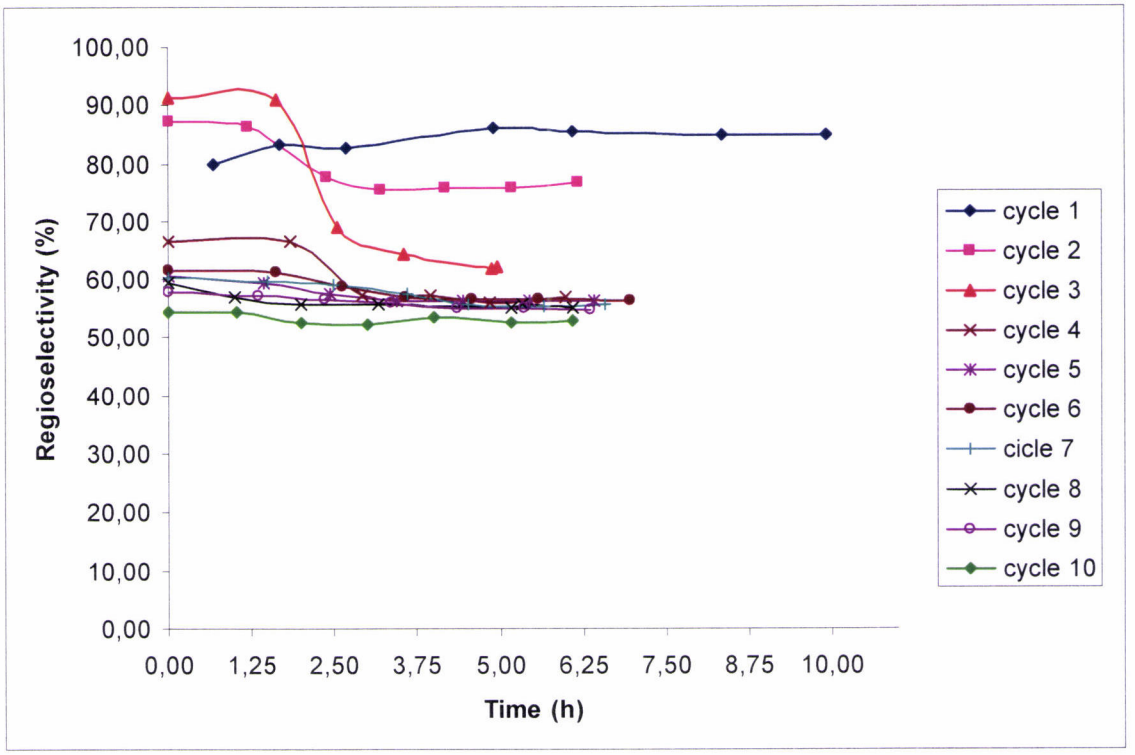


Figure 7. Representation of the regioselectivity (%) vs time.

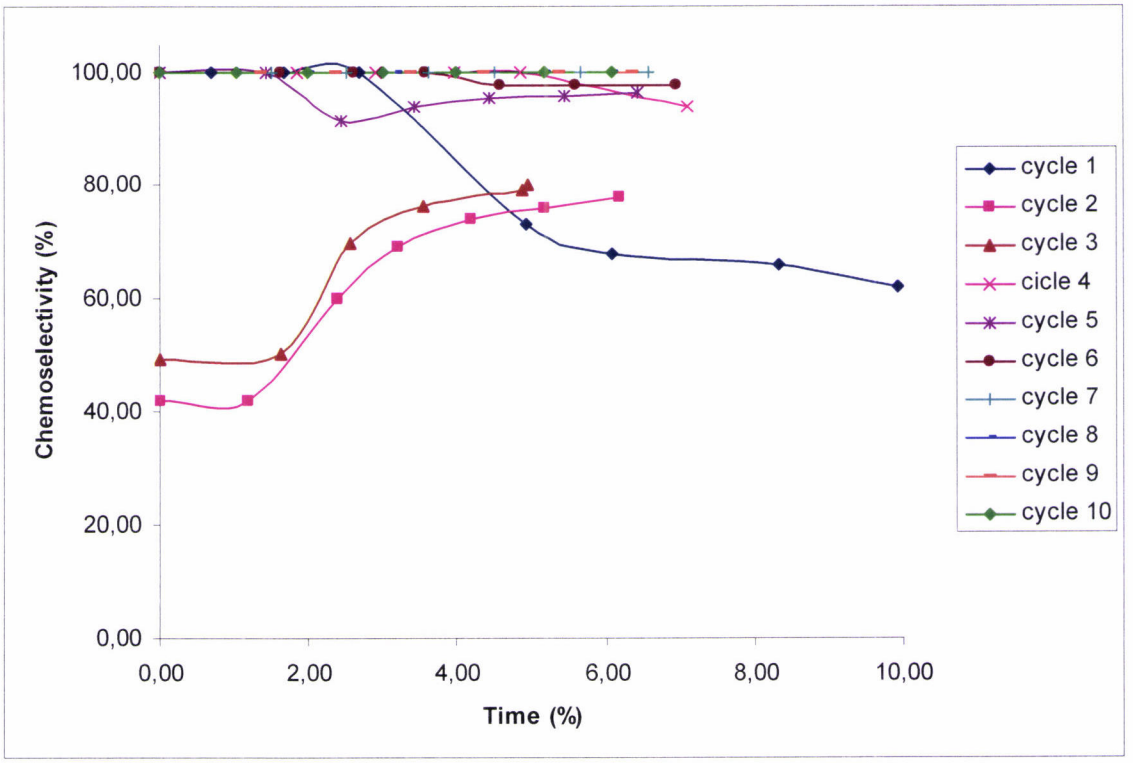
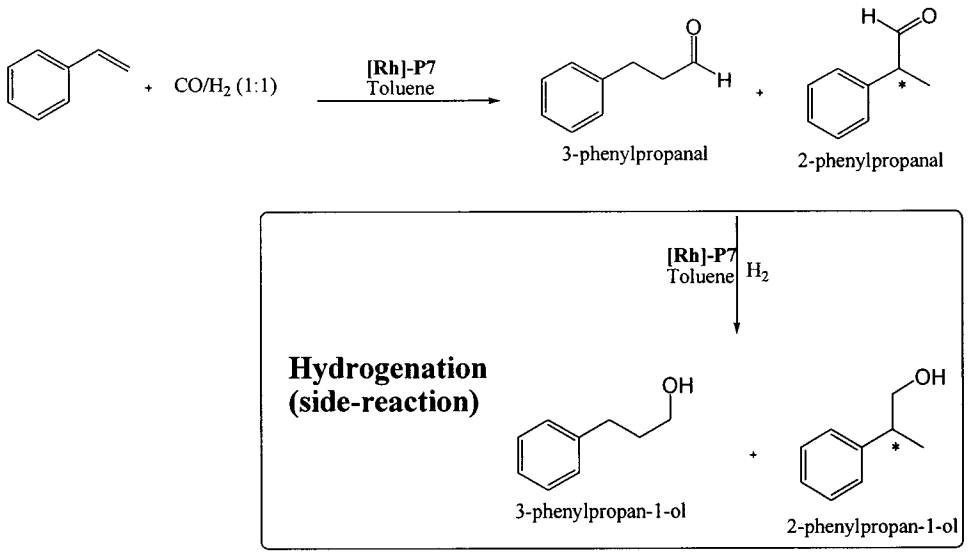


Figure 8. Representation of the chemoselectivity (%) vs time.

The [Rh]-**P7** could be recycled up to ten times without being washed. The active catalyst gave satisfactory conversions and regioselectivities (% of desired branched aldehyde), but not enantioselectivities and in some cases gave low chemoselectivities (% of desired products). Generally the ees were inferior to those of the homogeneous system with a best ee of only 10% being obtained in the 2nd cycle, but the ees observed can be considered as constant over the sequence of consecutive runs. These results might have been affected by the already mentioned impurities in the catalyst, so that here a more general comparison over the 10 consecutive experiments in the CAHF had to be considered. Under these conditions, the CAHF with the heterogeneous catalyst also gave alcohols as hydrogenation side-products (Scheme 7), these products were well identified by GC-MS, and these compounds weren't formed in the CAHF with the homogeneous catalysts. The best conversions and regioselectivity observed were 86% with 85% rs and 80% with 77% rs, in the 1st and 2nd cycles, respectively, but in these cases a significant quantity of hydrogenation products were obtained. Over the 10 experiments a general decrease of the activity was observed from *ca* 85 to *ca* 60 % which could be a sign of catalyst deactivation or leaching. The regioselectivity also decreased from 85 to 52% (Figures 7 and 8). This effect could be explained hypothetically, for example by the oxidation of the catalyst since the values were closer to that obtained with the ligand **17**. Or that the immobilized catalysts constituted of immobilized **17** were less prone to deactivation than the catalysts formed from the immobilized phosphine and thus persisted longer. On the other hand the decrease in the regioselectivity is accompanied by an increase in the chemoselectivity from 62 to 100% so that in the latter experiments no hydrogenation products were formed any more (Figures 6 and 8). All these findings show that the catalyst changes during the repetitive runs till the end reaching a plateau level with constant catalytic behavior of unfortunately low enantioselectivity. These findings may be due to several factors: (i) uncontrolled cleavage of the acetals and thus release of the free catalyst from the polymer, and/or (ii) uncontrolled leaching of the Rh into the organic phase without any deprotection of the acetals from the polymer and/or (iii) formation of less active complexes on the polymer with possible partial leaching of the metal.

To answer these questions more detailed investigations on the catalyst system are required which will be addressed at a future date.



Scheme 7. CAHF of styrene using the immobilized catalyst with subsequent hydrogenation to alcohol products (side-products).

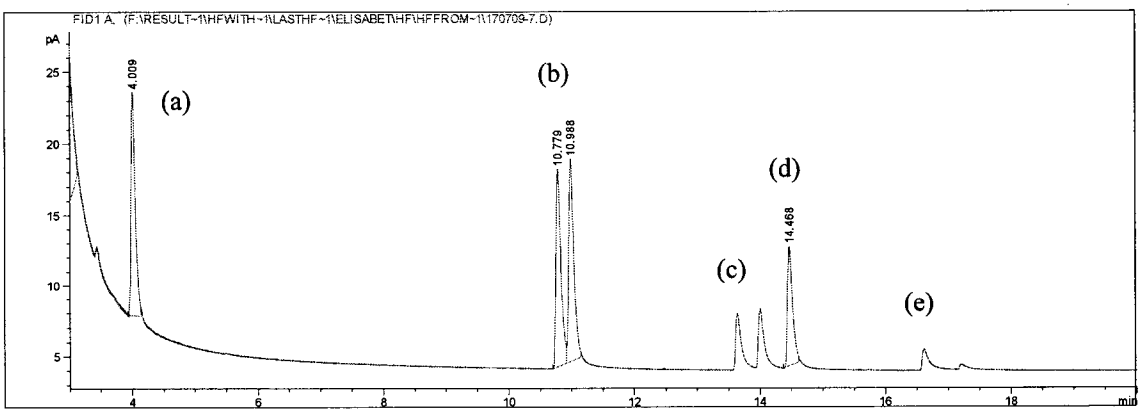


Figure 9. Chromatogram of CAHF of styrene with heterogeneous catalyst: (a) styrene; (b) branched aldehydes; (c) branched alcohols, (d) linear aldehyde; (e) linear alcohol.

3. Conclusions

A new method for the functionalization of PYRPHOS with a diacetal group bearing appendage was successfully developed. The successful immobilization of this PYRPHOS analogue to PVA was described. The PYRPHOS analogue was introduced onto the polymer by a one-step transacetalation reaction showing a good degree of acetalation.

The best ee obtained in this study for the CAHF of styrene with DEGUPHOS ligand **4** was 42% with 93% regioselectivity at 18 % conversion, without any alcohol side-product, at 80°C and 20 bar in THF. The CAHF in toluene gave better conversions but lower ees and regioselectivities.

The immobilized catalyst [**Rh**]-**P7** was evaluated in the CAHF under similar conditions, but the highest ee over ten cycles was only 10%. The activity of the immobilized catalyst decreased during the recycling experiments from 80 to 60 % accompanied by a loss in regioselectivity from 70 to 10 % but an increase in the chemoselectivity, so that at the end no hydrogenation side-products were formed. The catalyst turned out to have reached a plateau in activity, regio- and chemoselectivity as well as in the enantioselectivity which was low, but anyhow observable, which was a strong chemical indication for the successful application of the immobilization principle.

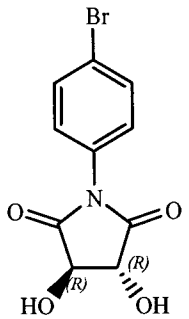
4. Experimental Procedure

General remarks

All the experiments which were sensitive to moisture or air were carried out under an argon atmosphere using standard Schlenk techniques. Compounds **14**, PYRPHOS **3** and DEGUPHOS **4** were synthesized using the Nagel's procedure.[11e] PVA with a molecular weight of 22,000 daltons was purchased from Aldrich. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on an Avance 250 (^{1}H 250 MHz, ^{13}C 63 MHz, ^{31}P 101 MHz) and an Avance 400 (^{1}H 400 MHz, ^{13}C 100 MHz, ^{31}P 162 MHz) spectrometers. Mass spectra were recorded on a VG Autospec M(Waters-Micromass) spectrometer using the FAB technique, Waters-Micromass GC-TOF and MicroTOF Focus (Bruker Daltonics) using the TOF technique. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. Column chromatography was carried out on silica gel (sds, 70-200 μm) and flash column chromatography (Merck, 40-63 μm and sds, 40-63 μm). TLC was carried out on aluminium backed Kisel-gel 60 F254 plates (Merck). Plates were visualised either by UV light or phosphomolybdic acid in ethanol. Gas chromatographic (GC) analyses of the products were performed on a Hewlett Packard (HP) 6890 series instrument equipped with a flame ionization detector (FID). The chromatograph was fitted with a Supelco Beta Dex 225 column.

4.1 Synthesis of PYRPHOS derivatives:

(3*R*,4*R*)-*N*-(4-bromophenyl)-3,4-dihydroxypyrrolidine-2,5-dione 10



10

4-Bromoaniline **9** (34.41 g, 0.2 mol) was added dropwise to a refluxing slurry of *L*-(2*R*,3*R*)-tartaric acid **8** (30.00 g, 0.200 mol) in 375 mL of THF. After 45 minutes, the slurry was cooled to room temperature and stirred for an additional 48h. The resulting white solids were filtered and dried in vacuum. Yield: 43.33 g (71%);

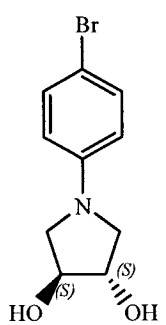
(20.46 g, 0.067 mol) of this solid was heated at 150 °C in the solid state. After 8h, the resulting yellow solids were slurried in methanol and filtered (3 x 150 mL). Concentration of the methanol filtrate afforded a yellow solid after 18 h. Yield: 13.00g (67%); mp 243 °C (decomposition);

^{1}H NMR (250 MHz, DMSO-d_6): δ= 7.69 (d, 2H, *J*=8.4 Hz, C*H*(Ar)), 7.29 (d, 2H, *J*= 8.4 Hz, C*H*(Ar)), 6.41 (s, 2H, -O*H*), 4.56 (d, 2H, *J*= 3.9 Hz, C*H*) ppm.

^{13}C NMR (63 MHz, DMSO-d_6): δ= 173.74, 131.84, 131.25, 128.94, 121.19, 74.32 ppm.

TOF-MS *m/z*: 284.96 $[M]^+$; 286.96 $[M+2]^+$ HRMS (TOF) found, 284.9633; $C_{10}H_8NO_4Br$ requires 284.9637.

(3*S*,4*S*)-*N*-(4-bromophenyl)pyrrolidine-3,4-diol 11



11

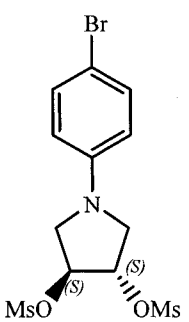
A 0.5 L two-neck round-bottom flask was fitted with a magnetic stir bar and a reflux condenser. The flask was charged with 100 mL of dry diglyme and BF_3-Et_2O (25.85 mL, 0.204 mol) and the flask was cooled to 0 °C in an ice bath. Compound **10** (15.0 g, 0.052 mol) was added followed by sodium borohydride (5.11 g, 0.135 mol) which was added in small portions. The mixture was stirred at room temperature until the gas evolution had ceased, the flask was heated to 70°C for 2 h and then cooled to room temperature, and HCl 6M (69.33 mL, 0.416 mol) was added cautiously. The mixture was heated at 70 °C over 15 min. Under stirred, NaF (31.89 g, 0.759 mol) was added to the mixture and heated at 100°C over 30 min (the mixture had to be acid). The mixture was cooled to 20 °C and NaOH 20% (81 mL) was added. The solid was filtered and the organic layer dried under *vacuo*. The solid was dissolved in water (100 mL) and this was extracted with Et_2O over 24h. The solvent was removed under *vacuo* and the solid was recrystallized with ethyl acetate to give the *title compound* **11** as a white solid. Yield: 8.36 g (62%); mp. 156°C

^{1}H NMR (250 MHz, DMSO-d_6): δ= 7.26 (d, 2H, J= 9 Hz, C*H*(Ar)), 6.43 (d, 2H, *J*= 9 Hz, C*H*(Ar)), 5.12 (d, 2H, *J*= 2.5 Hz, CH), 4.03 (s_b, 2H, OH), 3.39 (dd, 2H, *J*= 4, 10 Hz, CH_2), 3.03 (d, 2H, *J*= 10 Hz, CH_2) ppm.

^{13}C NMR (63 MHz, DMSO-d_6): δ= 146.71, 131.27, 112.95, 105.54, 74.53, 53.48 ppm.

TOF-MS *m/z*: 257.01$[M]^+$ HRMS (TOF) found, 257.0122; $C_{10}H_{12}NO_2Br$ requires 257.0051.

(3*S*,4*S*)-*N*-(4-bromophenyl)pyrrolidine-3,4-diyl dimethanesulfonate 12



12

A 100 mL two-neck round-bottom flask was fitted with a magnetic stir bar. The flask was charged with compound **11** (2.00 g, 7.75 mmol), dry CH_2Cl_2 (50 mL) and Et_3N (2.7 mL, 19 mmol) and the mixtures was cooled at 0 °C. Methanesulfonylchloride (1.47 mL, 19 mmol) was added dropwise over 30 min. The mixture was stirred over 30 min, and

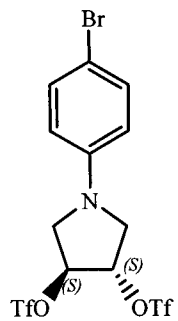
filtered to remove the salt. The organic solvent was removed by evaporation and the resulting solid was recrystallized with hexane/ethyl acetate giving the *title compound* as a white solid: Yield: 2.89 g (90%);

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.33 (d, 2H, *J*=8.2 Hz, CH(Ar)), 6.43 (d, 2H, *J*=8.2 Hz, CH(Ar)), 5.33 (s, 2H, CH), 3.81 (d, 2H, *J*=11 Hz, CH_2), 3.54 (d, 2H, *J*=11 Hz, CH_2), 3.12 (s, 6H, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ= 145.17, 132.12, 113.78, 79.67, 51.57, 38.54 ppm.

FAB-MS m/z: 414.92 [M+1].

(3*S*,4*S*)-*N*-(4-Bromophenyl)-3,4-bis(trifluromethanesulfonyloxy)pyrrolidine 13

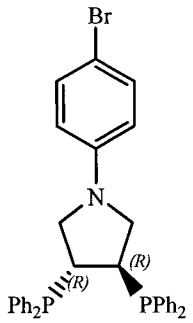


13

To a solution of (3*S*,4*S*)-*N*-(4-bromophenyl)pyrrolidine-3,4-diol **11** (1.0 g, 3.87 mmol), in CH_2Cl_2 (80 mL) under nitrogen, dry pyridine (0.657 mL, 8.13 mmol) was added. After stirring for 10 min, the reaction temperature was lowered to -85°C and trifluoromethanesulfonic anhydride (1.31 mL, 7.74 mmol) was added by directly bubbling it into the reaction solution. The temperature of the reaction mixture was warmed to room temperature and stirred for 18h. Work-up consisted in adding $NaHCO_3$ sat (30 mL) to the mixture and the aqueous phase was extracted (3 x 30 mL) with Et_2O. The organic phases were collected, dried with dry $MgSO_4$, filtered and concentrated under *vacuo*, to give a brown-orange semi-solid. The crude product was purified by flash column chromatography over silica gel eluting with 1:5 ethyl acetate:hexane. The appropriate fractions were combined and evaporated to give **13** as a pink solid. Yield: 0.49 g, (24%);

^{1}H NMR (300 MHz, $CDCl_3$): δ=7.39 (d, 2H, *J*=9 Hz, C*H*(Ar)), 6.47 (d, 2H, *J*=9 Hz, C*H*(Ar)), 5.53 (s, 2H, C*H*OTf), 3.95 (dd, 2H, *J*=12, 4.6 Hz, CH_2), 3.65 (dd, 2H, *J*=11.4, 1.8 Hz, CH_2) ppm.

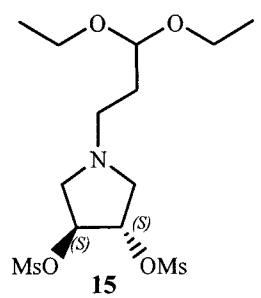
Attempted Synthesis of (3*R*,4*R*)-*N*-(4-Bromophenyl)-3,4-bis(diphenylphosphine)pyrrolidine 5



5

A 25 mL two-neck round-bottom flask was fitted with a magnetic stirbar under nitrogen. The flask was charged with dry dioxane (5 mL), $ClPPh_2$ (0.26 mL, 1.43 mmol), and Na (0.13 g, 5.65 mmol), the mixture was warmed at 110°C and stirred overnight. This yellow-orange mixture was added to a solution of compound **13** (0.350 g, 0.67 mmol) in dry DMF (60 mL) at -40°C, and stirred for 24h. The mixture was filtered and the DMF was removed. The residue was dissolved in EtO_2 (5 mL) and extracted with water (3 x 3 mL). The organic layer was dried with dry $MgSO_4$, filtered and the solvent was removed *in vacuo*. The *title compound* **5** was not obtained.

(3S,4S)-*N*-(3,3-diethoxypropyl)pyrrolidine-3,4-diyl dimethanesulfonate 15



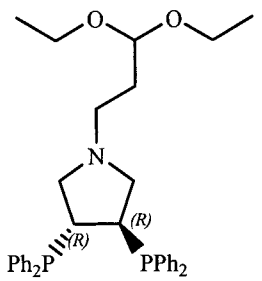
15

A 25 mL two-neck round-bottom flask was fitted with a magnetic stirbar under nitrogen. The flask was charged with compound **14** (0.1 g, 0.31 mmol), dry DMF (5 mL), Et_3N (0.35 mL, 2.5 mmol, 8 eq.) and 3-chloropropanaldehydediethylacetal **16** (0.16 mL, 0.9 mmol). The mixture was heated to 70 °C and stirred for 3 days. The mixture was then cooled to 40 °C and the DMF was removed. The residue was dissolved in CH_2Cl_2 (5 mL) and extracted with water (3 x 3 mL). The organic layer was dried with dry $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography with ethyl acetate to give *title compound* **15** as a brown oil. Yield: 0.054 g (44%);

^{1}H NMR (300 MHz, $CDCl_3$): δ= 5.14 (t, 2H, *J*= 4.7 Hz, RC*H*OH), 4.57 (t, 1H, *J*= 5.6 Hz, C*H*(OEt)$_2$), 3.65 (sextuplet, 2H, R-O-C*H*$_2$CH$_3$), 3.5 (sextuplet, 2H, R-O-C*H*$_2$CH$_3$), 3.11 (s, 6H, -SO_2CH_3), 2.78 (dd, 2H, *J*= 10, 4 Hz, RC*H*H-NR_2), 2.61 – 2.50 (m, 2H, RCH*H*-NR), 1.80 (dd, 2H, *J*= 7, 13 Hz, RCH_2CH_2-NR_2), 1.29 – 1.18 (m, 8H, RCH_2CHROCH_2CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ= 101.01, 82.29, 61.39, 58.27, 50.27, 38.35, 32.14, 15.27 ppm.

(3*R*,4*R*)-*N*-(3,3-diethoxypropyl)-3,4-bis(diphenylphosphine)pyrrolidine 7



7

A 25 mL two-neck round-bottom flask was fitted with a magnetic stirbar under nitrogen. The flask was charged with PYRPHOS **3**.HCl (0.7 g, 1.47 mmol), dry DMF (10 mL), Et_3N (1.23 mL, 8.82 mmol, 6 eq.) and 3-chloropropanaldehydediethylacetal (0.74 mL, 4.41 mmol). The mixture was heated to 70 °C and stirred for 2 days. The mixture was cooled to 40 °C and the DMF was removed. The residue was dissolved in CH_2Cl_2 (10 mL) and water (5 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography with (9:1) ethyl acetate:hexane to give *title compound* **7** as a yellow oil. Yield: 0.582 g (69%).

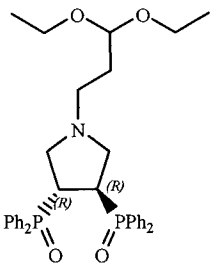
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.41 – 7.12 (20H, m, C*H*(Ar)), 4.50 (1H, t, *J*= 5.8 Hz, RC*H*(OEt)$_2$), 3.65 – 3.53 (m, 2H, -OC*H*$_2$CH$_3$), 3.51 – 3.40 (m, 2H, -OC*H*$_2$CH$_3$), 3.14 – 3.04 (m, 1H, RC*H*PPh_2), 2.87 (s_b, 1H, RC*H*PPh_2), 2.59 – 2.41(m, 4H, C*H*$_2$), 1.71 (q, 1H, *J*=9Hz, C*H*$_2$), 1.27 – 1.12 (m, 8H, C*H*$_2$, C*H*$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ= 137.05 (m, *C*(Ar)), 133.76 – 133.49 (m, CH_{ortho}), 128.81 – 128.20 (m, CH_{meta} and CH_{para}), 101.48 (s, *C*H(OCH_2CH$_3$)$_2$), 61.25, 61.08, 57.03 – 56.86 (m), 51.51, 38.16, 38.11, 29.68, 15.33 ppm.

^{31}P NMR (121.5 MHz; $CDCl_3$): δ= -7.7 ppm.

ESI-MS *m/z*: 570.27 [M+1].

(3*R*,4*R*)-*N*-(3,3-diethoxypropyl)-3,4-bis(diphenylphosphine)pyrrolidine oxide 17



17

Compound **17** was as a yellow spongy solid.‡

^{1}H NMR (400 MHz; $CDCl_3$): δ= 7.69 – 7.10 (20H, m, C*H*(Ar)), 4.37 (t, 1H, *J*=5.6H, C*H*), 3.70 (s_b, 2H, C*H*PPh_2), 3.56 – 3.50 (m, 2H, CH_2), 3.43 – 3.31 (m, 2H, CH_2), 2.91 – 2.83 (m, 2H, CH_2), 2,66 (s_b, 2H, CH_2), 2.41 – 2.34 (m, 1H, C*H*H), 2.31 – 2.28 (m, 1H, CH*H*), 1.48 (q, 2H, *J*=6.8 Hz, CH_2), 1.12 (d, 6H, CH_3) ppm.

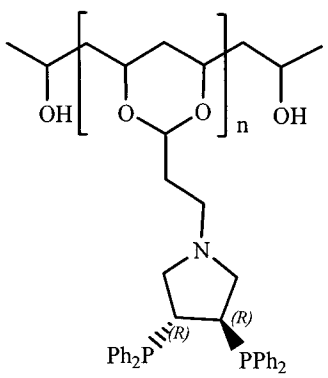
^{13}C NMR (100.61 MHz; $CDCl_3$): δ= 131.55, 131.42, 130.91, 130.78, 128.42, 128.37, 101.27, 61.22, 55.17, 50.32, 36.62, 35.94, 32.58, 15.28 ppm.

^{31}P NMR (161.97 MHz; $CDCl_3$): δ= 34.15 ppm.

$[\alpha]_D^{22} = +159.0 (c = 0.52, CHCl_3)$

TOF-MS *m/z*: 602.28 [M+1].

4.2. Immobilization of Ligand 7 to a PVA Support - P7



P7

An over stoichiometric amount of the diphosphino-functionalised benzaldehyde-diethylacetal **7** (0.79 g, 1.4 mmol), together with a stoichiometric amount of PVA (0.23 g), were dissolved in an appropriate amount of *N*-methyl-2-pyrrolidinone (11 mL). Gaseous HCl was added and the reaction mixture was warmed to *aprox.* 115 °C for a minimum of 12 h. The majority of the solvent was removed in vacuum, and the

‡ When inert handling conditions were not used.

polymers were precipitated by the addition of basic water (1g KOH in 30 mL H_2O). For removal of the salts, the polymers were purified by extraction with water for several days. Subsequent extraction with diethyl ether over CaH_2 for several hours eliminates the remaining traces of water and gives the supported phosphine **P7** as a colorless or slightly colored powder upon drying under vacuum. Yield: 0.64 g (80%); Acetalation degree: 52%.

^{1}H NMR (300 MHz; $CDCl_3$): δ= 7.72 – 7.20 (m, 20H, CH(Ar)), 3.60 (s_b,), 3.29 (s_b,), 2.67 (s_b,), 2.16 (s_b,), 2.18 (s_b,), 1.35 (s_b,) ppm.

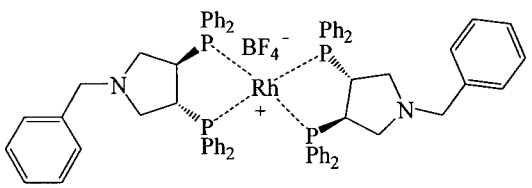
^{31}P NMR (121 MHz; $CDCl_3$): δ= -7.67 ppm.

Complexation of P7 to $[Rh(COD)_2]BF_4$

$[Rh(COD)_2]BF_4$ (0.48 g, 1.2 mmol) was added to a schlenk tube containing **P7** and NMP (20 mL). The mixture was warmed to 50 °C overnight, the color changed from brown to orange. Al_2O_3 pellets (78 g) were added to this mixture, the solvent was removed and the solid was extracted with Et_2O overnight to give the purified immobilized catalyst (77,937g).

^{31}P NMR (121 MHz; DMSO-d_6): δ= 34.0 – 36.0 (m) ppm.

4.3 Synthesis of bis[(3*R*,4*R*)-1-Benzyl-3,4-Bis(diphenylphosphino)pyrrolidin-P,P']rhodium-tetrafluoroborate 18



18

51 mg (0.124 mmol) $[Rh(COD)_2]BF_4$ were dissolved in 2 mL CH_2Cl_2, 130.9 mg (0.247 mmol) DEGUPHOS were added and CH_2Cl_2 (7 mL). There was a color change from red to orange. The mixture was stirred for 2 h at rt. The solvent was removed *in vacuo*, the residue was washed with pentane and Et_2O and dried under *vacuo*. The *title complex* **18** was obtained as a yellow-orange solid. Yield: 0.12 g (77%);

^{1}H NMR (250 MHz; $CDCl_3$): δ= 7.60 – 7.49 (m, 12H, CH(Ar)), 7.40 – 7.17 (m, 34H, CH(Ar)), 6.97 – 6.94 (m, 4H, CH(Ar)), 3.37 (dd, 4H J_{AB}=13, 41 Hz, CH_2NR_2), 2.98 (s_b, 4H, $CHPPh_2$), 2.45 (s_b, 4H, CH_2), 2.25 (s_b, 4H, CH_2) ppm.

^{31}P NMR (101 MHz; $CDCl_3$): δ= 35.3 (d, J_{RhP}=131 Hz) ppm.

4.4 Catalytic Asymmetric Hydroformylation

Hydroformylation experiments

Caution! The hydroformylation experiments are performed with syngas (1:1 = CO/H_2) which is extremely poisonous. Accidents may be lethal. When working with carbon monoxide a sensitive personal detector should be carried and all experiments are to be performed in a well ventilated fume hood equipped with a detector, maintaining the CO concentration in the fume hood below the MAC-value.

CAHF of styrene with homogeneous catalyst

Hydroformylation experiments were carried out in an autoclave. The styrene (5.0 mL, 43.5 mmol), $Rh(CO)_2acac$, chiral ligand and solvent were introduced to the autoclave which was then purged with syngas, pressurized to 10 or 20 bar and heated to 80°C for the duration of the reaction (6-20 h). In order to determine the conversion, the enantioselectivity and the regioselectivity, 1 mL aliquots of the mixture was removed hourly over a 6 - 8 hour period. A 0.1 mL aliquot of sample was taken out and diluted with 1.0 mL of CH_2Cl_2, which was analyzed by gas chromatography under the following conditions: Supelco Beta Dex 225 column, column temperature program maintained at 100°C for 5 min, then 4°C/min to 160°C.

Retention times:

4.00 min for styrene

10.78 min for (*R*)-2-phenyl-propionaldehyde (branched regioisomer)

10.99 min for (*S*)-2-phenyl-propionaldehyde (branched regioisomer)

14.16 min for 3-phenylpropionaldehyde (linear regioisomer)

CAHF of styrene with a heterogeneous catalyst

The previous procedure was used with the immobilized catalyst [**Rh**]-**P7** (67.7g), the quantities of styrene, toluene at 80°C and 20 bar. The reaction times are indicated in table 3. A 0.1 mL aliquot of sample was taken out and diluted with 1.0 mL of CH_2Cl_2, which was analyzed by gas chromatography under the following conditions: Supelco Beta Dex 225 column, column temperature program maintained at 100°C for 5 min, then 4°C/min to 160°C.

Retention times:

4.00 min for styrene

10.78 min for (*R*)-2-phenyl-propionaldehyde (branched regioisomer)

10.99 min for (*S*)-2-phenyl-propionaldehyde (branched regioisomer)

14.16 min for 3-phenylpropionaldehyde (linear regioisomer)

13.65 min (*R*)-2-penhylpropanol (branched regioisomer)

14.01 min (*S*)-2-penhylpropanol (branched regioisomer)

16.63 min 3-phenypropanol (linear regioisomer)

Table 3. Quantities of reagents, solvents and reaction times for the heterogeneous CAHF.

Cycle	Styrene (mL)	Toluene (mL)	t (h)
1	5	173,7	9,92
2	5	156	6,18
3	5	170	4,95
4	5	180	7,08
5	5	160	6,43
6	5	166	6,95
7	5	160	6,58
8	5 (4,7g)	(139,7 g)	6,08
9	5	168	6,37
10	5	160	6,08

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