Synthesis and Evaluation of Chiral Phosphine and NHC-Ligands for Heterogeneous Asymmetric Catalysis

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ORIENTADOR: *Professor Doutor Anthony J. Burke*

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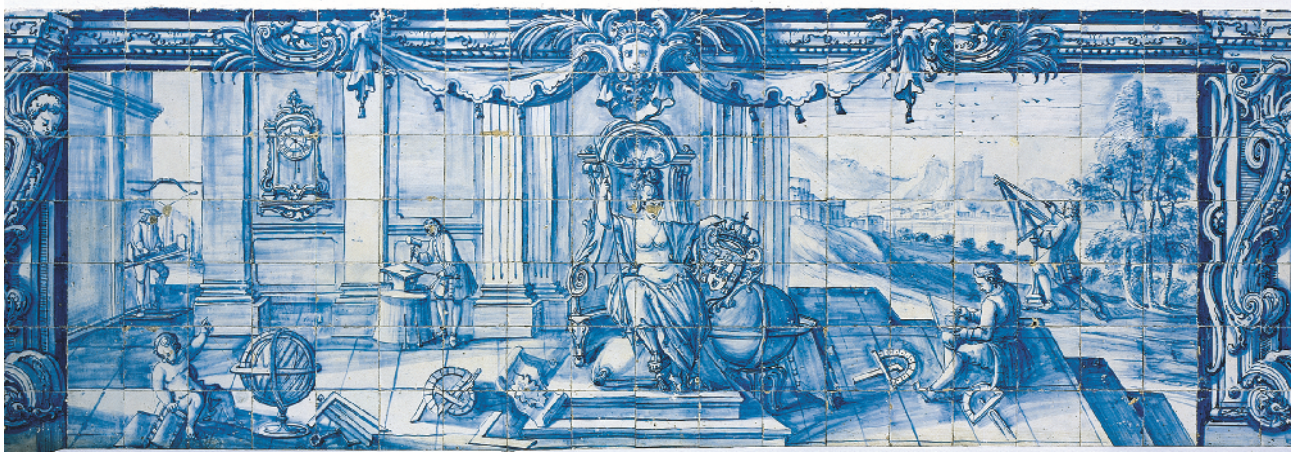

INSTITUTO DE INVESTIGAÇÃO E FORMAÇÃO AVANÇADA

To my Grandparent João,
my greatest treasure and exceptional storyteller, and
in memory of my beloved aunt Graça.

Ackowledgments

All the work presented in this document describes a long and hard journey through the field of Organic Chemistry (bridged with Organometallic Chemistry). The disappointments and frustrations were there almost all the time, but the good moments, although few, balanced in a very positive way all the knowledge gained with personal growth. My persistence and determination, along with a fantastic supportive background of persons, make my words in this small text look so insufficient, but really heartfelt.

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Abstract

The study of catalytic asymmetric arylations of appropriate substrates, using both known and novel chiral transition metal based catalysts was the focus of this thesis. This methodology leads to formation of C-C bonds, leading to the synthesis of interesting biologically active compounds.

Chiral amines, α-hydroxyesters, α-amino esters and acids, and bi-aryldiarylamines were synthesized using a variety of different substrates and transition metal catalysts, based on Pd, Rh and Ru.

Organoboron reagents were used successfully in all of these studies.

A novel family of *N*-heterocyclic carbene (NHC) ligand precursors were synthesized in good yields, and applied successfully in these catalytic reactions.

A novel homogeneous one-pot catalytic arylation/Suzuki-Miyaura sequence was developed to access bi-arylarylmethylamines. This was later transformed into an efficient heterogeneous variant, based on the Supported Ionic Liquid Phase Catalysis (SILPC) approach, which to date has never been used in such one pot procedures.

Keywords: Catalysis, Organoboron Reagents, Arylation, Palladium, Ruthenium, Rhodium, NHCs

Resumo

Síntese e Aplicação de Ligandos Quirais Fosfinas e NHCs em Catálise Assimétrica Heterogénea

No âmbito deste trabalho, foram estudadas as reacções de arilação catalítica assimétrica em vários substratos, utilizando novos e já conhecidos catalisadores quirais, possuindo metais de transição. Esta metodologia levou à formação de novas ligações C-C, fornecendo uma panóplia de interessantes compostos, podendo-se revelar intermediários extremamente úteis na síntese de compostos biologicamente activos.

Deve-se salientar a síntese de aminas quirais, α-hidroxiésteres, α-amino-ácidos e α-aminoésteres e também bi-arildiarilaminas, utilizando catalisadores de metais de transição, baseados em Pd, Rh e Ru.

Reagentes organoboronados foram aplicados com sucesso neste estudo.

Uma nova família de carbenos *N*-heterocíclicos (NHCs) foi obtida com bons rendimentos e aplicada, com sucesso, nas reacções catalíticas acima referidas.

Um novo método de catálise homogénea sequencial (arilação/Suzuki-Miyaura) foi desenvolvido na síntese de bi-arilarilmetilaminas. Este método foi transformado eficientemente numa versão heterogénea utilizando Catálise com uma Fase líquida Iónica Suportada (SILPC), aplicado pela primeira vez neste tipo de catálise sequencial.

Palavras-chave: Catálise, Reagentes Organobóricos, Arilações, Paládio, Ruténio, Ródio, NHCs

Abbreviations

Ac	Acetyl
acac	Acetylacetone
AcOEt	Ethyl acetate
AIBN	Azobisisobutyronitrile
API	Active pharmaceutical ingredient
Ar	Aromatic group
BARF	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BER	Benzylic ester rearrangement
Bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
BOX	Bis(oxazoline)
bpy	2,2'-Bipyridine
br	Broad
Cat	Catalyst
COD	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
Cy	Cymene
d	Doublet
dd	Double doublet
dba	Dibenzylideneacetone
DPPF	Bis(diphenylphosphino)ferrocene
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	*N*,*N'*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppp	1,3-Bis(diphenylphosphino)propane
dppe	1,2-Bis(diphenylphosphino)ethane
d.r.	Diastereomeric ratio
DTPF	1,1'-bis(di-*o*-tolylphosphino)ferrocene

EA	Elemental Analysis
EDG	Electron-donor group
ee	Enantiomeric excess
Et	Ethyl
ESI	Electrospray Ionization
EWG	Electron-withdrawing group
FAB	Fast Atom Bombardment
FTIR	Fourier Transform Infrared Spectroscopy
Fur	Furyl
Hex	Hexane
HMDS	Hexamethyldisilazide (bis(trimethylsilyl)amide)
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
ICP	Inductively Coupled Plasma
IL	Ionic Liquid
IUPAC	International Union of Pure and Applied Chemistry
J	Nuclear Magnetic Resonance Coupling Constant
LG	Leaving group
m	Multiplet
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
m.p.	Melting point
MS	Mass Spetrometry
M.S.	Molecular sieves
Ms	Mesyl
Naph or Nap	Naphthyl
NMR	Nuclear Magnetic Ressonance
NHC	*N*-Heterocyclic carbene
Ns	Nitrobenzenesulfonyl (nosyl)
Nuc	Nucleophile
PEPPSI	Pyridine-Enhanced Pre-catalyst Preparation Stabilization and Initiation
PG	Protecting group

Ph	Phenyl
Ph-B	Phenyl boron reagent
ppm	Parts per million
^{i}Pr	*iso*-Propyl
Py	Pyridine
q	Quartet
s	Singlet
t	Triplet
^{t}Bu	*tert*-Butyl
TBAB	Tetra-*n*-butylammonium bromide
TEM	Transmission Electron Microscopy
TEG	Tetra(ethylene)glycol
Tf	Triflyl
THF	Tetrahydrofuran
TMOF	Trimethyl orthoformate
TLC	Thin Layer Chromatography
TOF	Turnover Frequency
TOF MS	Time-of-Flight Mass Spectrometry
***p*-Tol**	*para*-Tolyl
TON	Turnover Number
TosMiC	Tosylmethyl isocyanide
Ts	*p*-Toluenesulfonyl (tosyl)
t_R	Retention time (HPLC)
rt	Room temperature
SEM	Scanning Electron Microscopy
SILPC	Supported Ionic Liquid Phase Catalysis
S_N2	Bimolecular nucleophilic substitution

Index

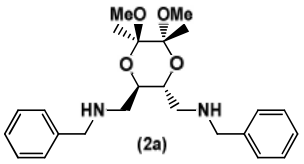
Index Illustrations

Index Figures

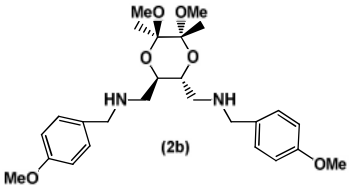
Index Schemes

Index Tables

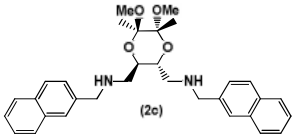
Compound Index



Sec. 1.2.1. Page 25



Sec. 1.2.1. Page 25



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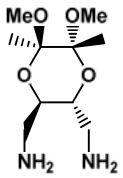

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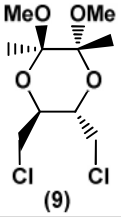
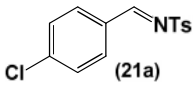
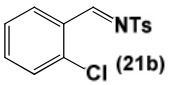


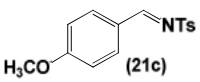
Sec. 1.2.2. Page 29



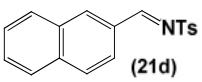
Sec. 2.2.1. Page 67



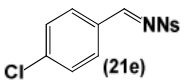
Sec. 2.2.1. Page 67



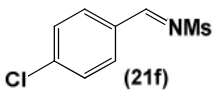
Sec. 2.2.1. Page 67



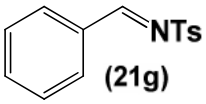
Sec. 2.2.1. Page 67



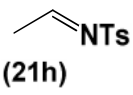
Sec. 2.2.1. Page 67



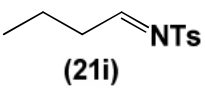
Sec. 2.2.1. Page 67



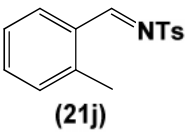
Sec. 2.2.1. Page 67



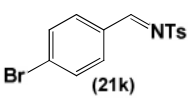
Sec. 2.2.1. Page 67



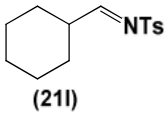
Sec. 2.2.1. Page 67



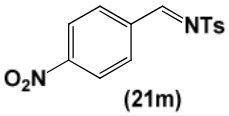
Sec. 2.2.1. Page 67



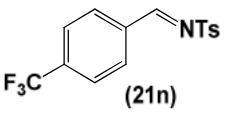
Sec. 2.2.1. Page 67



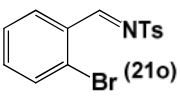
Sec. 2.2.1. Page 67



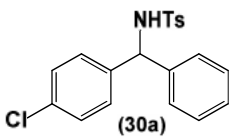
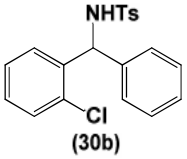
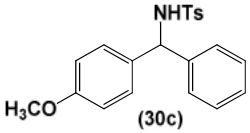
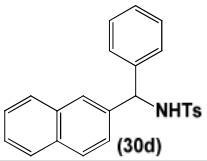
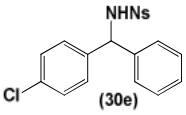
Sec. 2.2.1. Page 67

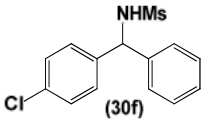
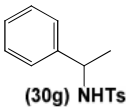
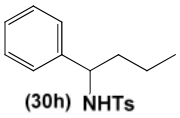
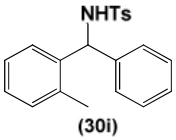
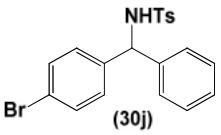


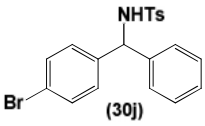
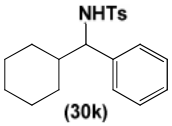
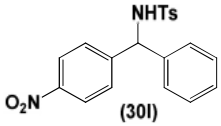
Sec. 2.2.1. Page 67

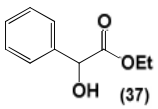
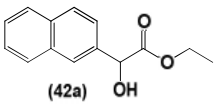
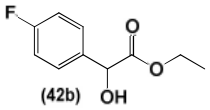
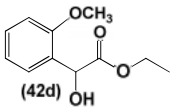
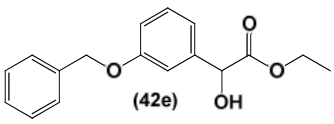


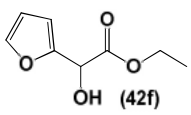
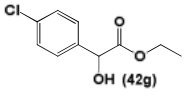
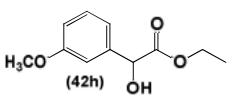
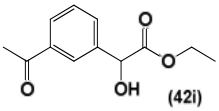
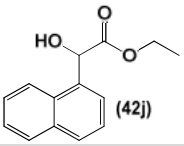
Sec. 2.2.1. Page 67

				
Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72

				
Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72

		
Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72	Sec. 2.2.2. Page 72

				
Sec. 3.2. Page 106	Sec. 3.2. Page 120	Sec. 3.2. Page 120	Sec. 3.2. Page 120	Sec. 3.2. Page 120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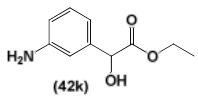
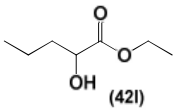
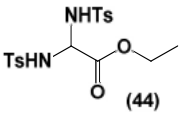
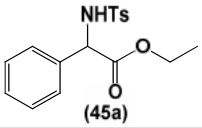
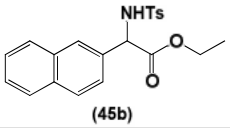
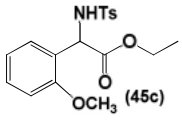
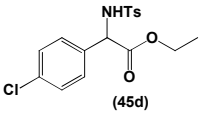
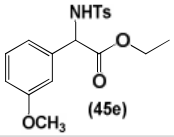
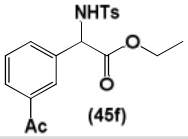
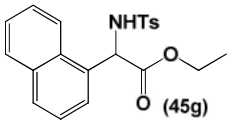
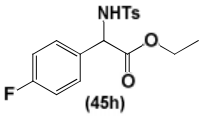
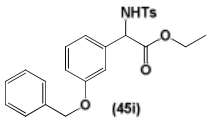
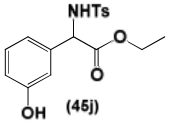
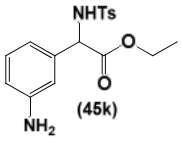
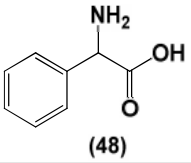
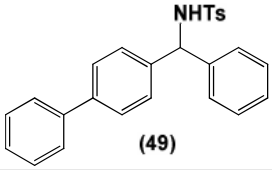
 (42k)	 (42l)	 (44)	 (45a)	 (45b)
Sec. 3.2. Page 120	**Sec. 3.2. Page 120**	**Sec. 4.2.1. Page 141**	**Sec. 4.2.2. Page 144**	**Sec. 4.2.2. Page 144**

 (45c)	 (45d)	 (45e)	 (45f)	 (45g)
Sec. 4.2.2. Page 144	**Sec. 4.2.2. Page 144**	**Sec. 4.2.2. Page 144**	**Sec. 4.2.2. Page 144**	**Sec. 4.2.2. Page 144**

 (45h)	 (45i)	 (45j)	 (45k)	 (48)
Sec. 4.2.2. Page 144	**Sec. 4.2.2. Page 144**	**Sec. 4.2.2. Page 144**	**Sec. 4.2.2. Page 144**	**Sec. 4.2.4. Page 157**


(49)

Sec. 5.2.1. Page 178

Commercial Ligands Index

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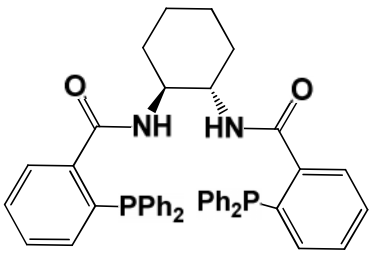
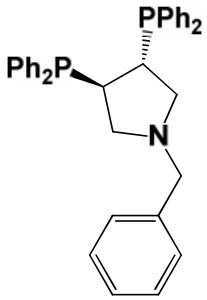
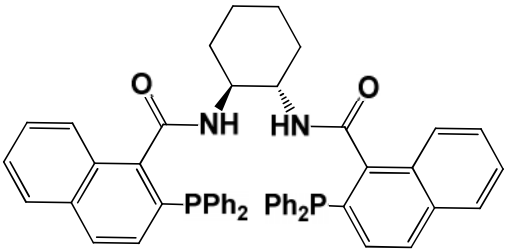


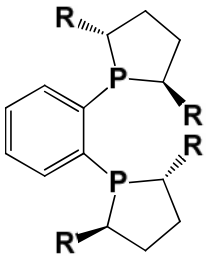
(*R,R*)-Trost (22)



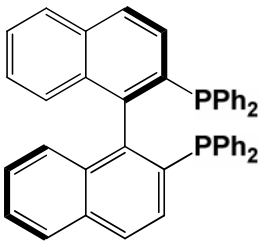
(*R*)-DeguPhos (23)



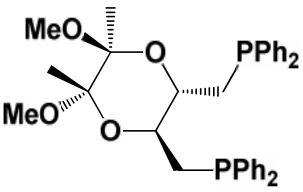
(*R,R*)-Naph Trost (24)



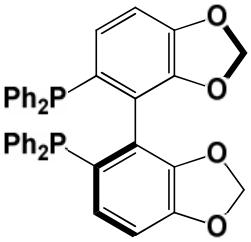
(*R,R*) DuPhos (25) R= *i*-Propyl
(26) R= Methyl



(*R*)-BINAP (27)

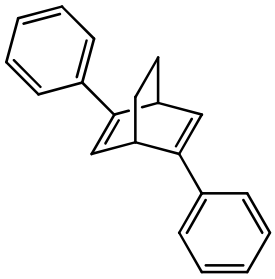


(*R*)-DioxPhos (28)

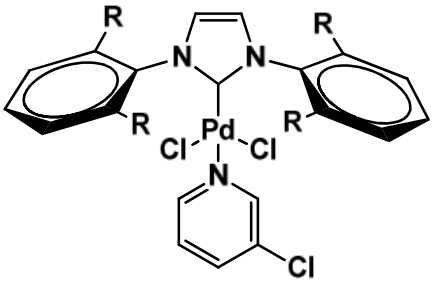


(*R*)-SegPhos (29)

Other ligands:



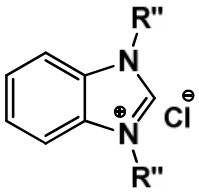
(1*S*,4*S*)-2,5-Diphenylbicyclo [2,2,2]octa-2,5-diene (46)



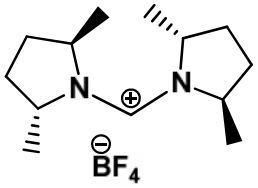
R= *i*-Pr

PEPPSI-*i*Pr

NHC precursors:



R''= ^{t}Bu (38)
cyclohexyl (39)



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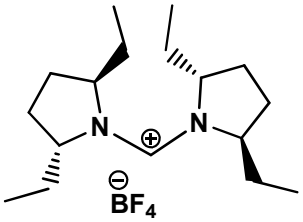
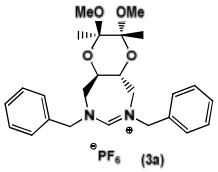
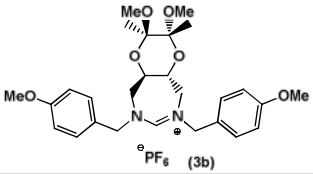


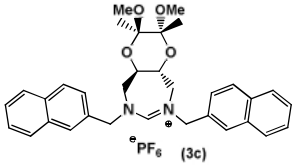
(41)



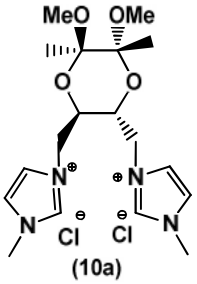
Sec. 1.2.1.
Page 25



Sec. 1.2.1.
Page 25

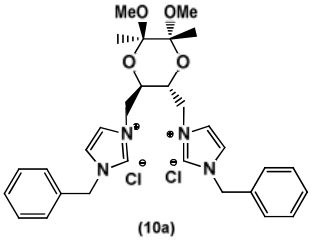


Sec. 1.2.1.
Page 25



(10a)

Sec. 1.2.2.
Page 29



(10a)

Sec. 1.2.2.
Page 29

Highlights

"Saímos pelo mundo em busca de nossos sonhos e ideais. Muitas vezes colocamos nos lugares inacessíveis o que está ao alcance das mãos."
Paulo Coelho

Asymmetric Catalysis, an important and evolving Chemical and Biochemical tool

The constant quest to create new and more efficient catalytic processes that fits the modern demands of the chemical industry from an environmental and economic point of view, still remains a key priority for chemists from all around the world. In 1836, it was the Swedish chemist J. J. Berzelius who came up with a new concept that unsettled the scientific community that led to a striking paradigm shift in the way chemical processes were viewed. Berzelius wrote an essay proposing the existence of a new force, which operated in a plethora of chemical reactions; this was called a "catalytic force". The term "catalysis" then emerged as being the decomposition of bodies by this force.[1]

"It is, then, proved that several simple or compound bodies, soluble and insoluble, have the property of exercising on other bodies an action very different from chemical affinity. By means of this action they produce, in these bodies, decompositions of their elements and different recombinations of these same elements to which they remain indifferent."

J.J. Berzelius, 1885

Besides, catalysis had already been exploited and applied much earlier, but nonetheless this is, probably the first recognition of it as a wide-ranging natural phenomenon. Thereafter, the catalysis concept, could then explain the process of fermentation and the use of metallic catalysts. So, the contributions from Berzelius, Faraday, Davy (finely divided platinum soaked in wine for the conversion of ethyl alcohol to acetic acid), Döbereiner (oxidation of alcohol to acetic acid, using platinum), Dulong (along with Priestley, Döbereiner, Payen, Persoz and Thénard, discovered that ammonia decomposed when passed through a red-hot porcelain tube containing iron, copper, silver, gold or platinum), Thénard (studies of hydrogen peroxide decomposition by metals), Phillips, Ostwald, Henry, Wilhelmy and Kuhlmann opened a new vista on the exploitation of efficient and economic synthetic processes.[2]

Catalysis remains a strategic field of chemistry because of its implication in many research areas, which include industrial chemical processes, energy, environment, biotechnology and life sciences.[3,4]

Chirality exists in our everyday life! Driven by structural asymmetry, a chiral molecule is types of molecules that has a non-superimposable mirror image, thus leading to the existence of two distinct molecules, differing only in their orientation in space, and are known as enantiomers. The pharmaceutical, agrochem, fine chemicals and semi-conductor industries, have shown increased demands for single enantiomer compounds, over the last number of years. By selecting certain single enantiomer catalysts, whether totally organic or organic-metallic combination, and using them in catalytic processes leading to the preferential formation of one enantiomer of the product, the field of asymmetric catalysis was born. This cutting-edge field has shown an exponential growth output, leading to the creation of new bio-, organo- and organometallic catalysts that strongly helped chemists successfully access new chiral compounds and to develop new chemical processes.[5]

The formation of C-C single bonds, crucial in the construction of elaborate chemical products, remains, a key challenge to chemists in all areas of synthesis.

The overall objective of this project was the study and applications of the catalytic asymmetric arylation of appropriate substrates, using both known and novel chiral transition metal based catalysts, and develop a supported or heterogeneous catalytic system. This procedure gave rise to many types of interesting compounds like chiral amines, α-hydroxyesters, α-amino acids and bi-aryldiarylamines. But on the way, some interesting novel chiral catalysts based on *N*-Heterocyclic Carbene (NHC) ligands were developed, including pioneering work on the use of Ru based catalysts for the arylation of imines.

Organoboron reagents were applied in all these studies. Their low levels of toxicity, along with their easy handling were some of the principle reasons for applying them in this project. At the moment, a great variety of useful boron reagents are commercially available.

The thesis is structured in a very logical manner with the main purpose of being easily read and understood by the reader.

In Chapter 1, the synthesis and general application of NHC chiral ligands, including chiral versions is described. Our research on the synthesis of novel chiral NHC ligands derived from 1,2-diacetal backbones, is also described.

Chapter 2 focuses on the synthesis of chiral amines from imine substrates using arylboron reagents and it presents an overview of the field of imine arylation from stoichiometric to catalytic methods. It also gives an overview on the chemistry of organoboron reagents, including their synthesis and general applicability. Chapters 3 and 4 focus on the synthesis of α-hydroxyesters and chiral aryl-amino acids *via* arylboron reagents. Chapter 5 looks at studies on the development of a sequential imine arylation-Suzuki-Miyaura procedure for accessing useful chiral bi-aryl amines, including a novel heterogeneous method of accessing these compounds.

Finally, the last chapter is the classical experimental section that contains all the physical information (characterization data) and reaction data, for all the compounds synthesized or reactions studied in this research project. The experimental data is organized in topics, according to each of the chapters presented in the thesis.

Regarding the nomenclature that is used in this work, all the new compounds were described according to current IUPAC's nomenclature rules for organic compounds.[6] It is important also to underline that for many of the known and published compounds described in the literature the nomenclature already given in the relevant publications was used.

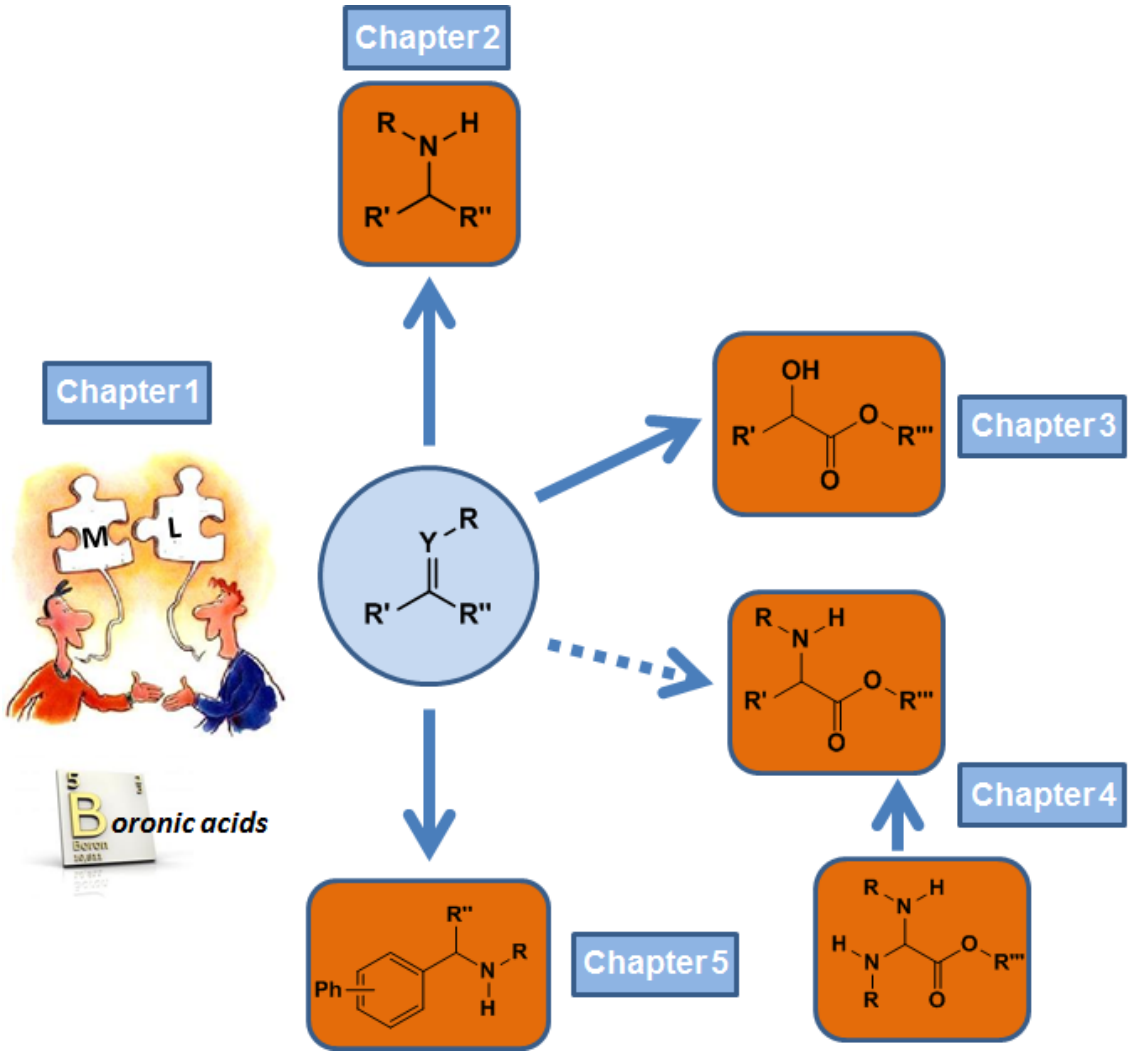


Illustration 1. Dissertation Layout.

References:

(1) Campbell, J. A. *J. Chem. Educ.* **1946**, 23, 582.

(2) Robertson, A. J. B. *Platinum Metals Rev.* **1975**, 19, 64-69.

(3) Blaser, H. U.; Schmidt, E. *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches and Solutions*; Wiley-VCH, 2004.

(4) Chorkendorff, I.; Niemantsverdriet, J. W. *Concepts of Modern Catalysis and Kinetics*; Wiley-VCH, Wienheim, 2003.

(5) van Leeuwen, P. W. N. M. *Homogeneous Catalysis – Understanding the Art*; Kluwer Academic Publishers, the Netherlands, 2004.
(6) IUPAC Commission on Nomenclature of Organic Chemistry *A Guide to IUPAC Nomenclature of Organic Compounds* (Recommendations 1993); Blackwell Scientific Publications, 1993.

1. Synthesis of New Catalysts

"To understand science it is necessary to know its history."
Augusta Comte

1.1. Introduction

1.1.1. Carbenes, an overview

By definition, carbenes are compounds possessing a neutral divalent carbon atom with six electrons on its valence shell (Figure 1.1).[1] This highly reactive and short lived species, useful to introduce a single carbon atom into a molecule, became an interesting and valuable class of compound in the middle of 20th century. They remained theoretical abstractions for a long time, sharpening the curiosity of the scientific community, raising questions about their electronic configuration, geometry, synthesis and isolation. These putative non-isolated intermediates attracted continuous research efforts and later became a central topic in coordination chemistry. Among the panoply of authors[2], from the 1950s and the 1960s, Doering and Fisher, provided the most crucial input on the chemistry of this very fascinating species in the field of organic and organometallic chemistry.

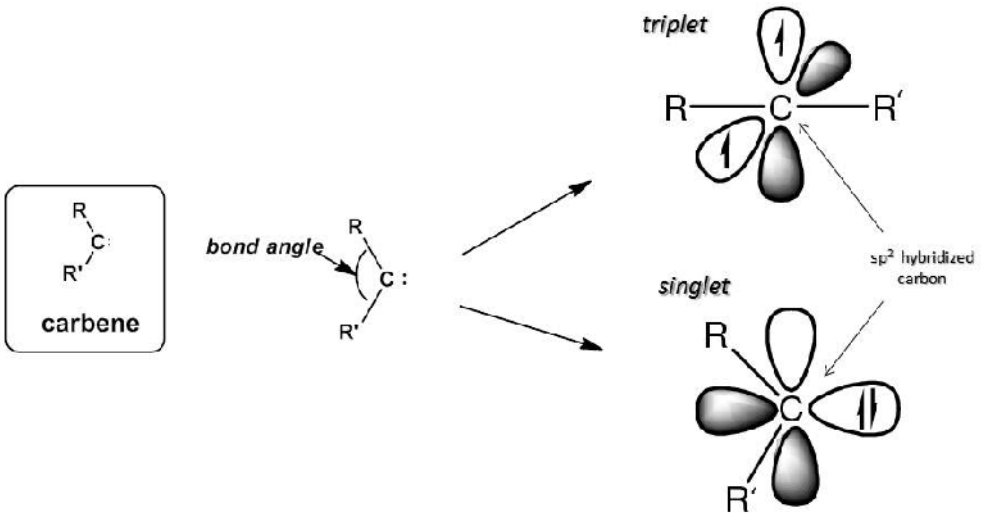


Figure 1.1. Schematic representation of a carbene and the two types of spin states possible for carbenes.

Spectroscopic measurements of several carbenes with different structures allowed their division into two different groups, depending on their electronic states: triplet and singlet carbenes (Figure 1.1). Triplet carbenes have unpaired electrons and the bond angle at the carbene C is around 130-150°. On the other hand, singlet carbenes have one lone electron pair and angles at the carbene C of around 100-110°. The nature of the substituents attached to the carbon atom plays a significant role in their stability and determines whether a free carbene exists in the ground state as a triplet or whether it exists as a singlet, in the excited state. For instance, triplet carbenes usually bear two α-phenyl groups and their radical like behavior makes them very reactive and difficult to isolate.[1] In 2002, Tomioka and co-workers[3] synthesized a triplet carbene which was stable for up to one week in solution at room temperature. To stabilize the filled non-bonding orbital of the singlet carbenes, the negative inductive effect afforded by the electron-withdrawing groups in the α-position favors the singlet state.[4]

Although carbenes were useful as building blocks in organic synthesis, these intriguing species later became a central topic in coordination chemistry, forming complexes with a wide variety of main group elements and transition metals in both high and low oxidation states.[5] Just as there are two types of free carbene, there are two types of metal-carbene complex. The notion of a metal–carbon double bond was first brought forward by Fischer[6], who used tungsten and a few years later, Schrock[7] prepared tantalum complexes. Both were found to generate stable carbenes in the coordination sphere of transition metals (Figure 1.2).

Figure 1.2. Representation of the metal-carbene complexes discovered by Fisher and Schrock.

These two varieties of metal-carbene complexes depend upon the nature of the substituents on the carbene atom, as occurs with free carbenes. In a general way, carbene complexes having π-donor substituents on the methylene group, such as alkoxy or amino groups, with electrophilic behavior, are designated Fischer-type carbenes (Figure 1.2). The metal atom also exists in a low oxidation state. On the other hand, carbenes with a metal atom in a higher oxidation state having an alkyl group (an electron donating group) attached to the carbene carbon, giving it a nucleophilic character, are characteristic Schrock-type complexes.

Inspired by this work, Wanzlick and Öfele[8-10] discovered an interesting class of metal carbene-complexes (Figure 1.3). These singlet type carbenes, in which the divalent carbonic center is connected directly to at least one nitrogen atom within the heterocycle, were defined as *N*-Heterocyclic Carbenes (NHCs). Despite the fact that Wanzlick was the pioneer in the synthesis of NHC-type metal-carbene complexes, it was indeed Arduengo and co-workers[11], in 1991, who were the first to report the synthesis of remarkably stable crystalline free carbenes and crack the ongoing myth. The story begun with the full characterization of the free NHC shown in Figure 1.3. It was derived from an imidazolium salt, and its stability was explained by stereoelectronic effects, which is marked by electronic donation from the electron-rich π-system (N-C=C-N), along with an σ-electronegativity effect. The substituents also had an additional effect that compensated the stabilization of the conjugated system.

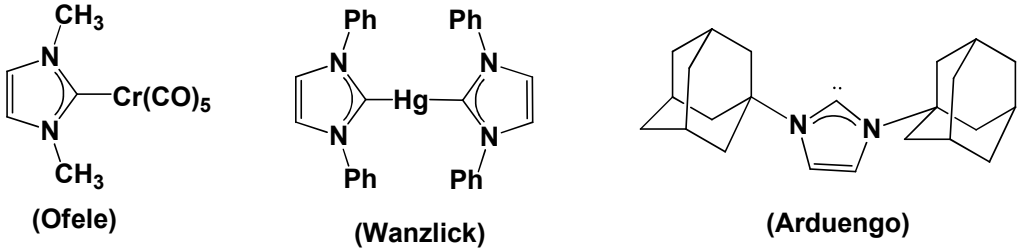


Figure 1.3. Early examples of metal complexes of *N*-heterocyclic carbenes (Öfele and Wanzlick[8-10]) and the first free crystalline carbene (Arduengo[11]).

1.1.2. *N*-Heterocyclic Carbenes (NHCs)

1.1.2.1. General, nomenclature

As the name suggests, *N*-Heterocyclic carbenes (NHCs) are cyclic carbenes bearing at least one α-amino substituent, also commonly called Arduengo carbenes or diaminocarbenes. To date NHCs with three, four, six and seven membered heterocycles have been reported. In Figure 1.4 the most frequently used NHC ligands are represented, these are: five-membered imidazolin-2-ylidenes (**A)**, imidazolidin-2-ylidenes (**B)**, benzimidazolin-2-ylidenes (**C)** and triazolidin-2-ylidenes (**D)**. The first two ones are relatively stable in air, and therefore, the most robust. Their decomposition products are usually formamides or ureas.[12]

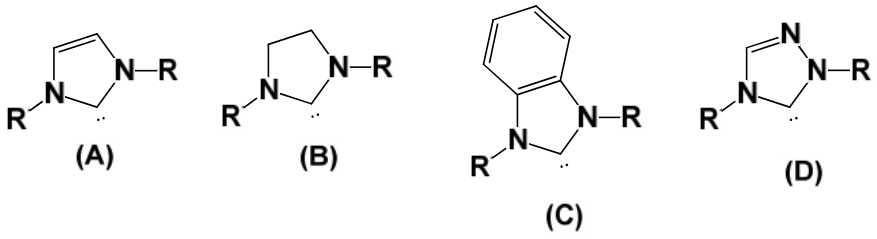
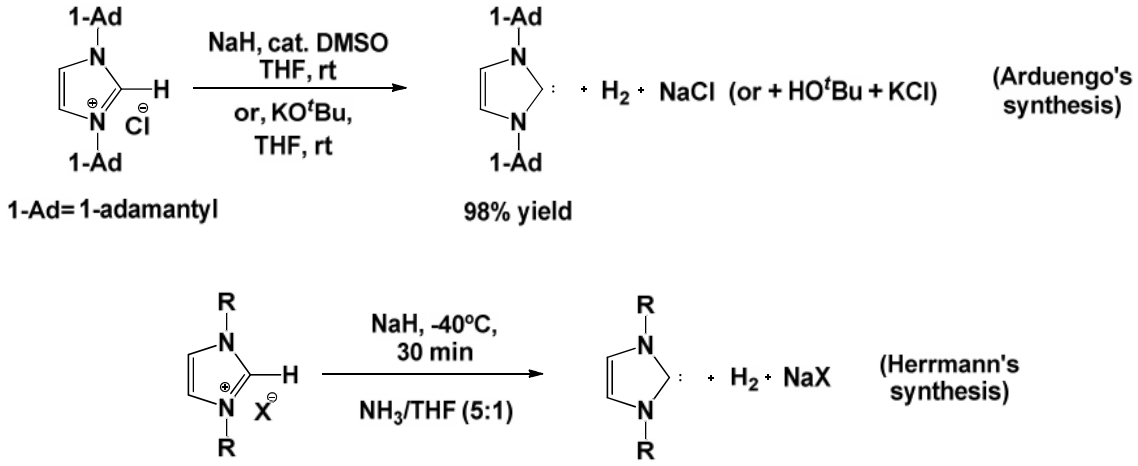


Figure 1.4. Commonly used NHCs.

1.1.2.2. Synthesis

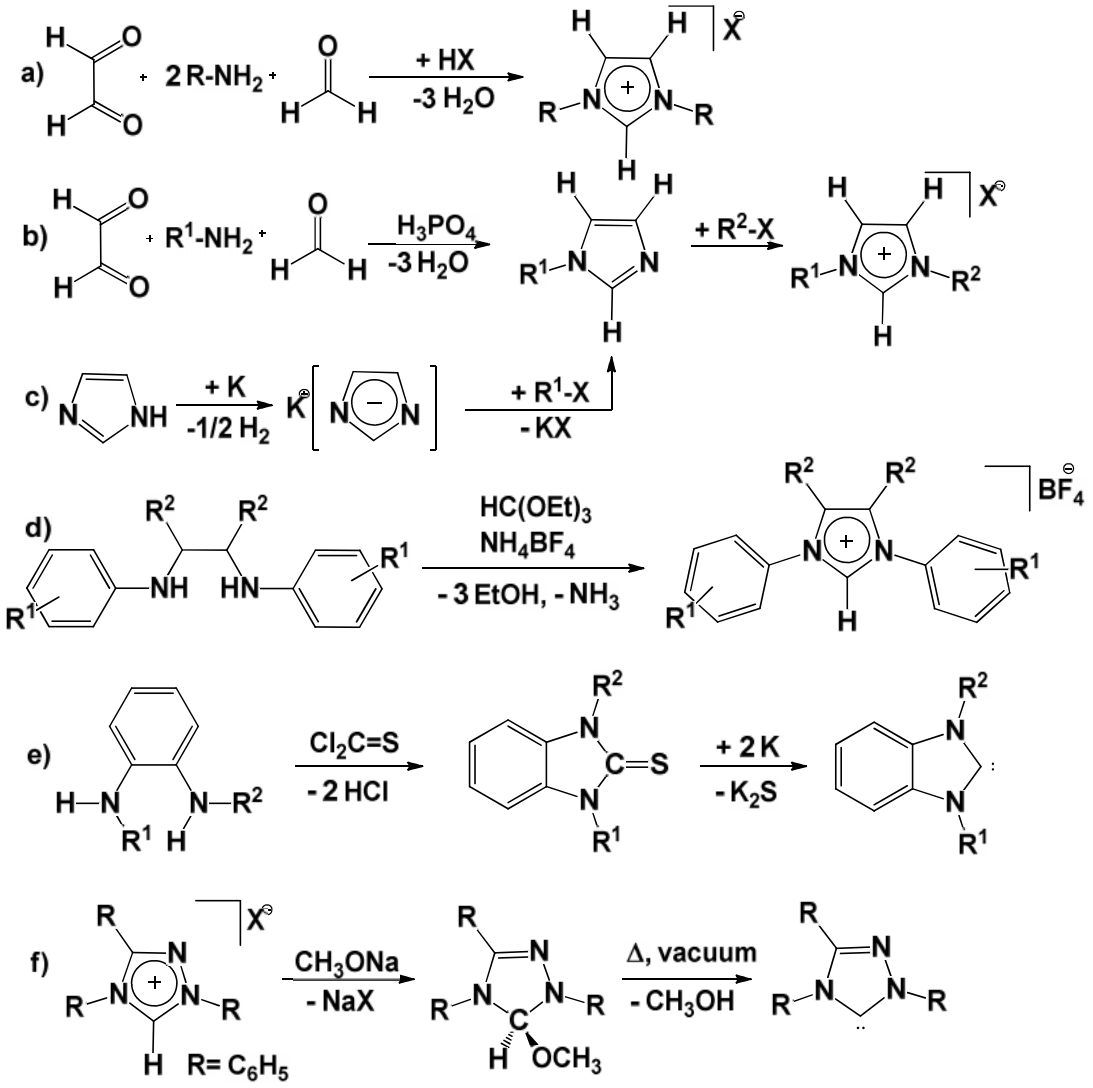
The procedure used to synthesize the first NHCs by Arduengo involved the deprotonation of their corresponding imidazolium salts with a strong base (NaH, KH or KO^{t}Bu) in THF (Scheme 1.1).[11] A few years later, Herrmann and co-workers reported an efficient method where liquid ammonia was used, under mild reaction

conditions (Scheme 1.1).[13] The advantage of using liquid ammonia, which is an excellent solvent for singly-charged ionic or aromatic compounds, along with other organic solvents (e.g., THF or CH_3CN) was noted, as high yields were obtained.



Scheme 1.1. Most common procedures to synthesize NHCs.

The most readily assessable NHCs derived from imidazolium salts, can be obtained from several reliable routes.[14] In Scheme 1.2, several convenient routes to a variety of imidazolium salts and the corresponding imidazolin-2-ylidenes are presented. Generally, the synthesis of the heterocyclic ring is straightforward (Scheme 1.2 (a), (b), (c)). The orthoformate route[15] which converts easily available 1,2-diamines into the aryl-substituted imidazolium salts is also frequently used (Scheme 1.2 (d)). This route has been generally used for the synthesis of imidazolium salts with bulky substituents. The desulfurization of a cyclic thiourea derivative works well in several cases, but requires relatively drastic reaction conditions (Scheme 1.2 (e)).[16,17] In the case of triazolium derived NHCs, the formation of the carbene in the 5 position of the ring can be done in an alternative way (Scheme 1.2 (f)).[18] This route involves methanol elimination.



Scheme 1.2. Convenient synthetic routes to imidazolium salts and their corresponding imidazolin-2-ylidenes.

1.1.2.3. Bonding with NHCs

With respect to their behavior when coordinated to transition metals, NHCs, in fact, behave like typical σ-donor ligands that can substitute classical two electron donor ligands (like amines, ethers and phosphines).[19] Nolan and co-workers[20,21] on the basis of a calourimetric study between phosphines and NHC ligands concluded that NHCs are in general better donors, with the exception of the adamantyl carbenes, which due to their bulkiness, impede the interaction between de free ion pair from the carbene with the metallic center. In this study, Nolan concluded that saturated NHCs are better donors comparatively to their unsaturated analogous. Later on, the groups of Meyer[22] and Frenking[23] have estimated that NHC ligands interact with metal centers primarily through strong σ-donation and to a lesser degree through π-back-donation.

By definition, the distance between the carbonic carbon and the metal in organometallic complexes gives an insight on the ability of the carbene to receive electron density from the metal via π-back-donation.[5] Therefore, it is important to point out that NHC ligands show both strong σ donor properties and substantial π-back-donation from the metal to the ligand (Figure 1.5).[24-27] In the last few years, several theoretical studies have suggested several degrees of π-bonding in transition metal-NHC complexes.[27] Frenking and Boehme[28] demonstrated, in theoretical studies, that transition metal-NHC bonds have large electrostatic contributions and orbital interactions shows negligible π-backbonding from the metal to the NHC ligand. In a more recent computational study, Frenking[23] estimated that the orbital interaction part of the bonding was approximately 20% π-backbonding. Among other authors, Nolan's group[29] and Jacobsen's group[30] concluded that the key in understanding the unusual stability of specific complexes lies in the π-donation of the NHC ligands. Their results confirm the idea that NHCs are not pure σ-donors, leading to at least a 10% π-contribution. These contributions (the back-bonding contribution) showed significance increases with increasing d-electron count of the transition metal. Recent calculations suggest that NHC ligands in transition metal complexes exhibit an ambivalent π-bonding character, depending on the metal-complex fragment coordinated to the carbene.[27] Furthermore, it has been shown that π-back-donation is favored in

saturated imidazolidinylidenes (**B**, Figure 1.4) when compared to unsaturated imidazolylidenes (**A**, Figure 1.4).[31]

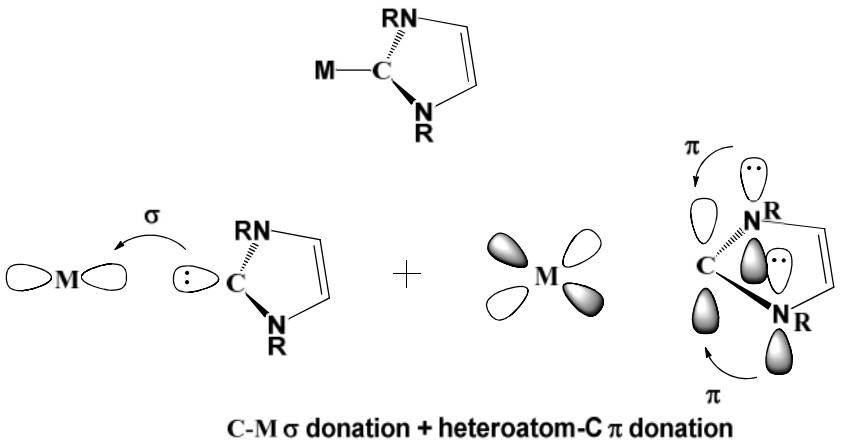
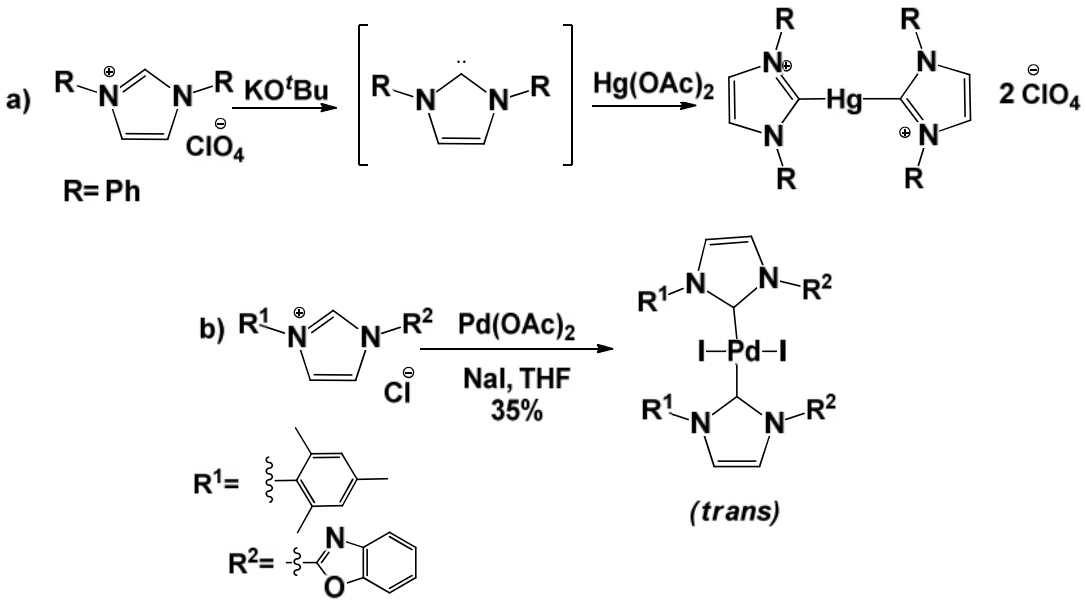


Figure 1.5. Molecular orbital description of NHC bonding to metal centers.

Despite all the research that has been carried out to understand the metal-NHC bond, it is still hard to attribute a precise description of the exact stereoelectronic factors involved, due to their dependence on the nature of the metal and NHC ligand.

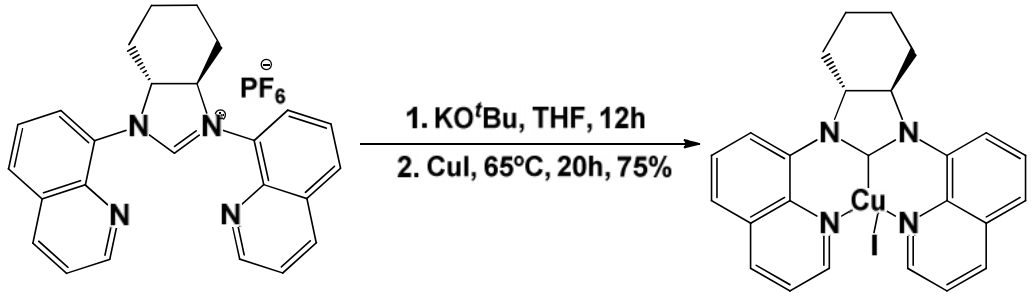
A full account of the synthesis of these metal complexes in catalysis was published by Herrmann and co-workers in 1996.[32] Overall, NHCs react with a broad range of organometallic precursors by direct addition or by replacement of two-electron donor ligands. The most common ligands displaced by NHCs are nitriles, phosphines, tetrahydrofuran, carbonyl compounds (e.g. CO) and pyridines, etc. Imidazolium salts can be converted into transition metal complexes *in situ*, by their deprotonation and the subsequent complexation of the resulting NHC with a metal, or by direct conversion of the imidazolium salt to the NHC in the presence of metallic species (which induces this deprotonation event) followed by complexation. The first route presented major advantages, being useful in situations where the free NHC is unstable and hard to handle. This methodology

was introduced by Wanzlick[8], applying mercuric acetate in the synthesis of a complex with a coordinated NHC ligand, after deprotonation of the corresponding imidazolium salt with a base (Scheme 1.3 (a)). At the moment, the later methodology is applied with success in the synthesis of Pd(II) and Ni(II) complexes (Scheme 1.3 (b)).[33]



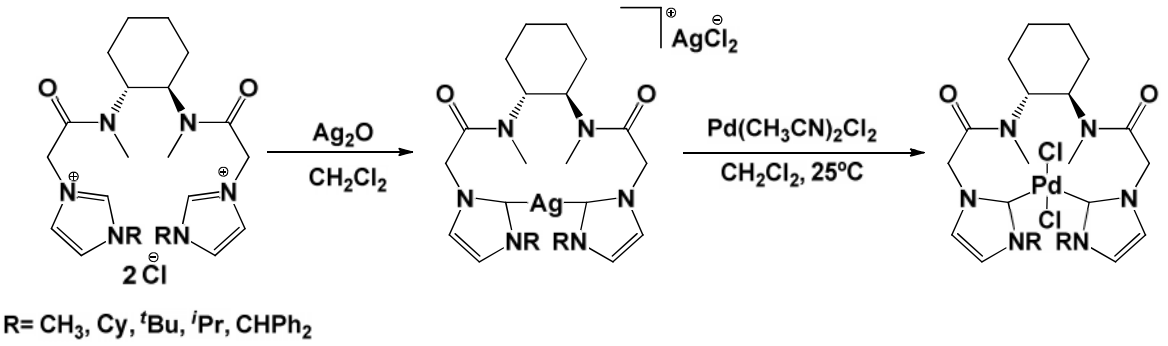
Scheme 1.3. a) Pioneering work developed by Wanzlick[8] in the synthesis of an NHC-Hg complex. b) The synthesis of an NHC-Pd complex by Poyatos *et al*.[33]

In Scheme 1.4 the synthesis of an NHC-Cu complex is reported by Angelici's group (using Wanzlick's approach with KO^{t}Bu).[34]



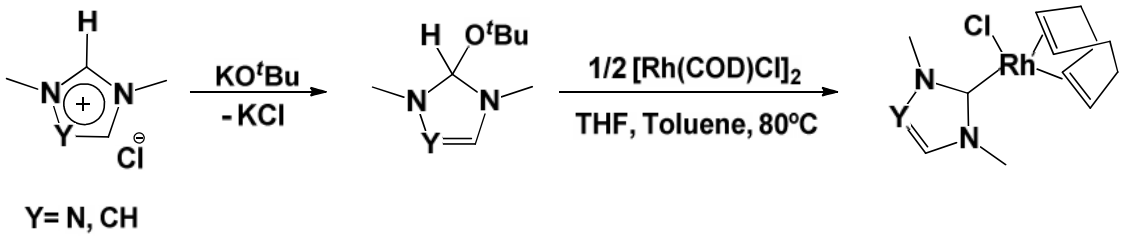
Scheme 1.4. Synthesis of Cu(I) complexes by deprotonation of the imidazolium salt with KO^{t}Bu.[34]

Transfer of the carbene ligands from silver (transmetalation) is also an effective way to form NHC-metal complexes (Scheme 1.5).[35] This method was explored by Lin and co-workers, using silver (I) oxide.[36-38] A major advantage of this particular method lies in the ease of the formed NHC-Ag(I) complex to suffer transmetalation with a variety of transition metals, like: Au(I), Cu(I), Cu(II), Ni(II), Pd(II), Pt(II), Rh(I), Rh(II), Ir(I), Ir(III), Ru(II) and Ru(III).[35] The driving force for this reaction is the formation of insoluble silver salts, which are easily removed from the reaction media.



Scheme 1.5. Alternative (transmetalation) route using silver (I) oxides as the transmetalation agents.[36]

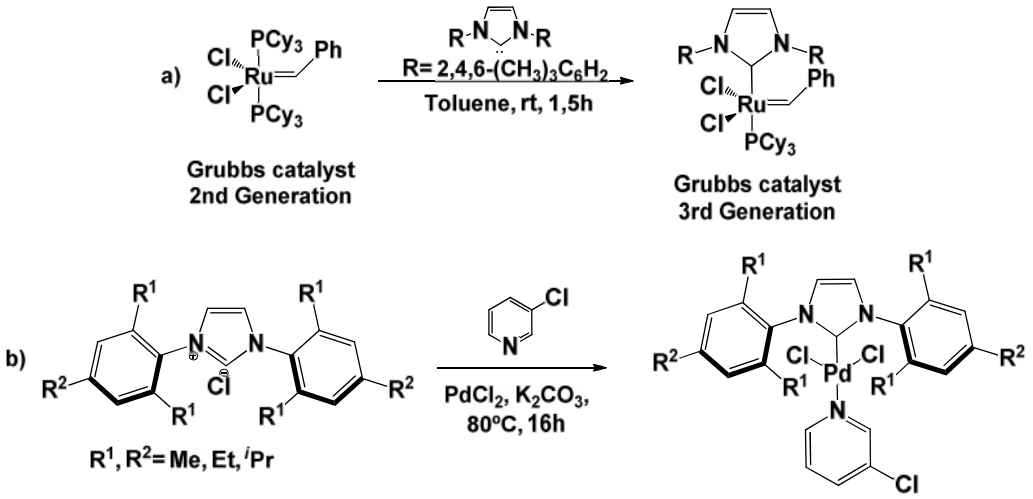
Another approach to prepare NHC-metal complexes (Scheme 1.6) lies in the *in situ* removal of alcoholate adducts before the addition of the transition metal precursor.[39] The resulting potassium salt is almost insoluble in ethanol and THF and can be removed by simple filtration of the suspension.



Scheme 1.6. Synthesis of NHC complex via ^{t}BuOH elimination.[39]

Phosphine ligands are generally labile ligands, which can be replaced by NHC ligands in the preparation of new catalysts. Taking into account the reaction conditions, generally only one phosphine ligand is replaced, providing a complex phosphine-NHC mix. A classic example of this methodology is the synthesis of the well-known 3rd generation Grubbs catalysts.[40] In this case there is the substitution of only one phosphine ligand in the coordination sphere of the Ru transition metal (Scheme 1.7 (a)).

This approach could be extended to other ligand types, like amines (Scheme 1.7 (b)) and in fact the popular PEPPSI catalysts are prepared in this fashion.[41] These catalysts can be prepared in up to kilogram quantities, under very smooth reaction conditions, without any additional precautions like: inert atmosphere and anhydrous conditions. PEPPSI catalysts are commercially available.



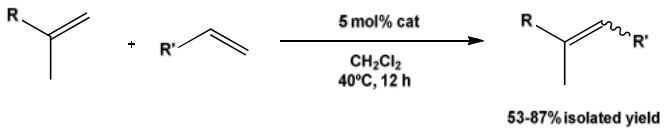
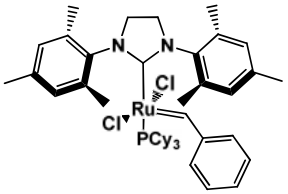
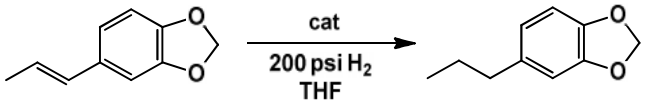
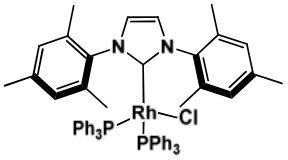
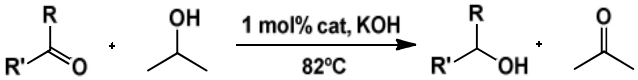
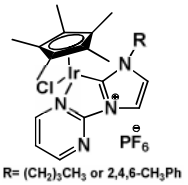
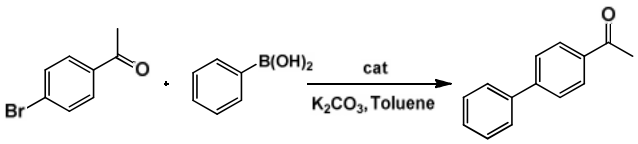
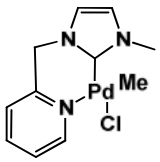
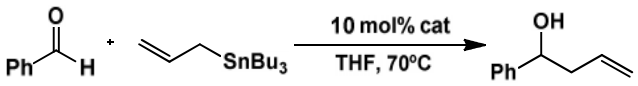
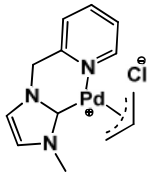
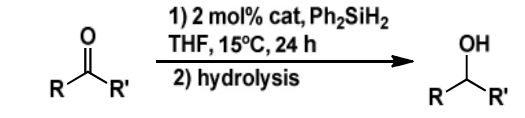
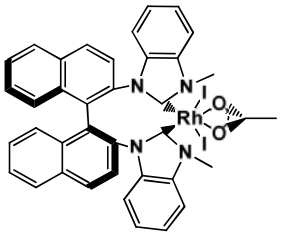
Scheme 1.7. (a) Synthesis of the Grubbs 3rd generation catalyst. **(b)** Synthesis of PEPPSI catalysts.

1.1.2.4. Applications – catalysis and medicine

As NHCs became ubiquitous ligands in organometallic chemistry,[42] they have shown many applications in various fields of chemistry like: catalysis[43] and medicinal chemistry.[44] It should also be mentioned that NHCs in their own right are excellent nucleophilic monofunctional organocatalysts.[45]

NHCs have been by simple analogy, nominated the best phosphine substitutes available and their use as ligands in organometallic complexes has been exhaustively applied in bench-mark reactions, such as: olefin metathesis,[46,47] hydrogenation and hydride transfer,[48] Pd catalyzed C-C coupling,[49] alkylation,[50,51] etc. The applications of chiral NHC-metal complexes lead to the development of asymmetric versions of these common reactions, giving satisfactory results.[52] In Table 1.1 some examples of the application of NHC-metal complexes in relevant catalytic reactions is presented.

Table 1.1. Bench-mark reactions with NHC-metal catalysts.

Bench-mark reaction	Catalyst
Olefin metathesis:[53] 	
Hydrogenation:[54] 	
Hydride transfer:[55] 	 R= $(CH_2)_3CH_3$ or 2,4,6-CH_3Ph
C-C coupling – Suzuki-Miyaura:[56] 	
Alkylation:[57] 	
Asymmetric Hydrosilylation:[58]  R= aryl, R'= alkyl ee: 92-98%	

1.2. Results and Discussion

1.2.1. Synthesis of mono-NHC-type ligands

The screening of novel catalysts obtained from interesting easily synthesized NHC precursors was an important goal of this project. The main objective was to find catalysts with high activity and enantioselectivity, and to apply them in the synthesis of relevant target compounds. Our group has some experience in the application of modified 1,2-diacetal moieties with C_2-symmetry derived from tartaric acid for chiral ligand synthesis.[59-62] These compounds have been used as ligands or auxiliaries in asymmetric synthesis (Figure 1.6).[63-66]

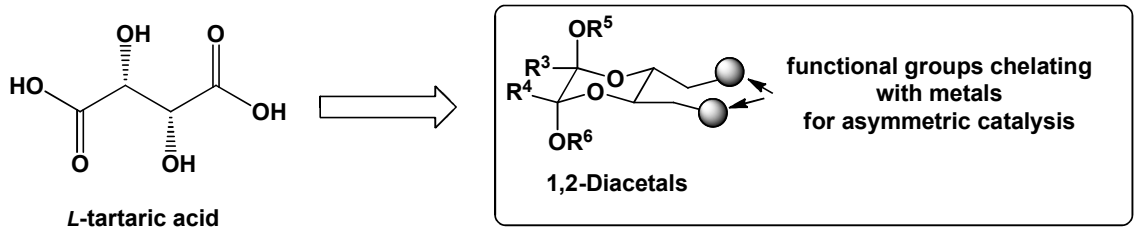
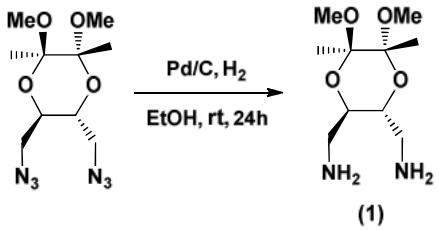


Figure 1.6. 1,2-Diacetals, synthesized from *L*-Tartaric acid.

We decided to look at this structural type as the framework for a family of novel mono-NHC-type ligands. The advantage of using such a framework lies in its inherent stability which derives from the operation of a double anomeric effect.[67,68] The chiral diamine **(1)** was chosen as the precursor.

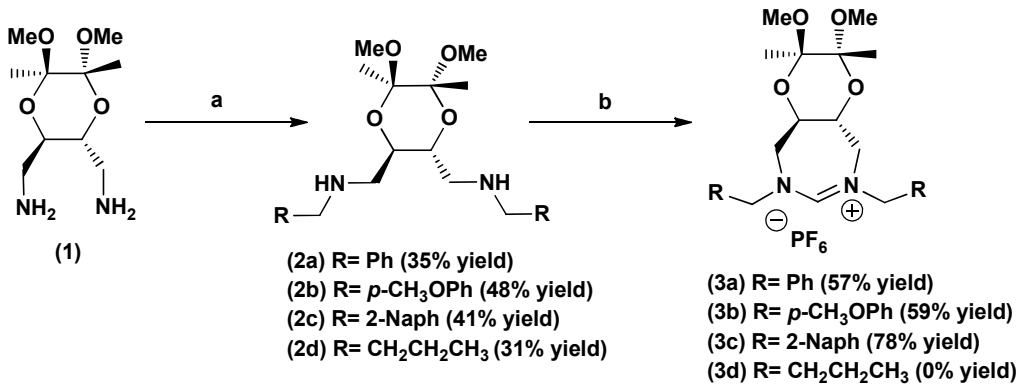
In the quest for the synthesis of new C_2-symmetric ligands, Roos and Donovan[69] developed an interesting methodology to obtain diphenyl-1,3-propanediol ligands from their parent diphenyl diamines. We decided to apply this method for the synthesis of the diamine **(1)**. The synthetic route, using the

commercial di-azide precursor, is shown in Scheme 1.8. The yield obtained for the synthesis of **(1)** was 81%.



Scheme 1.8. Synthesis of the chiral diamine **(1)**.

The diamine **(1)** was then alkylated and cyclized to give the *N*-alkylated 1,3-diazepinium salt **(3)** according to Scheme 1.9. The alkylation was performed *via* a one-pot condensation/reduction sequence. Benzaldehyde, *p*-anisaldehyde, 2-naphtaldehyde and propionaldehyde were used as the alkylating reagents.

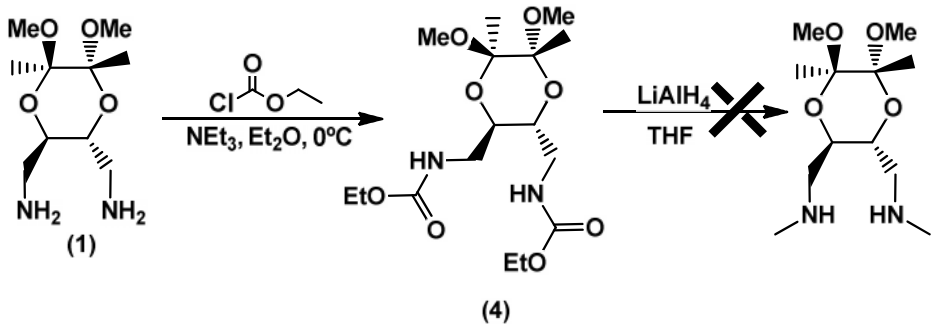


Scheme 1.9. *Reagents and conditions*: **(a)** RCHO, MeOH, reflux, 3h, $NaBH_4$, Toluene, rt, 2h. **(b)** $HC(OEt)_3$, NH_4PF_6, 120ºC, 3h.

There were no significant differences in the yields obtained for the diamine intermediates **(2)**, they were in the range 31-48%. The subsequent formation of the diazepinium ring (Scheme 1.9 (b)) was achieved on the basis of the method developed by Saba and Kaloustian.[70] In this case by using equimolar amounts of

an orthoester and an ammonium salt it was possible to obtain the corresponding 1,3-diazepinium salts **(3a-c)** in reasonable yields. All these compounds were novel. 1,2-Diamines are known to undergo facile ring closure to form the corresponding 4,5-dihydroimidazoles when treated with the proper electrophile[71], like for example, an orthoester. Extreme temperature conditions were applied to force the ring closure reaction and the ethanol formed was evaporated under *vacuum*. Unfortunately, the corresponding 1,3-diazepinium salt **(3d)** could not be obtained. This might possibly have been due to significant steric hindrance effects in operation.

As another approach to the synthesis of **(3d)**, we considered the inclusion of the *N*-alkyl groups in the system prior to cyclization to the dihydroimidazolium ring. As a model reaction we attempted to synthesize the methylated diamine using the carbamate intermediate **(4)** (Scheme 1.10). It is well known from the literature that to make carbamates from amines it is necessary to use a carbamoyl chloride. By using ethyl chloroformate and an organic base (NEt_3) the desired carbamate intermediate **(4)** was obtained in 53% yield. Carbamates are an important class of organic compounds[72] with wide utility in areas such pharmaceutical and agrochemical production (pesticides, herbicides, insecticides[73], fungicides etc.), as well of course, as intermediates in organic synthesis.



Scheme 1.10. Synthesis of the carbamate intermediate **(4)** and corresponding synthetic route (failed) to the desired methylated diamine.

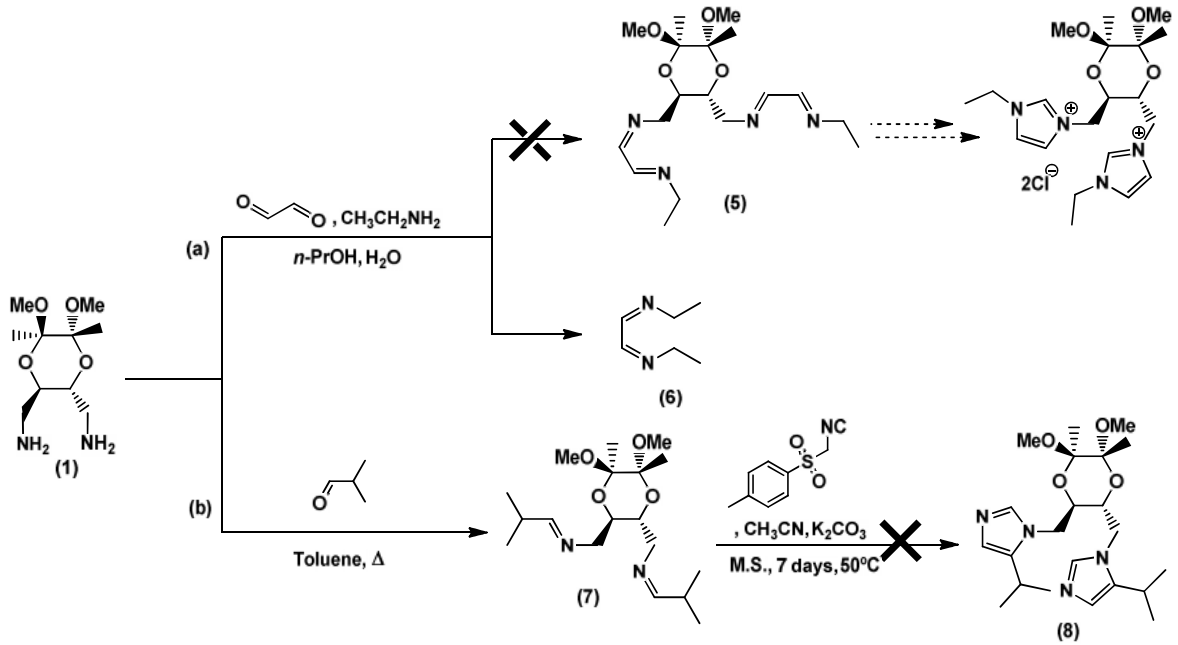
The carbamate **(4)**, however, failed to undergo reduction to *N*,*N'*-methylamine derivative *via* lithium hydride reduction. Several attempts lead us to conclude that this reduction method was too hostile to the carbamate type molecule **(4)**, due to the presence of only decomposition products, as confirmed by NMR.

These compounds **(3a-c)** were subsequently evaluated in catalytic asymmetric arylation reactions (Chapters 2 to 5).

1.2.2. Synthesis of di-NHC-type ligands

For the synthesis of dihydroimidazolium salts we decided to use another method from the literature[14] but which used the diamine molecule **(1)** as the starting material. The strategy adopted was based on the work developed by Arduengo's group[15] which used glyoxal and two equivalents of a substituted amine to form the corresponding imidazolin-2-ylidenes. Our synthetic strategy is shown in Scheme 1.11 (a) and involved the synthesis of the bis(di-imine) **(5)**, starting from the diamine **(1)**, by co-condensation with glyoxal and ethylamine, in *n*-propanol.

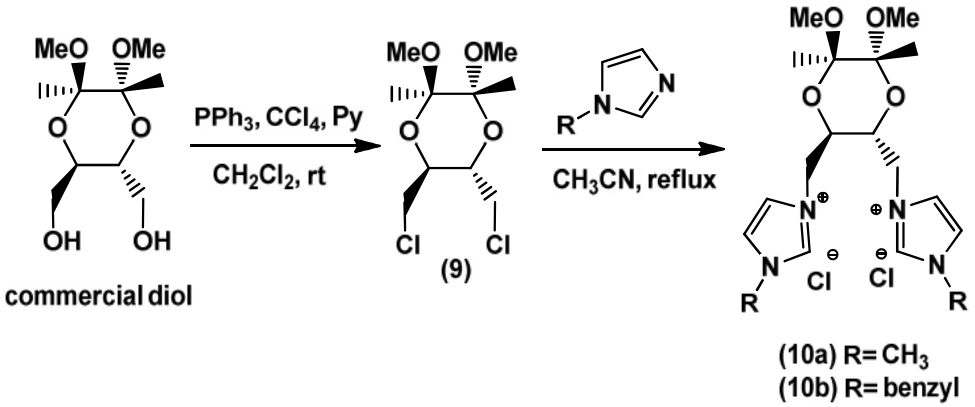
In fact, the reaction didn't give the desired bis(di-imine) product **(5)** but the corresponding bis(di-imine) undesired product **(6)** (Scheme 1.11 (a)), which yield wasn't determined. There seemed to be competition between the diamine substrate **(1)** and the corresponding ethylamine reagent for the glyoxal, and thus we decided to change the method. Bonnet and Hodgson[74] have described the successful synthesis of constrained chiral di-NHC ligands from 1,2-diaminocyclohexane. We decided to adapt this procedure to our particular problem (see Scheme 1.11 (b)). The simple condensation of the diamine **(1)** with *iso*-butyraldehyde under reflux conditions in toluene (with azeotropical removal of water) gave the bis(di-imine) **(7)** in 88% yield. By reacting this compound with tosylmethyl isocyanide (TosMIC) - a useful reagent for preparing imidazoles,[75,76] it was hoped to be able to access the bis(dihydroimidazolium) salt **(8)** (Scheme 1.11 (b)). Unfortunately, we only obtained the corresponding TosMic reagent and several decomposition products, which were not identified by NMR. The fact that this procedure didn't work may be due to the weakness of the base used.



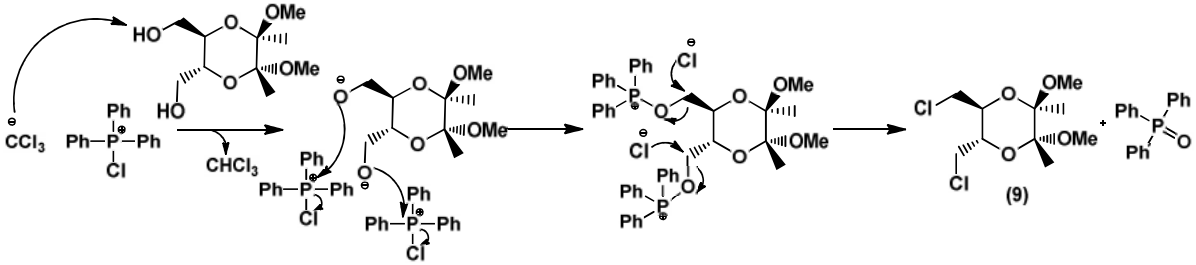
Scheme 1.11. Strategy applied in the synthesis of the bis(di-imine) **(5)** (a) and **(7)** (b), and corresponding bis(dihydroimidazolium) **(8)**.

The method of Kuhn and Grubbs[77], which was further developed by Özdemir and co-workers[78,79] using imidazolium chlorides under solvent-free conditions was investigated. Further work by Özdemir's grown focused on the development of a more electron-donating imidazolinylidene type structures with flexible *ortho*-xylyl N-CH_2-C_6H_4-CH_2-N bridges, in order to bring the two NHC groups closer together. We decided to adopt the strategy (presented in Scheme 1.12) in order to access the di-NHC-type salt. The novel di-chloride molecule **(9)**, derived from the commercial diol was synthesized in 99% yield, following a known procedure from the literature.[66] In fact, the conversion of alcohols to their corresponding alkyl halides can be accomplished by the well-known Appel reaction.[80] The mechanism is illustrated in Scheme 1.13. The reaction starts by the activation of the triphenylphosphine with the tetrahalomethane (in this case, CCl_4), followed by the attack of the alcohol oxygen at phosphorus atom to generate an oxyphosphonium intermediate. The oxygen is then transformed into a leaving group, and an S_N2

displacement by the chloride takes place. The driving force behind this reaction is the formation of the strong P=O bond in the side product.



Scheme 1.12. Synthesis of the di-NHC-type salts **(10a)** and **(10b)** using an Apple reaction as the key step.

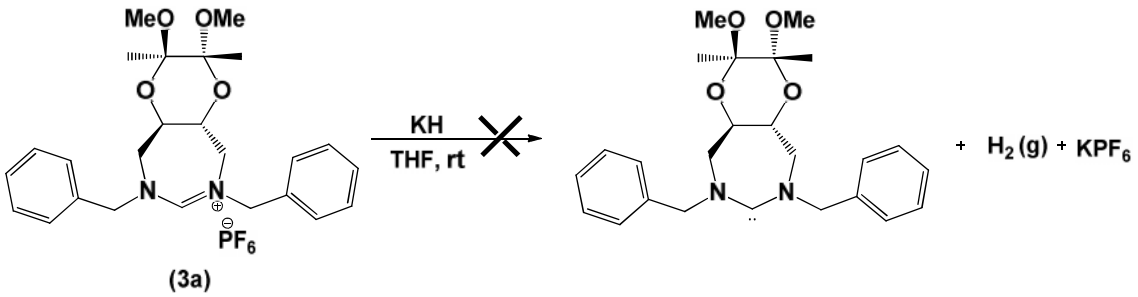


Scheme 1.13. Proposed mechanism for the synthesis of the novel di-chloride molecule **(9)**.

This new molecule **(9)** underwent an S_N2 type reaction with 1-methylimidazole, under reflux temperature to afford the di-NHC-type salt **(10a)** in 47% yield (Scheme 1.12). Using 1-methylimidazolium and 1-benzylimidazolium it was possible to synthesize two di-NHC type salts with aliphatic substituents in the imidazolium ring **(10a)** and aromatic substituents in the imidazolium ring **(10b)**. This simple procedure has been applied with success in the synthesis of 1-butyl-3-methyl imidazolium-base ionic liquids.[81]

1.2.3. Synthesis of metal complexes from mono and di-NHC type salts

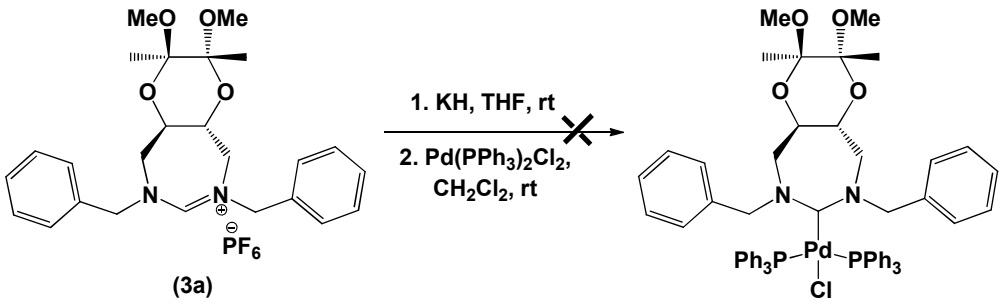
With catalytic asymmetric processes in mind, (see Chapters 2 to 5) we decided to proceed with the synthesis and isolation of a variety of metal complexes using our NHC-type salts precursors and a variety of common transition metals, such as Pd, Rh and Ru. Before carrying out the complexation with the metal pre-catalysts we decided to evaluate the stability of our 1,3-diazepinium salts **(3)** as free carbene units. We treated **(3a)** with a strong base (KH) in THF under an inert atmosphere (Scheme 1.14). ^{1}H NMR analysis was performed on the crude product. The key –N-**HC**=N- signals were present in the spectra (8.29 ppm), which is testimony to the fact that the corresponding de-protonation did not occur. It was hypothesized that the precursor was still humid and the hydride was destroyed by hydrolysis.



Scheme 1.14. Strategy for the synthesis and isolation of the free-NHC unit from 1,3-diazepinium salt **(3a)**.

1.2.3.1. Palladium, Rhodium and Ruthenium

We therefore decided to make the complexation *in situ*. Thus, the same procedure as above was repeated (Scheme 1.14), and commercial $Pd(PPh_3)_2Cl_2$ in CH_2Cl_2, under an inert atmosphere was added (Scheme 1.15). Analysis of the corresponding product by FTIR and NMR spectroscopy we concluded that the formation of the Pd-complex did not take place. This was concluded from the following observation: the acidic proton of the imidazolium precursor appears in ^1H NMR spectrum. Taking into account the characterization results, we assumed that only 1,3-diazepinium **(3a)** and pre-catalyst $Pd(PPh_3)_2Cl_2$ were present, along with impurities (Scheme 1.15).



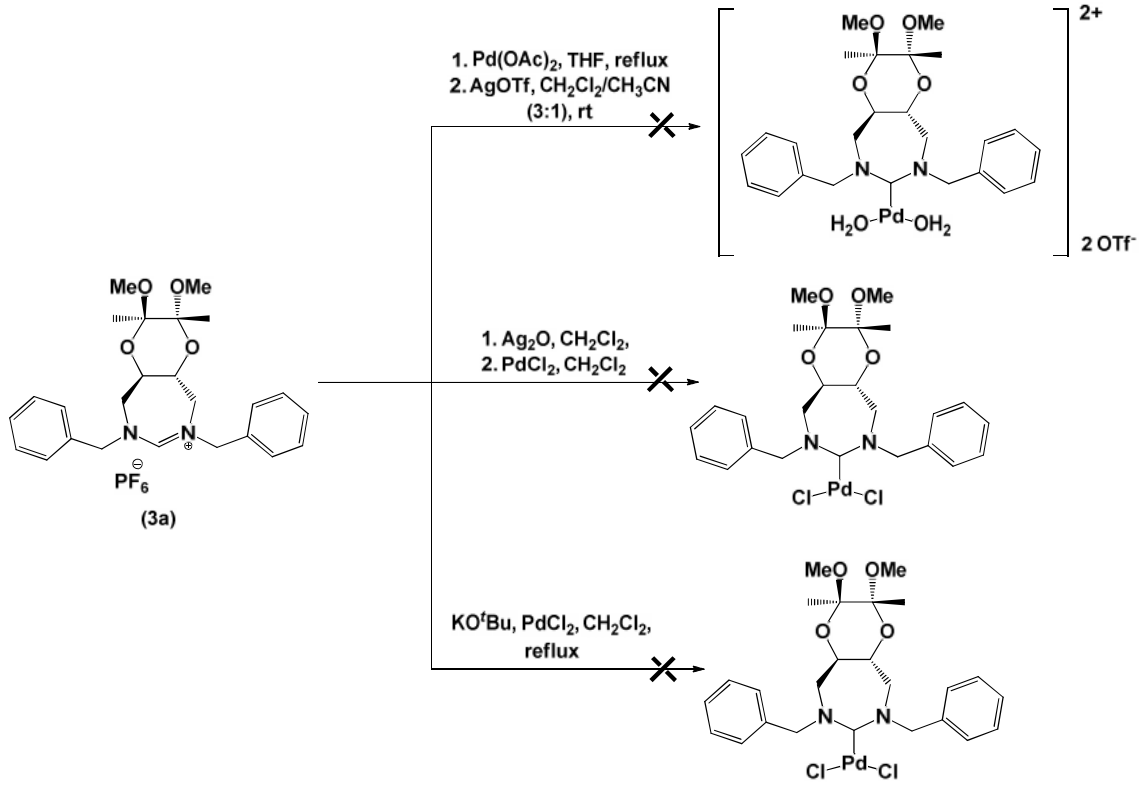
Scheme 1.15. Attempted complexation using 1,3-diazepinium salt **(3a)** with $Pd(PPh_3)_2Cl_2$.

We decided to review our methods. Ma and Shi[82] developed an interesting synthesis of cationic Pd^{2+}-NHC diaquo complexes. We decided to adapt this procedure, to make the complexation in two reaction steps, first using $Pd(OAc)_2$ as the pre-catalyst in THF, using reflux temperatures to force the complexation to occur, and then with AgOTf to form a cationic Pd complex coordinated with two water molecules. Unfortunately we only obtained decomposition products. We think that the counter-ion effect had a role in this particular mechanism, although we used triflate, Ma and Shi successfully used di-imidazolium-type salts with the halide counter-ions, Br^- or I^-.

Silver salts are often employed for the *in situ* generation of cationic transition-metal catalysts.[37,83,84] They behave as halide scavenger agents, forming a weak

Ag–NHC bond, and easily undergo a transmetalation step with the required metal atom.[38,85] Even on applying these key methods, no Pd-mono-NHC-type complexes were obtained.

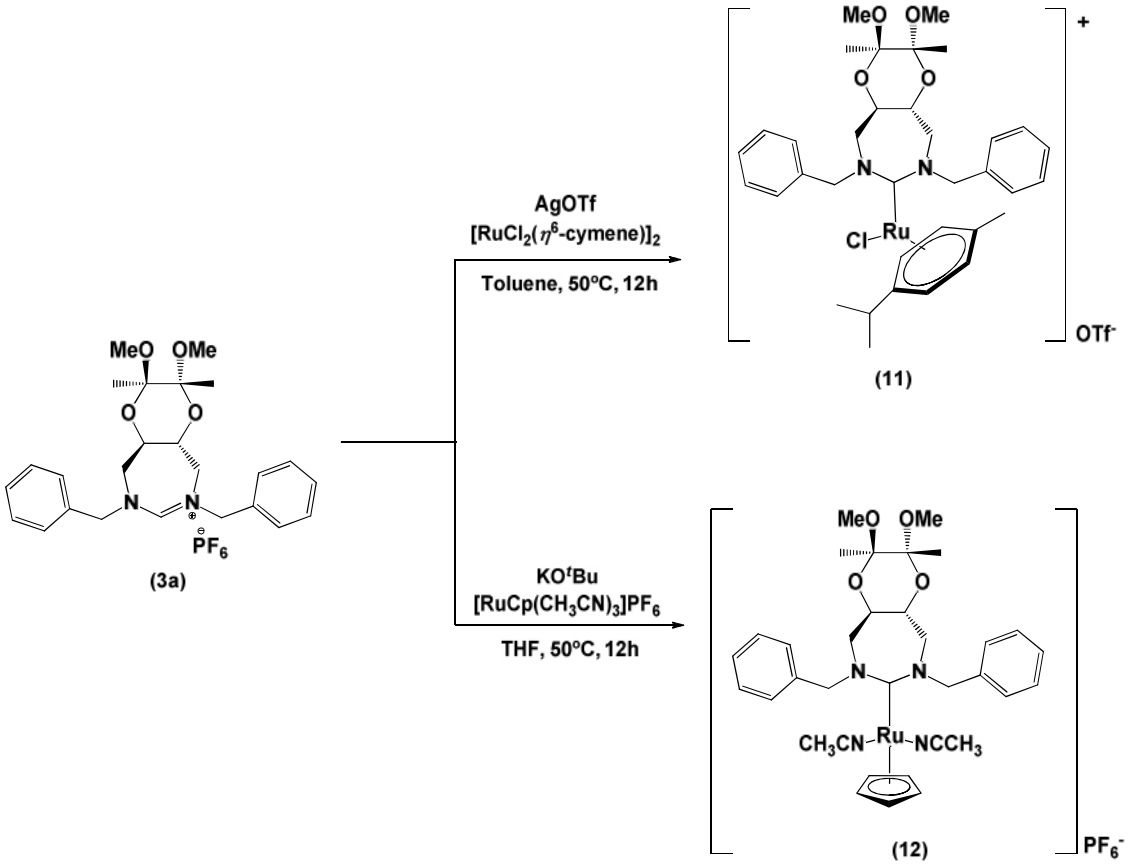
As a last effort, a different base was applied in an attempt to de-protonate the 1,3-diazepinium salt and, coordinate *in situ* with the pre-Pd precursor. No complex was isolated, only decomposition products. Scheme 1.16 shows a variety of attempts to synthesize a stable Pd-NHC-complex starting from the 1,3-diazepinium salt **(3a)**, described above.



Scheme 1.16. Attempts at the synthesis and isolation of a Pd-mono-NHC complex using several strategic routes.

Disappointed by the results that were obtained, we decided to try some complexation reactions applying the di-imidazolium salt **(10a)** (see Scheme 1.12). The same procedures were applied (Scheme 1.16) unsuccessfully. It seems that these Pd-NHC-type complexes couldn´t be isolated using traditional procedures.

At this point we decided to evaluate other transition metals like Rh and Ru. All the procedures described above were tested using both the 1,3-diazepinium and di-NHC imidazoliums **(3a)** and **(10a)**, respectively. As metal pre-catalysts we used $[Rh(COD)Cl]_2$, $[Ru(\eta^6\text{-cymene})Cl_2]_2$ and $[RuCp(CH_3CN)_3]PF_6$. The procedures applied were based on the methods described earlier and on the procedure applied by Poyatos and co-workers.[86] In the case of Ru, two complexes **(11)** and **(12)** were isolated and characterized (Scheme 1.17).



Scheme 1.17. Novel Ru-NHC complexes **(11)** and **(12)**.

In the first synthetic route (Scheme 1.17), the formation of the complex **(11)** is easily accomplished by an *in situ* transmetalation step. Namely, the silver salt (AgOTf), coordinates with the NHC ligand acting like a halide scavenger and forming a weak Ag-NHC bond, in turn it undergoes substitution by $[RuCl_2(\eta^6\text{-}$

cymene)]$_2$. The cationic Ru(II) complex **(11)** is stabilized by the triflate counter-anion and possess a coordination sphere with 16 electrons. This was confirmed by NMR and MS analysis. During the work-up the AgCl salt formed in the transmetalation step was filtrated by cannula. Taking into account the difficulties in preforming these complexations, we decided to use water-insoluble non-polar toluene due to its solvation capacity and high boiling point.

On the other hand, by applying a strong base to enable carbene formation *in situ*, [RuCp($CH_3CN)_3$]PF_6 was used as the precursor to afford the Ru(II) complex **(12)** (Scheme 1.17). We used a moderately poor coordinated solvent[87] (like THF) in order to stabilize the complex. This Ru(II) complex **(12)** obeys the 18 electron rule, with PF_6 as counter-ion species. Both these Ru(II) complexes **(11)** and **(12)** have been evaluated in asymmetric catalysis, and their application discussed in Chapter 2.

1.2.4. Synthesis of novel NHC-oxazoline-type ligands and others

1.2.4.1. State of the art

In general, there are three main families of compounds which function as universal ligands, in asymmetric catalysis. These are: phosphines, NHCs and oxazolines.[88] Our ambition was the design of new chiral NHC based bi-dentate ligand containing catalysts, containing other potential ligand classes like oxazolines[89] (Figure 1.7), a privileged structural motif in ligand design for asymmetric catalysis.

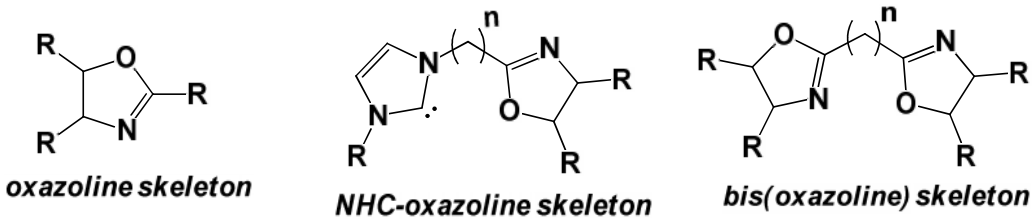
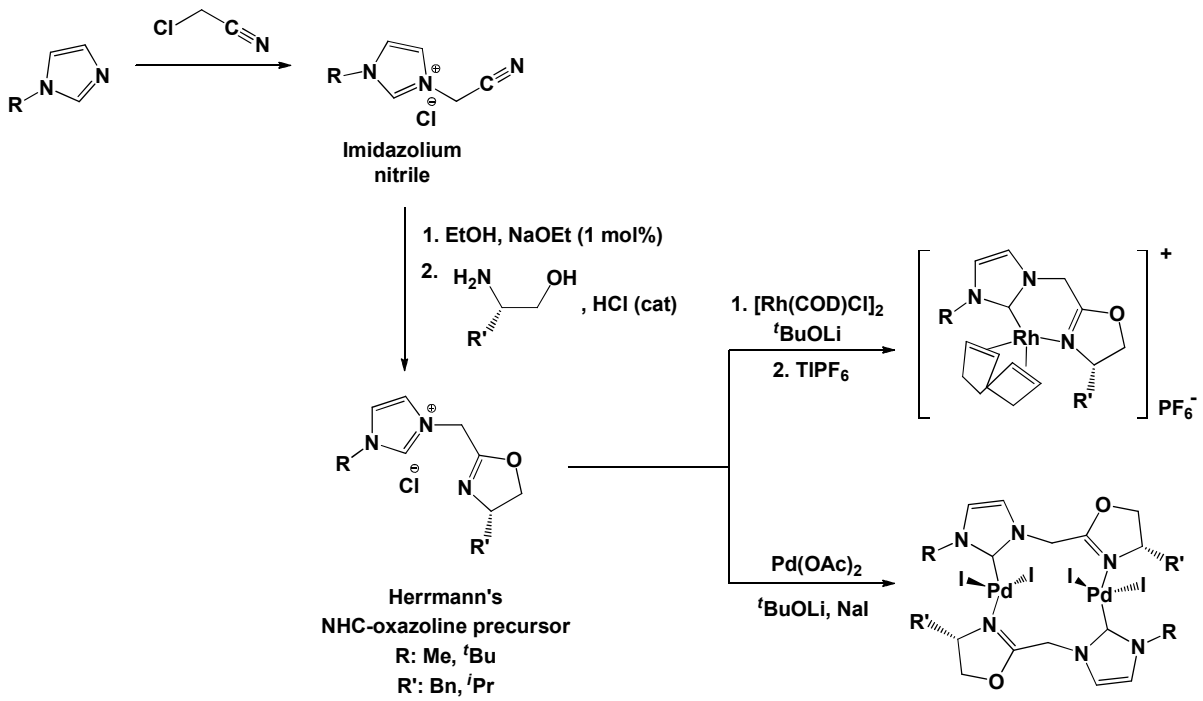


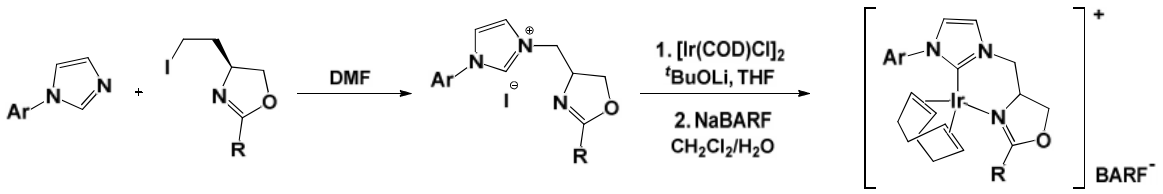
Figure 1.7. Some oxazoline-type ligands.

Their easy synthesis by condensation of an amino-alcohol with a carboxylic acid derivative, along with key features such as its rigidity, quasi-planarity and remarkable stability in the presence of nucleophiles, bases and radicals led us to focus on these new ligand backbones.[90] It was therefore of interest to combine this structural element of chiral ligand design with an NHC unit. The first chiral carbene containing an oxazoline unit was synthesized by Herrmann and Spiegler.[91] The key step in the synthesis of this bidentate ligand, where the oxazoline ring is linked at its 2-position to the imidazolium ring via a methylene bridge, was the formation of the imidazolium imine ester from the imidazolium nitrilie allowed by *in situ* condensation and cyclization to Herrmann's NHC-oxazoline precursor (Scheme 1.18).



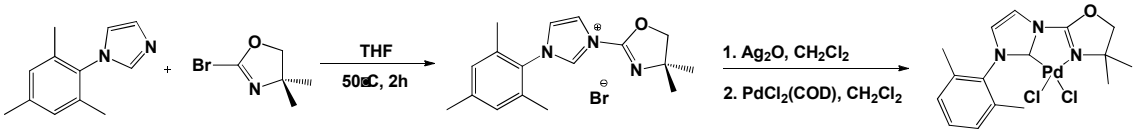
Scheme 1.18. Synthesis of Herrmann's oxazolinyl-carbene ligand and the corresponding Rh(I) and Pd(II) complexes.[91]

Further coordination of this carbene-oxazoline ligand to Rh(I) and Pd(II) pre-catalysts afford two interesting complexes, Rh(I) complex and a dinuclear Pd(II) complex with two oxazoline-carbene units acting as bridging ligands (Scheme 1.18). Moderate enantioselectivities were achieved using the Rh(I) complex for the hydrosilylation of ketones.[19] Burgess and co-workers[48] reported the asymmetric hydrogenation of alkenes with Ir(I) catalysts using the carbene-oxazoline ligand similar to the one synthesized by Herrmann but using another synthetic methodology, developed previously by Pfaltz and Lightfoot[92] (Scheme 1.19). The nucleophilic substitution of the iodo derivative by an imidazole lead to the oxazoline binds by the carbon atom in the 4-position. Further coordination of the bidentate ligand to Ir was achieved by *in situ* deprotonation.



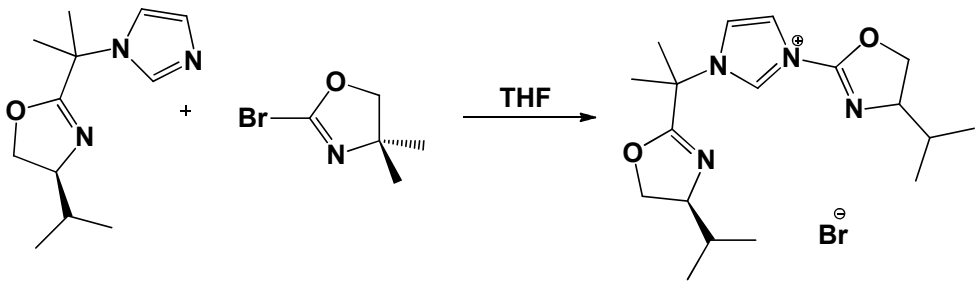
Scheme 1.19. Synthesis of an iridium(I) complex bearing Burgess's chiral oxazoline-imidazolylidene ligand.[48]

This modular design allows facile and rapid access to a large ligand library by variation of the substituents at the 2-position of the oxazoline and at the "terminal" N-atom of the heterocyclic carbene. Gade and César[93] reported the synthesis of an oxazolinyl-carbene which was obtained by direct linkage of the two heterocycles. The new ligand system was obtained, reacting the 2-bromo-oxazoline with an imidazolium precursor in THF (Scheme 1.20). Further transmetalation with silver oxide and addition of a Pd pre-catalyst afford a Pd oxazolinyl-carbene complex (Scheme 1.20), useful in catalytic Heck-Mizoroki-coupling reactions between styrene and several arylhalides.[93]



Scheme 1.20. Synthesis of an oxazolinyl-carbene, used to form an oxazolinyl-carbene Pd complex.[93]

This direct condensation provides a straightforward and modular route to a new family of stereodirecting ligands. The combination of the Herrmann's carbene ligand (Scheme 1.18) and the Gade's NHC family (Scheme 1.19) resulted in a new chiral tridentate NHC-bis(oxazoline) ligand (Scheme 1.21).[94]



Scheme 1.21. Synthesis of a bis(oxazoline)carbene ligand by Schneider *et al.*[94]

Inspired by the work developed previously, Crudden and co-workers[95] have prepared a chiral NHC-oxazoline Rh catalyst, possessing a rigid backbone (Figure 1.8) and Glorius and co-workers[96] reported the synthesis of novel imidazolium salts by cyclizing the corresponding bis(oxazolines) precursors (Figure 1.8).

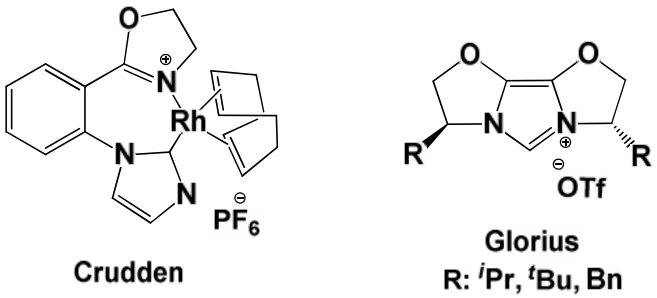
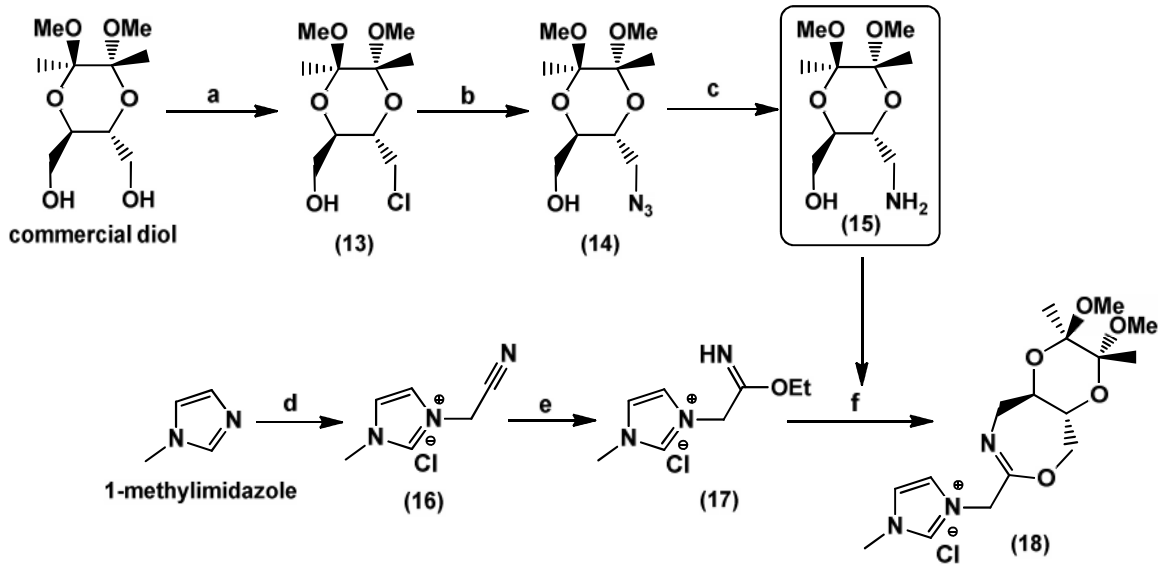


Figure 1.8. Crudden's NHC-oxazoline Rh catalyst[95] and Glorius' fused bis-oxazoline NHC precursor.[96]

1.2.4.2. Our strategy

We decided to design a novel NHC-oxazoline type ligand, taking advantage of the 1,2-diacetal backbone motif used previously by us (Scheme 1.22).

Applying the same methods used to obtained the diamine **(1)** and the dichloride **(9)** (see Scheme 1.8 and 1.13), but decreasing the molar quantities of reagents to half, and by allowing the controlled selective substitution of just one hydroxyl group, it was possible to obtain the alcohol-amine molecule **(15)** in 23% overall yield, in three steps (Scheme 1.22).



Scheme 1.22. Synthesis of the NHC-oxazoline precursor **(18)**. *Reagents and conditions*: **(a)** PPh_3, CCl_4, py, CH_2Cl_2, rt; **(b)** NaN_3, DMF, 80ºC, 4 days; **(c)** Pd/C, H_2, EtOH, rt, overnight; **(d)** $ClCH_2CN$, THF, reflux, 12h; **(e)** EtOH, NaOEt, rt, 16 h; **(f)** **(15)**, CH_3NO_2, HCl, 80ºC, 16h.

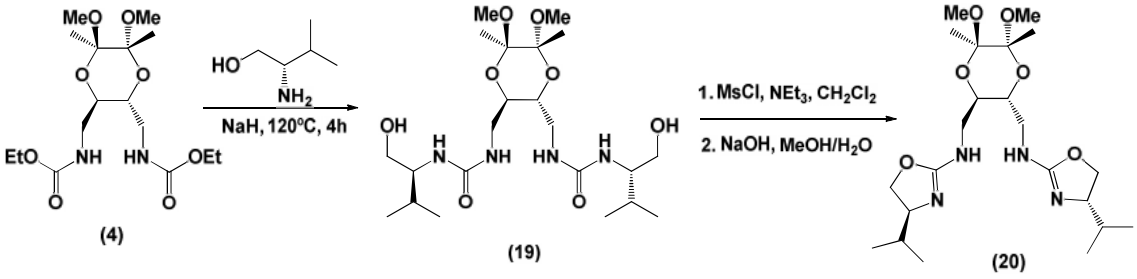
We subsequently synthesized the new NHC-oxazoline type ligand **(18)** (Scheme 1.22), in three consecutive steps, without purification of the intermediates involved. In the first step, 1-methylimidazole was converted into the corresponding cyanomethyl imidazolium chloride **(16)** by treatment with chloroacetonitrile. Addition of ethanol gave the imidoester intermediate **(17)**. Catalytic quantities of

sodium ethoxide were added to ensure the complete conversion. Final condensation of the imidoester intermediate **(17)** with the alcohol-amine compound **(15)**, achieved under acidic conditions, efficiently providing the corresponding NHC-oxazoline chiral ligand **(18)** in (92%) yield.

Attempts to form a stable metal complex with this particular NHC-oxazoline precursor ligand **(18)** were performed using Pd precursors. Unfortunately, only decomposition products were observed in these complexation attempts.

As a logical follow-up, attempts were made at accessing novel bis(oxazoline) (BOX) ligands (Figure 1.7). This family of useful ligands have been synthesized successfully by several groups[97-100] and have demonstrated excellent performance in catalytic asymmetric synthesis, due to their ability to coordinate with a large number of metals[101] (see Section 1.2.4.1). Hereupon we decided to design a BOX ligand using the 1,2-diacetal backbone, starting from the carbamate **(4)**, obtained by acylation of diamine **(1)** with a carbamoyl chloride, NEt_3, in THF (see Section 1.2.1., Scheme 1.10), adopting the methodology of Gade and co-workers.[94]

Using (*S*)-valinol and NaH it was possible to synthesize the diamine **(19)** in 20% yield (Scheme 1.23). *In situ* mesylation of this intermediate and subsequent cyclization in the presence of base (NaOH) gave the bis-oxazoline derivative **(20)** in 20% yield (Scheme 1.23).



Scheme 1.23. Synthesis of the novel bis-oxazoline derivative **(20)**.

The advantage of using such chiral nitrogen-containing compounds is that they are cheaply available from naturally occurring chiral amino acids.

1.3. Conclusion

It has been little more than 20 years since the isolation and full characterization of the first crystalline NHC ligand by Arduengo[11] and 17 years since the first application in homogeneous catalysis by Herrmann.[32] NHCs have seriously marked the field of late transition metal catalysis, furnishing a new tool to the synthetic organic and organometallic chemistry. The key to their rapid development is their ability to stabilize otherwise highly reactive intermediates and yet promote and enhance constructive chemical steps at the metal center. The ever-growing interest in NHCs leads us to believe that some of the current drawbacks (ea. lack of other electrophiles besides aldehydes, high catalyst loading, easy manipulation, etc) will be resolved in the very near future. With the design of a new family of mono and di-NHC type ligands, we hope to reach that goal. This perspective displays both our fascination and enthusiasm for these 1,2-diacetal based ligands for asymmetric catalysis. Despite the synthesis of new NHC type ligands, in good yields, their corresponding coordination with Ru afforded two isolable and characterized Ru(II)-NHC complexes. We soon realized that it is preferable to apply these NHC ligands *in situ*, in homogeneous catalysis, using Pd or Rh, due to their poor stability and reactivity.

Atracted by all the potential reports described in the literature about the synthesis and use of oxazolines as chiral ligands, we decided to prepare novel oxazoline-NHC derived ligands and use them to form new catalysts.

1.4. References

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2. Catalytic Arylation of C=N bonds: Enantioselective synthesis of chiral amines

"Research on transition metal templates in catalytic reactions has suggested that these easily tailored templates may become the "chemists' enzymes."
Barry M. Trost

2.1. Introduction

Chiral nitrogen-containing compounds are widely distributed in nature and play key roles as active pharmaceutical ingredients (APIs) in many well-known drugs (Figure 2.1). In Figure 2.1 a smorgasbord of chiral amine based drugs which exhibit antihistaminic, antiarrhythmic, diuretic, antidepressant and laxative properties, is presented. Thus, the development of many biologically active molecules, either natural or synthetic, relies on the development of general and efficient methods to prepare chiral amines.[1] One of the most promising and convenient routes to prepare enantiomerically pure amines bearing a stereogenic center at the α-position is *via* the use of imines.[2,3]

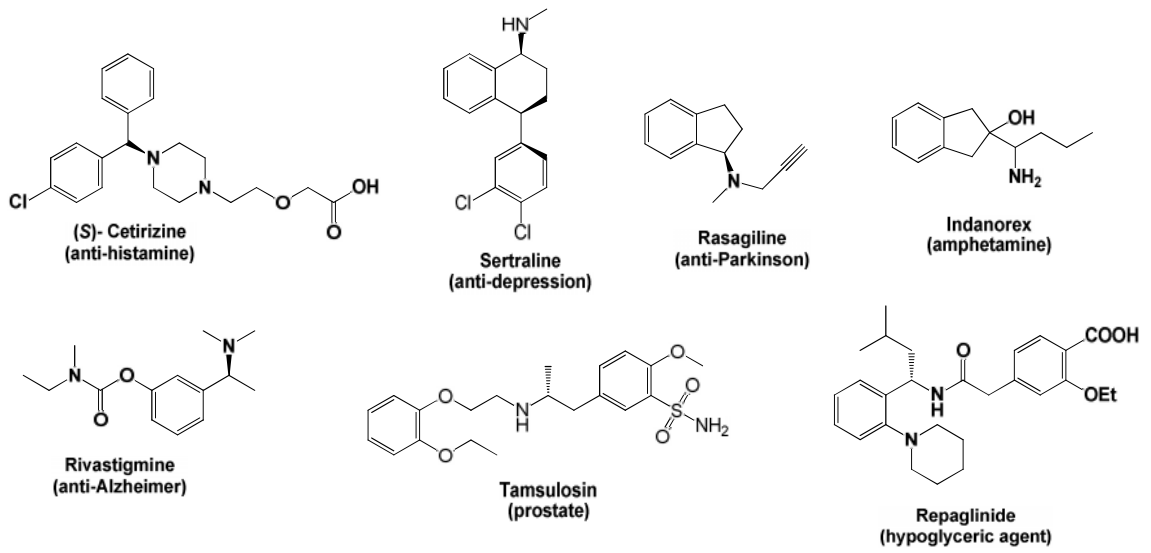
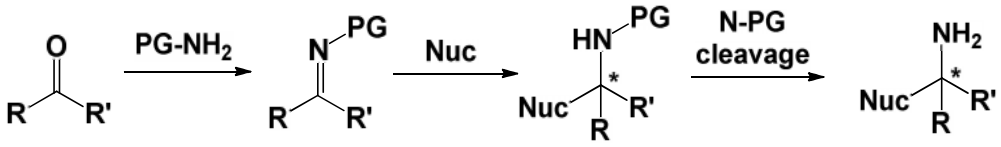


Figure 2.1. Important chiral amine pharmaceuticals.

2.1.1. Enantioselective Chiral Amine Synthesis – C-C bond formation

The importance of chiral amines in nature and as substructures in biologically active unnatural products led to the rapid development of many valuable

approaches to their enantioselective preparation, yet surprisingly few chiral amine structures can be efficiently synthesized, i.e. with high yields and enantioselectivities in a sustainable fashion. Current methods for the synthesis of amines can be grouped into the following categories: (a) reduction methods, (b) C-C bond formation and (c) C-N bond formation. In this work we will focus in the C-C bond formation, particularly in the nucleophilic addition of "unstabilized carbanions" to imines, a traditional approach to α-branched amines (amines bearing a stereogenic center α to the nitrogen atom) synthesis. The preparation of these common subunits in biologically active molecules from the corresponding carbonyl derivatives typically requires three steps, imine formation, nucleophilic addition and protecting group (PG) cleavage (Scheme 2.1).



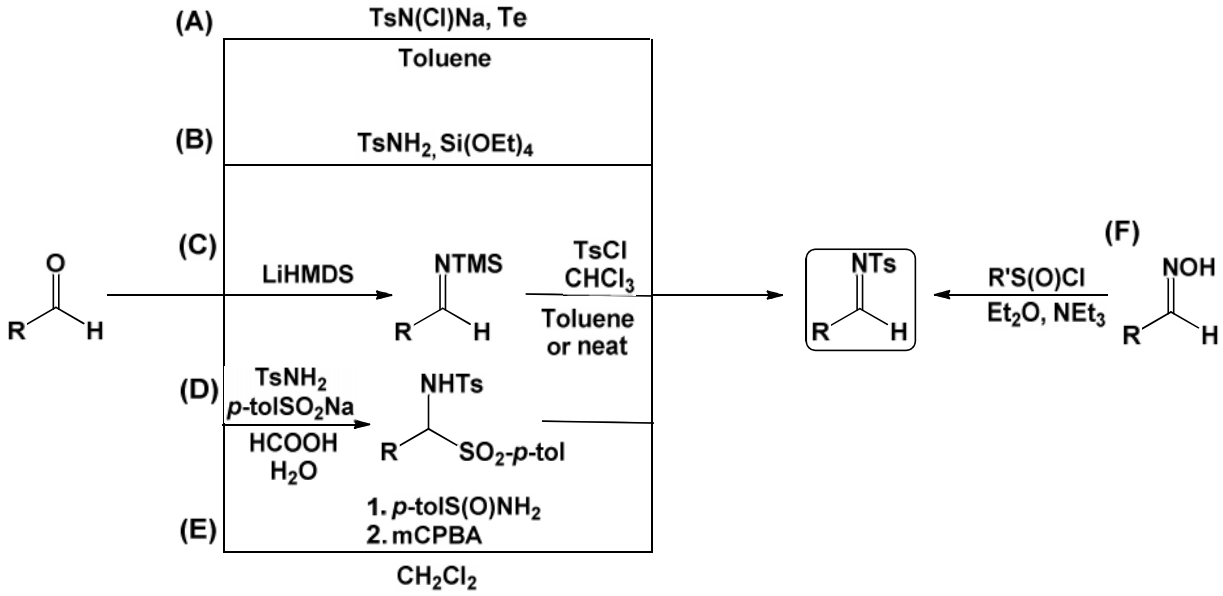
Scheme 2.1. Preparation of chiral amines from carbonyl derivatives.

The importance of the PG in the imine moiety lies in its ability to activate the imine for nucleophilic addition, thus it should preferably be an electron-withdrawing *N*-substituent.

2.1.2. Overview of the common methods for imine preparation

The most commonly used method for the preparation of imines consists in a condensation reaction between a nucleophilic amine and an aldehyde, under

Dean-Stark conditions or in the presence of a dehydrating agent such as magnesium sulfate or molecular sieves.[4,5] *N*-sulfonyl imines, where the PG comprises a group with the general formula R-S(=O)$_2$ (for instance tosyl, mesyl, nosyl, etc), can be easily accessed from a plethora of methods (Scheme 2.2).

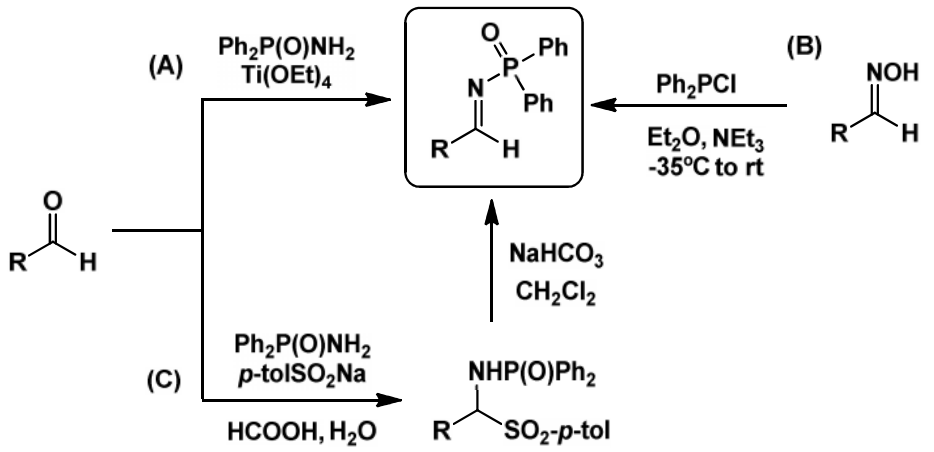


Scheme 2.2. Common methods for the preparation of *N*-sulfonyl imines.

Trost and Marrs[6] reported the synthesis of *N*-tosyl imines in high yields from aldehydes, using chloramide T and tellurium metal (Scheme 2.2, (A)). Alternatively, Love and co-workers[7] conducted the direct condensation of an aldehyde with *p*-toluenesulfonamide, using a strong Lewis acid such as Si(OEt)$_4$ (Scheme 2.2, (B)). A facile one-flask conversion of aldehydes and ketones to afford *N*-sulfonyl imines from *N*-(trimethylsilyl) imines is another method to take into account (Scheme 2.2, (C)).[8] A new practical and efficient synthesis of *N*-sulfonylimines derived from aliphatic and aromatic aldehydes was reported by Chemla and Normant[9] (Scheme 2.2, (D)), involving the initial formation of the sulfinic acid adduct of the imine from an aldehyde and *p*-toluenesulfinic acid formed *in situ* from formic acid and sodium benzene sulfinate. The subsequent base treatment affords the *N*-tosyl imine product. The more nucleophilic

sulfonamide could be used to prepare the *N*-sulfinyl imine, and by further oxidation with mCPBA generate the *N*-tosyl imine compound (Scheme 2.2, (E)).[10] Finally, oximes can be used as the initial precursor by treatment with sulfinyl chloride generating the *N*-tosyl imine (Scheme 2.2, (F)).[11] Among all methods described, perhaps method (D) is most effective in generating *N*-tosyl imines from either enolizable or non-enolizable aldehydes.

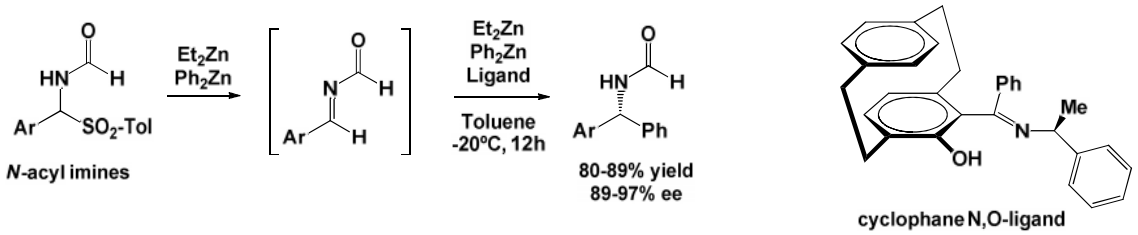
N-phosphinoyl imines, important imines where the PG is a phosphinoyl group represented by $–P(=O)(Ph)_2$, can be prepared using almost all of the methodology described above, with aldehydes or oximes as precursors (Scheme 2.3). Diphenylphosphonamide can be used along with an aldehyde, in the presence of a titanium Lewis acid[12] (Scheme 2.3, (A)) or with sodium benzenesulfinate, generating the *p*-toluenesulfinic acid adduct of the imine[13,14] (Scheme 2.3, (C)), which affords after treatment with base the *N*-phosphinoyl imine. These are the most reliable procedures to generate *N*-phosphinoyl imines from enolizable and non-enolizable aldehydes in a two-step synthesis. Finally, oximes could react with chlorodiphenylphosphine, at low temperature, and treatment with base leads to N-O bond homolytic cleavage, affording the *N*-phosphinoyl imine (Scheme 2.3, (B)).[15]



Scheme 2.3. Methods for the preparation of *N*-phosphinoyl imines.

2.1.3. Catalytic Asymmetric addition of sp^2 hybridized carbanions – Arylation of imines

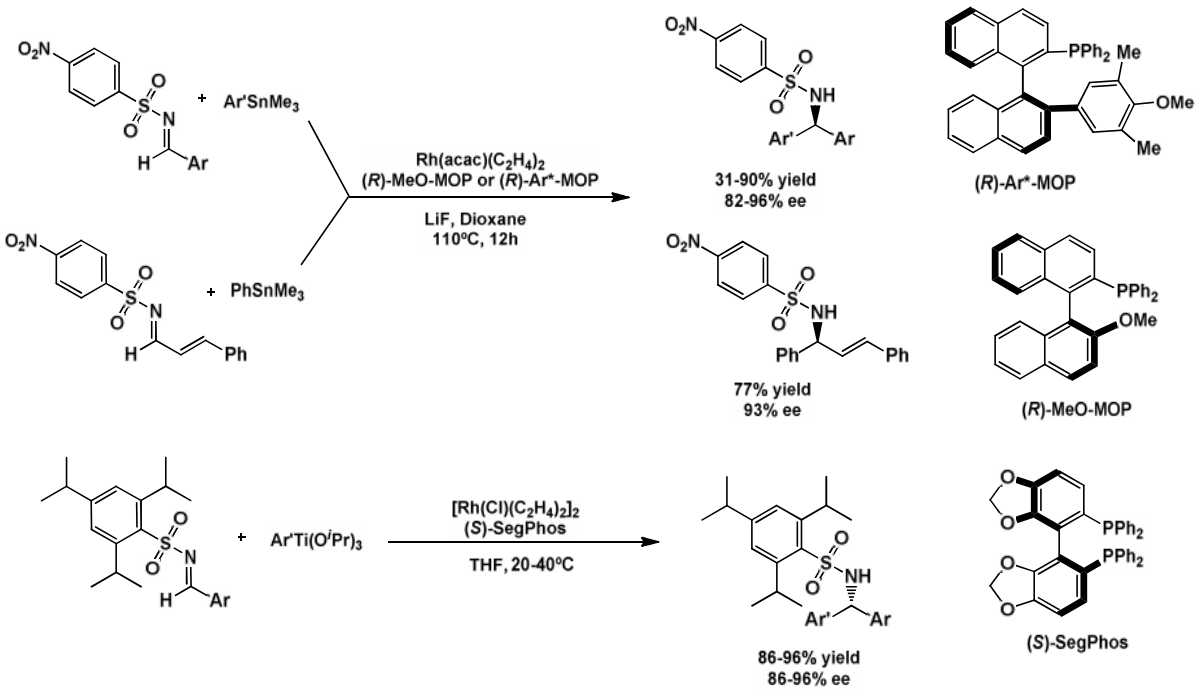
In the past, direct additions of aryl groups to the C=N bond was a popular method.[16] However, the significant electrofilicity of the azomethine carbon severely complicated this transformation, as there was a tendency for the imine and imine derivatives to enolize. Arylating agents containing zinc, tin and titanium were applied with success to afford enantiomerically pure chiral aryl-amine products.[17] For instance, Bolm and co-workers[18] reported the first catalytic and highly enantioselective synthesis of diarylmethylamines in excellent yields from imines using *in situ* prepared mixed di-organozinc reagents, catalyzed by a cyclophane N,O-chiral ligand (Scheme 2.4).



Scheme 2.4. Arylation of *N*-acyl imines with zinc by Bolm and co-workers.[18]

Hayashi and co-workers first reported some remarkable work on the rhodium phosphine-catalyzed arylation of imines with arylstananne[19,20] and aryltitanium[21] reagents (Scheme 2.5).

Despite these excellent results with such reagents, a major concern particularly in the context of both sustainability and API manufacture, was use of toxic reagents and the waste issue, including the issue of atom economy.

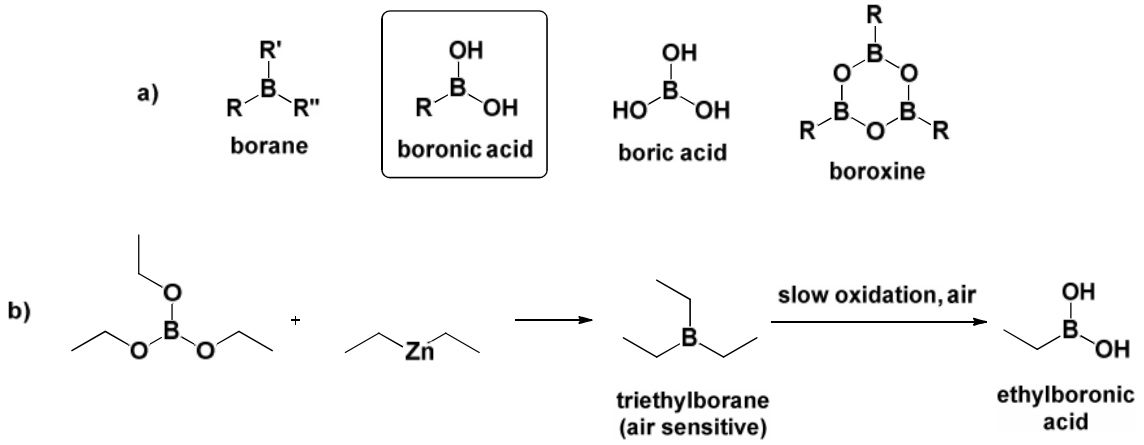


Scheme 2.5. Rhodium catalyzed addition of imines with tin and titanium reagents as reported by Hayashi's group.[19-21]

The authors presumed that all these reactions proceed *via* the formation of an arylrhodium species that is coordinated to the chiral ligand. The use of these arylating agents as stoichiometric nucleophiles was successfully applied in the synthesis of chiral amines. By screening several imine substrates with different PGs, the nosyl derivatives (*p*-nitrophenylsulfonyl groups) gave the highest ee and yield (applying 4 equivalents of the arylstannanes). The arylation of an α,β-unsaturated imine led to the formation of the 1,2-addition products with high ee values under the same conditions. (*S*)-SegPhos was the optimal ligand with the aryltitanium nucleophile, which worked best with imines substituted with 2,4,6-triisopropylbenzenesulfonyl groups, affording high enantioselectivities (see Scheme 2.5). Finally, the cleavage of the corresponding PG to liberate the free amine was accomplished with appropriate reagents (like, for example, thiophenol and potassium carbonate or samarium iodide and hexamethylphosphoramide (HMPA)) in high yields.

2.1.3.1. Organoboron Reagents

Organoboron reagents, derivatives of borane (BH_3), are important reagents in organic chemistry enabling many chemical transformations. Boronic acids, boron analogues of carboxylic acids, structurally, are trivalent boron-containing organic compounds possessing one alkyl or aryl substituent and two hydroxyl groups to fill the remaining valences on the boron atom (Scheme 2.6, (a)). Unlike carboxylic acids, boronic acids are not found in nature. They are derived synthetically from primary sources of boron, such as boric acid for instance and, it was Frankland[22,23] in 1860, who was the pioneer in the preparation and isolation of the boronic acid: ethylboronic acid, from triethylborate and diethylzinc (see Scheme 2.6, (b)).



Scheme 2.6. a) Organoboron compounds; **b)** Synthesis of the first boronic acid by Frankland.[22,23]

Their unique properties as mild organic Lewis acids and their low reactivity profile coupled with their stability, wide functional group diversity and ease of handling, makes boronic acids an attractive class of synthetic intermediates. Moreover, their degradation product is the environmentally friendly boric acid, thus labeling boronic acids as “green reagents”, with low toxicity. They are solids that can exist as mixtures of oligomeric anhydrides, such as six-membered boroxines (see Scheme 2.6, (a)).[24] In the past three decades, the status of boronic acids in chemistry has risen from insignificant and neglected compounds to a prime class of synthetic intermediates, reflected in hundreds of publications. Their role as therapeutic substances is high-lighted in the anti-cancer drug Velcade® (Figure 2.2), the first boronic acid containing drug ever commercialized.[25]

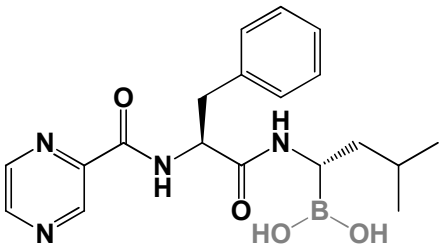


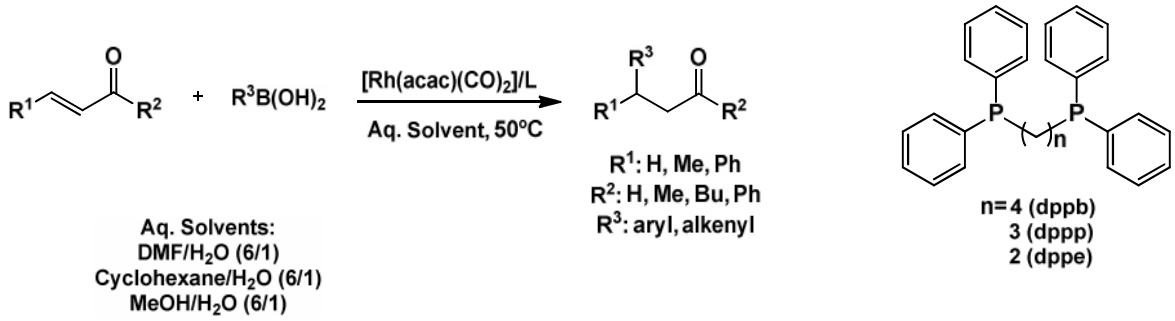
Figure 2.2. Velcade®.

2.1.3.2. Boronic Acids in Asymmetric Catalysis

In the asymmetric C-C bond forming reactions, the importance of boronic acids was reflected in the well-known Suzuki-Miyaura reaction,[26] where biaryl or substituted aromatic moieties where synthesized, using an aryl or vinyl-boronic acid and an aryl or vinyl-halide, catalyzed by palladium (0) complexes (see Chapter 5 for further information) and in the asymmetric 1,4-addition to enones or enoates catalyzed by transition metal complexes, like Rh. Like for the arylation of imine substrates (see section 2.1.3), Grignard reagents, organolithiums or

diorganozincs were employed as the organometallic component along with copper metal catalysts and while they provided high yields in many cases, the issues of chemoselectivity and environmentally friendliness limit their use.[27] And from here emerged rhodium-catalyzed reactions as alternative catalytic systems to these copper-catalyzed additions since key advantages such as insensitivity to water, mild reaction conditions and reagent diversity – substituted boronic acids could be used – were important issues to take into consideration.

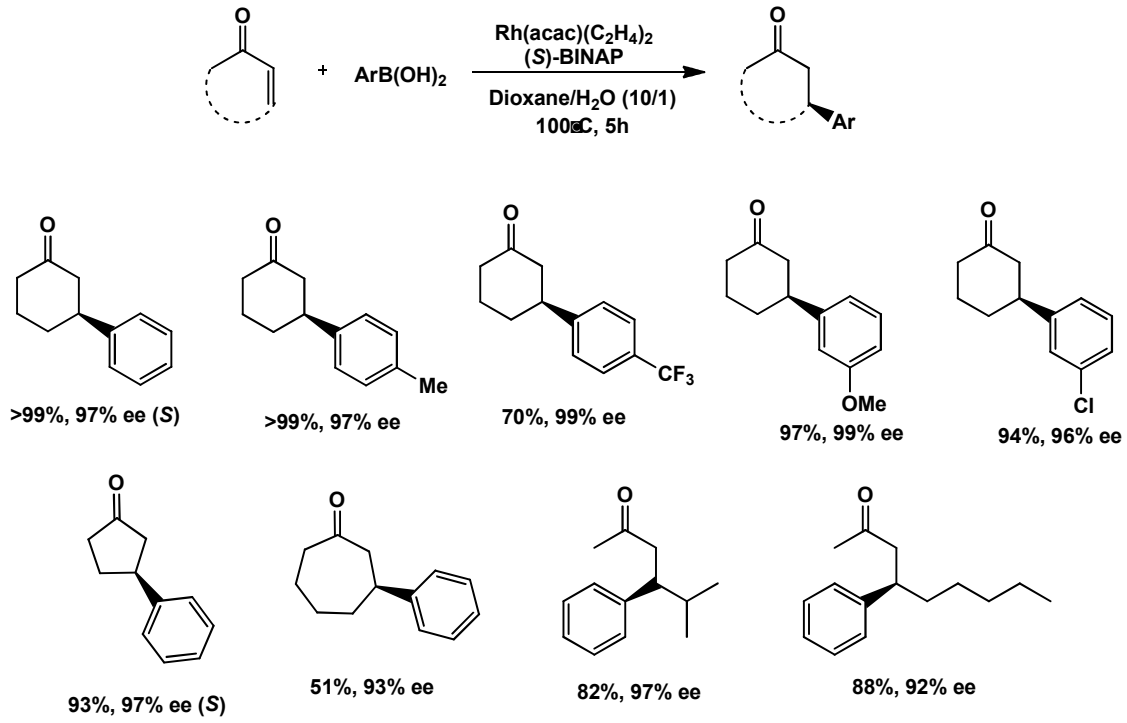
The first Rh-catalyzed arylation of arylboronic acids to enones, can be traced back to a publication in 1997 by Miyaura and Sakai.[28] The combination of [Rh(acac)(CO)$_2$] and a di-phosphine ligand could efficiently catalyze the addition of arylboronic acids to linear and cyclic α,β-unsaturated ketones in several aqueous solvent systems in high to moderate yield (Scheme 2.7). Despite the fact that low yields were obtained for 2-cyclohexenone, the scope of the reaction in terms of the wide range of boronic acids used marked the beginning of a new synthetic methodology.



Scheme 2.7. Initial report on the Rh-catalyzed arylation to enones by Miyaura and Sakai.[28]

Hayashi and co-workers[29] described the first enantioselective variant of this transformation. Using (*S*)-BINAP as the chiral ligand, and a broad range of arylboronic acids, it was possible to obtain a large selection of arylated adducts in high yields and excellent enantioselectivities (Scheme 2.8). Slight modifications were made to the original Miyaura procedure. A different Rh precursor was used,

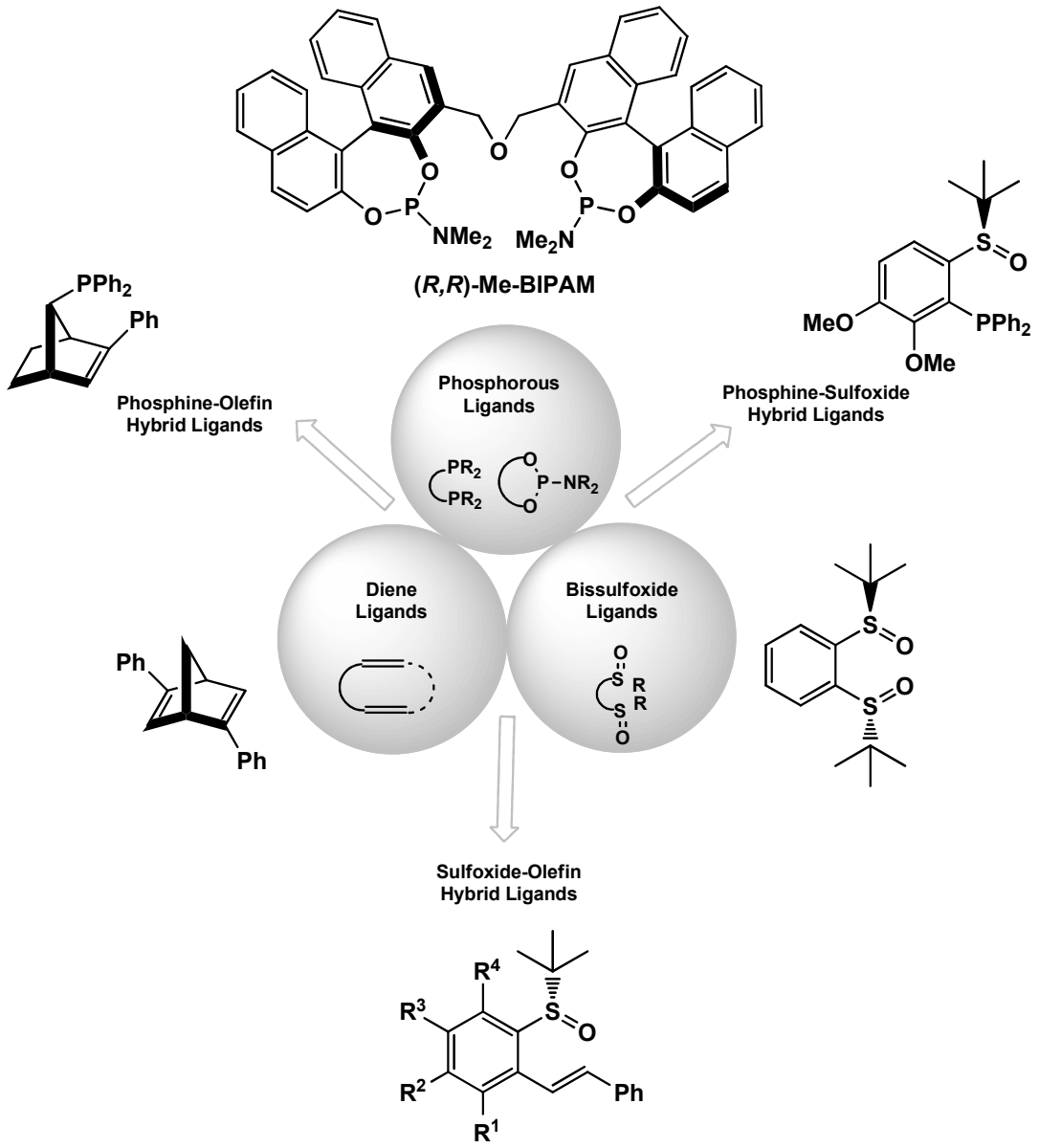
along with a different solvent system and higher reaction temperatures in order to achieve the optimal reaction protocol. Arylboronic acids with electron-donating and electron-withdrawing substituted groups were successfully added to both cyclic and trans-linear enones.



Scheme 2.8. Rh(acac)$(C_2H_4)_2$/(*S*)-BINAP catalyzed asymmetric arylation of arylboronic acids to enones by Hayashi and co-workers.[29]

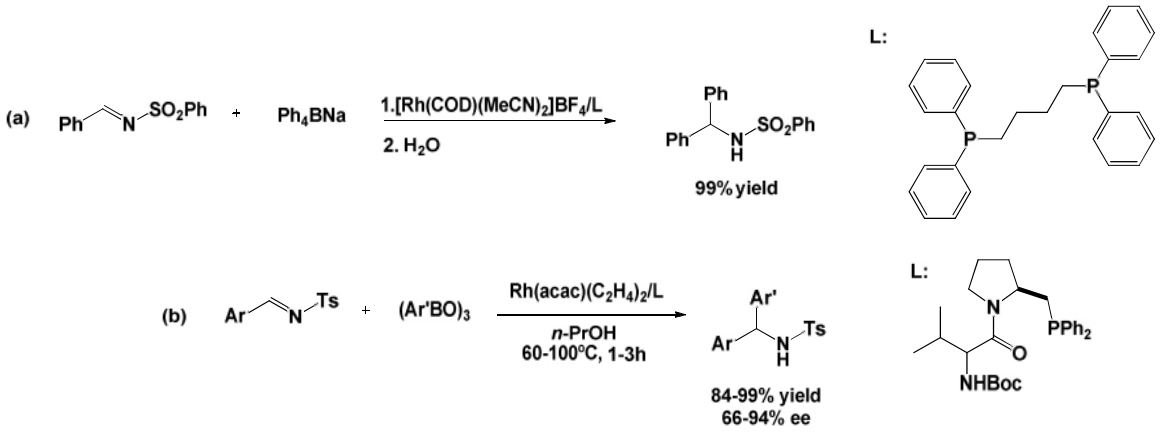
The remarkable work developed by Hayashi and Miyaura paved the way for intense research activity in this area and with related processes. Other chiral ligands were tested with success for this catalytic transformation, and reported by several other authors (Scheme 2.9).[30] A plethora of functional groups with potential to undergo the addition reaction were exploited, for example: alkenes, aldehydes, ketones and imines. In the context of this work, we focused initially on the addition to imine substrates.

Despite the fact that the first reports on the application of this methodology for the 1,4-arylation of enones appeared in 1997, the successful arylation of imines only took place about 10 years later. Their application has still been quite sluggish. Miyaura[31] was the first to report the non-asymmetric version of the arylation of aldimine substrates using an organoboronic salt derivative, in conjunction with Rh(I) catalysts (Scheme 2.10, (a)).



Scheme 2.9. Examples of some chiral ligands applied with success in the Rh-catalyzed asymmetric arylation.

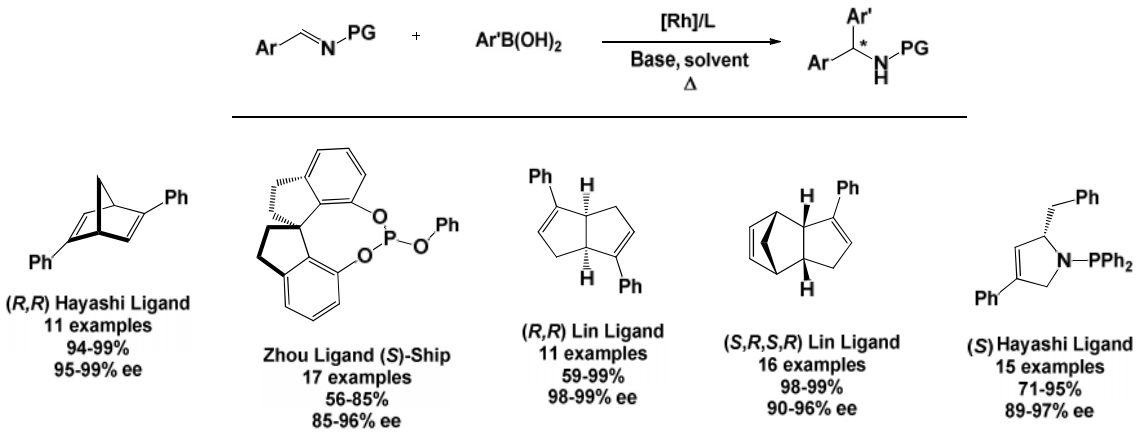
Subsequently Tomioka and co-workers,[32] published an asymmetric version of the catalytic arylation of aldimines with organoboron reagents applying Rh(I) catalysts with chiral amidomonophosphane ligands (Scheme 2.10, (b)). Hayashi and co-workers[33-35] applied bicyclo[2.2.2]octadiene ligands in the arylation of aldimines using arylboronic acids and arylboroxines, with Rh pre-catalysts (Scheme 2.11). In 2006, Zhou and co-workers[36] carried out the enantioselective arylation of *N*-tosylaldimines with arylboronic acids in aqueous media. A novel spiro monophosphate based ligand known as (*S*)-Ship was applied. Good yields and enantioselectivities (up to 96% ee) were obtained (Scheme 2.11).



Scheme 2.10. Arylation of aldimine substrates catalyzed by Rh in a **(a)** non-asymmetric and **(b)** asymmetric fashion.

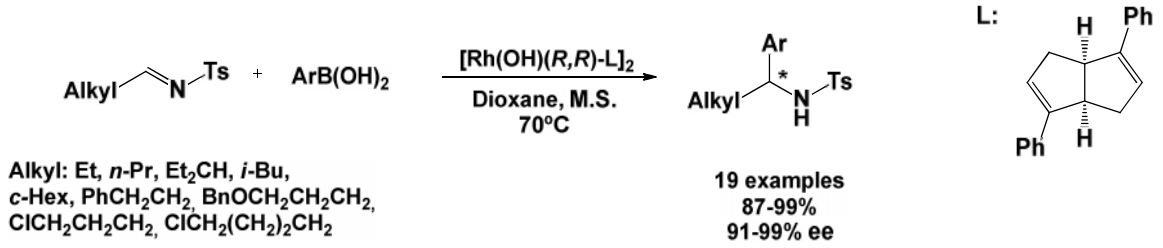
Wang and co-workers[37] have developed a new diene ligand with a non-bridge bicyclic[3.3.0] skeleton, found to be an excellent ligand for the arylation of sulfonyl imines, along with Rh metal catalysts. A wide variety of *N*-tosylaldimines with diverse steric and electronic properties successfully reacted with several arylboronic acids providing the desired chiral diaryl amines in excellent enantioselectivities (98-99% ee) (Scheme 2.11). Lin's group[38] developed a new class of monosubstituted C_1-symmetric diene ligands with a dicyclopentadiene backbone, affording the desired amine products in excellent yields (98-99%) and

high enantioselectivities (90-96% ee) using Rh (Scheme 2.11). More recently, Hayashi's group designed and synthesized a novel chiral phosphine-olefin hybrid ligand which was highly successful in these catalytic transformations using Rh (Scheme 2.11).[39]



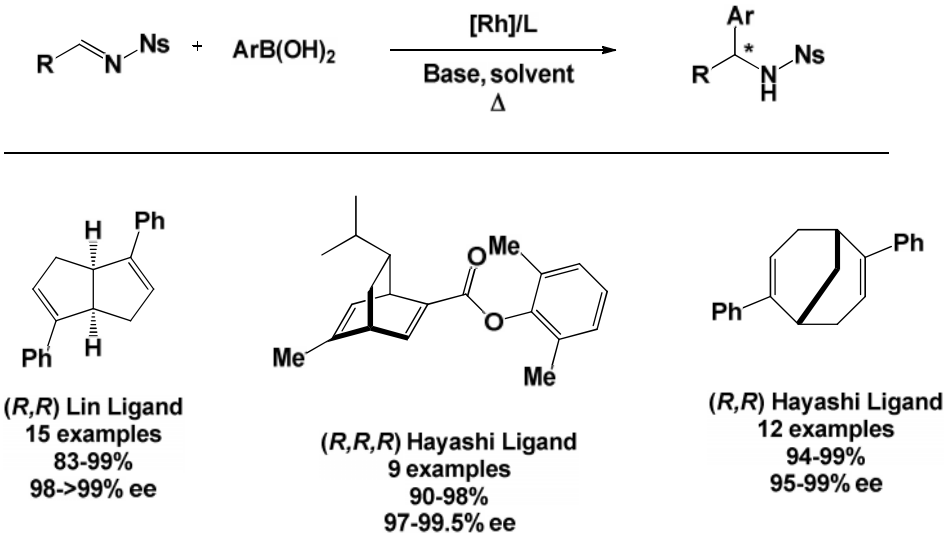
Scheme 2.11. Rh-catalyzed asymmetric arylation to *N*-protected aldimines (PG: protecting group).

In spite of some considerable advances, the imine substrates in this catalytic transformation type have been limited to aromatic imines. Recently, Lin and co-workers successfully extended the Rh catalyzed arylation to aliphatic *N*-tosyl imines using a chiral diene ligand, under neutral conditions (Scheme 2.12).[40] In these reaction conditions, the possible formation of non-desired secondary reaction products, such as those resulting from imine-enamine tautomerization, decomposition or self-condensation, weren't verified.



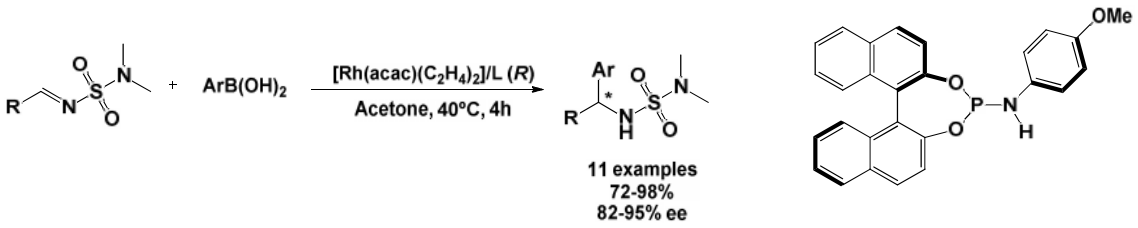
Scheme 2.12. Rh-catalyzed asymmetric arylation to *N*-tosylalkylaldimines by Lin and co-workers.[40]

It was verified by the authors that the removal of the tosyl group wasn't an easy process, so, several groups explored the Rh-catalyzed asymmetric arylation reaction with *N*-4-nitrobenzenesulfonylimines (i.e. with nosyl (Ns) as the PG) to facilitate the deprotection step. High enantioselectivities and high catalytic activities were observed using chiral diene ligands with easy removal of the Ns group without racemization or any side reactions (Scheme 2.13).[40-42]



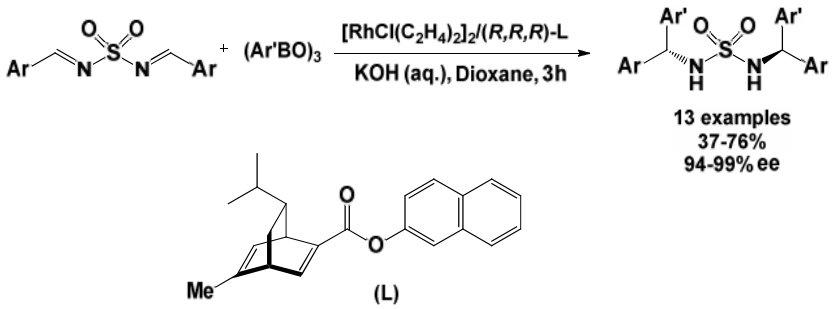
Scheme 2.13. Rh-catalyzed asymmetric arylation in *N*-(4-nitrobenzene)sulfonyl aldimines.[40-42]

Feringa and co-workers[43] used imines containing the small and cheap *N*,*N*-dimethylsulfamoyl protecting group for this Rh-catalyzed arylation process. High yields and enantioselectivities were achieved using a Rh(I)/phosphoramidite system (Scheme 2.14). Diarylmethylamines could be obtained easily by removal of the protecting group using microwave-assisted transamination.



Scheme 2.14. Rh-catalyzed asymmetric arylation with *N*,*N*-dimethylsulfamoyl aldimines, as developed by Feringa and co-workers.[43]

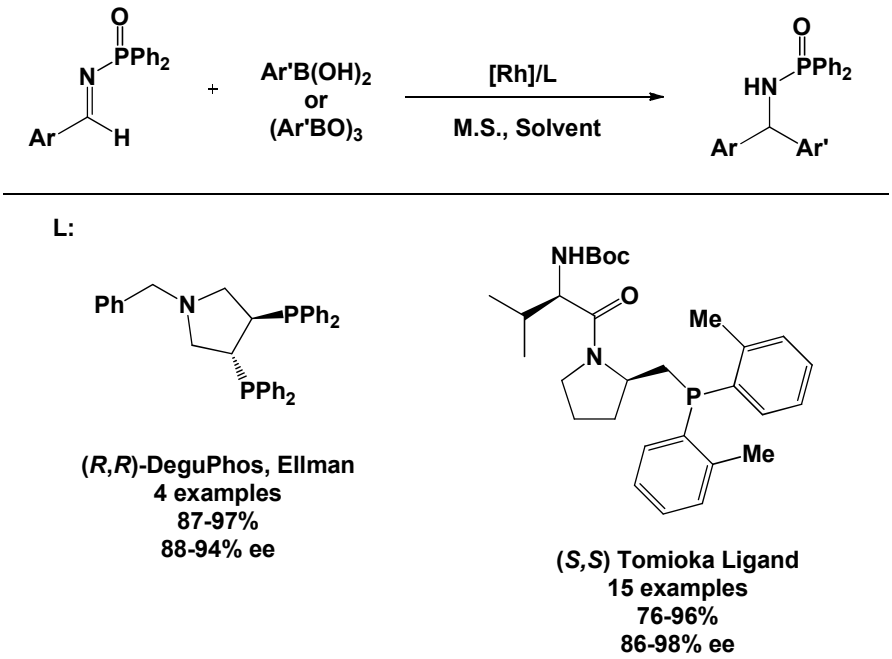
Recently Woodward's group[44] reported that bis-sulfamyl imines are potentially ideal substrates for the Rh-catalyzed asymmetric additions of boronic acids. Excellent enantioselectivities along with good to excellent diastereoselectivities and high functional group tolerance in the removal of protective group via mild heating in aqueous pyridine, was the prime advantage with this variant of the catalytic transformation (Scheme 2.15).



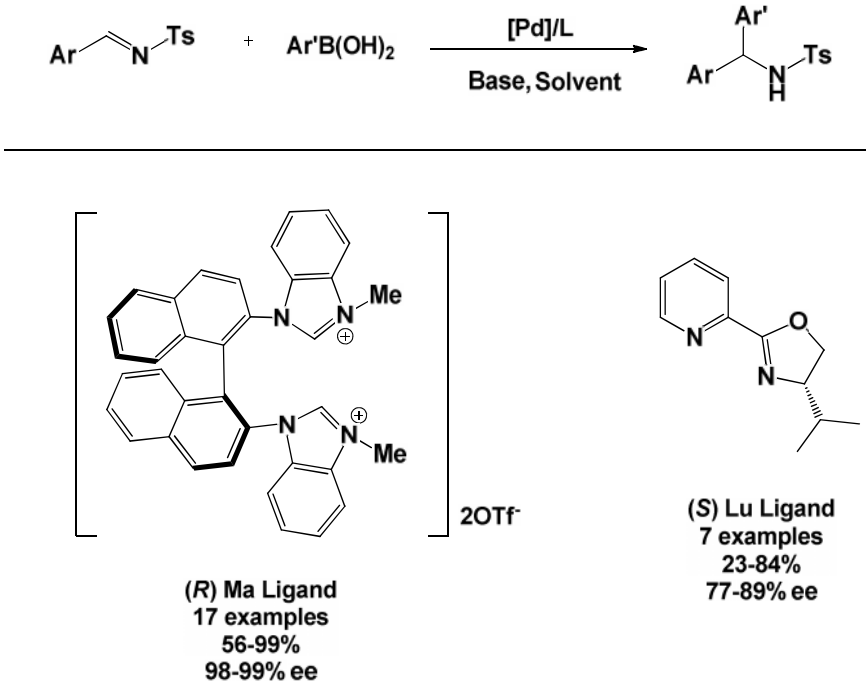
Scheme 2.15. Rh-catalyzed addition to bis-sulfamyl aldimines as reported by Crampton *et al*.[44]

Using the chiral di-phosphine ligand (*R*,*R*)-DeguPhos, Ellman's group[45] reported the highly enantioselective addition of arylboronic acids to *N*-diphenylphosphinoyl benzaldimines (Scheme 2.16), and later on, Tomioka's group applied arylboroxines with success in this catalytic reaction by sterically tuning the diphenylphosphorous moiety to a di(*o*-tolyl)phosphorous based ligand (Scheme 2.16).[46]

Many reports concerning Rh-catalyzed arylation of imine substrates were found, but, as far as we are aware, there are very few reports on the application of other metals, notably, Pd for instance. Ma's group[47] reported an interesting Pd-catalyzed arylation of *N*-tosylaldimines with boronic acids, in which a chiral NHC ligand was used to coordinate the Pd (Scheme 2.17). Almost simultaneously, Lu's group[48] reported the same catalytic reaction type, catalyzed by Pd-pyridine-oxazoline catalyst in moderate yields and enantioselectivities (Scheme 2.17).



Scheme 2.16. Rh-catalyzed addition to *N*-diphenylphosphinoyl aldimines by Ellman's[45] and Tomioka's[46] groups.



Scheme 2.17. Pd-catalyzed arylation of *N*-tosylaldimines by Ma's[47] and Lu's[48] group.

In order to study the mechanism of the Pd catalyzed version of this reaction and establish its scope, we decided to perform a study using Pd pre-catalysts and commercial phosphane ligands.

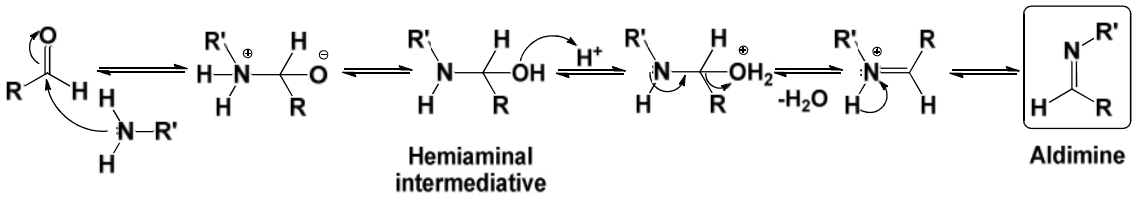
The reputation of the Group 8 transition metal complexes in metal-catalyzed reactions is well established due to their important contribution to modern organic synthesis, notably for cross-coupling reactions, such as the Mizoroki-Heck, Suzuki-Miyaura and Stille reactions, etc.[49] Among the elements of the Periodic Table, Ru has the widest oxidation state scope (from -2 to +8) with several coordination geometries in each electronic configuration, which is considered an advantage, particularly compared to the narrow oxidation state scope and the simple square planar structures for the corresponding palladium complexes. In the principal lower oxidation states (0, I and II) these ruthenium complexes normally adopt trigonalbipyramidal and octahedral geometries. Their relatively inexpensive cost, compared to Pd and Rh, along with their great potential for novel catalytic

processes makes Ru based catalysts good alternatives to traditional palladium catalysts. Ru based catalysis has undoubtedly benefited from the considerable progress made in the study of the coordination chemistry of ruthenium complexes. The ruthenium complexes can be divided, according to the type of coordinated ligands present: carbonyl type, tertiary phosphines type, cyclopentadienyl, arene/diene type and carbene types.[50,51] A large number of both novel and bench-mark reactions[50] were developed using catalytic amounts of ruthenium complexes, successfully, taking advantage of a variety of useful characteristics of their own, such as, low redox potential, high electron transfer ability, high coordination ability to heteroatoms and Lewis acid acidity. To put the importance of Ru chemistry into perspective, we should consider the view of Barry Trost when he said: *"Prospects are clearly bright for more reactions to be discovered"*.[52] In this chapter, our objective was the discovery of new reactions, all geared towards the catalytic enantioselective formation of C-C bonds with aldimine substrates, using organoboron reagents.

2.2. Results and Discussion

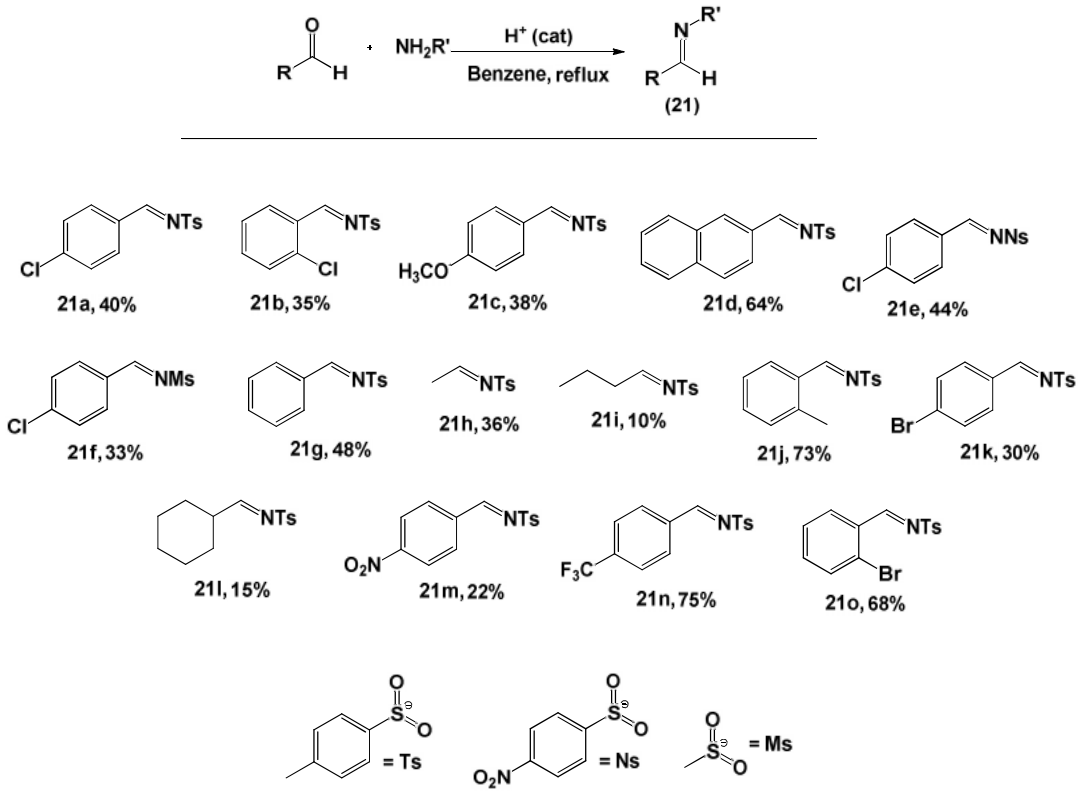
2.2.1. Synthesis of aldimines

Imines which have a structure analogous to aldehydes are referred to as aldimines. Aldimines are represented by the general formula R–CH=N–R', were R and R' could be an alkyl or an aryl group (Scheme 2.18). When R' isn't a hydrogen, these particular compounds are also called *Schiff bases* and it is the substituent on the nitrogen that gives stability to the imine. In order to study the formation of new C-C bonds with imine substrates we decided to synthesize a range of these molecules with various types of protecting group. They were simply prepared by the condensation of a primary amine with an aldehyde according to the mechanism presented in Scheme 2.18. The equilibrium of this reaction usually favors the carbonyl molecule and the amine, but, using a Dean-Stark trap, a drying agent or even molecular sieves, it was possible to remove the water formed.



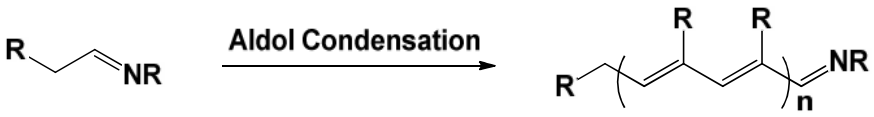
Scheme 2.18. Proposed mechanism for the synthesis of aldimines from aldehydes and amines.[53]

Fifteen aldimine substrates (**21a-o**, Scheme 2.19), were synthesized using a known literature procedure.[4] The activating group varied between tosyl (Ts), nosyl (Ns) and mesyl (Ms).



Scheme 2.19. Synthesis of *N*-aldimines from the corresponding aldehydes.

Overall the yields were moderate to good, with the best yield obtained for **(21n)** (75%, corresponding to *p*-CF_3benzaldehyde). **(21j)** and **(21d)** were obtained in 73% and 64% yields, respectively. The yields were much lower when aliphatic aldehydes were used. Among aliphatic aldehydes, small linear aldehydes are considered to be very problematic due to the difficulty in controlling their high reactivity, particularly when there is an α-hydrogen present (which is normally the case), the imines can be isomerized to enamines (Scheme 2.20), giving polymeric materials, by subsequent aldol condensation.[53]



Scheme 2.20. Possible formation of polymeric materials by aldol condensation with imine substrates.[53]

2.2.2. Palladium chemistry

In asymmetric organometallic catalysis the "laurel leaf" belongs to chiral phosphane ligands (commonly denominated phosphine ligands (PR_3)). Phosphane ligands are usually strong σ-donor ligands and weak π-acceptors with respect to their bonding to metal centers and, counting the numerous chiral phosphane ligands available to date, a general classification into three major categories could be assigned, depending on the location of the chiral center: Ligands presenting axial chirality (e.g. BINAP, for instance), those with central chirality (e.g. DIOP, for instance) and those bearing a chirogenic phosphorous (P-chiral) (e.g. DIPAMP, for instance) (Figure 2.3).[54] Despite the fact that for many phosphane ligands, their synthesis is not always simple, due to their relative instability to air and moisture, a great variety of phosphane ligands are commercially available.

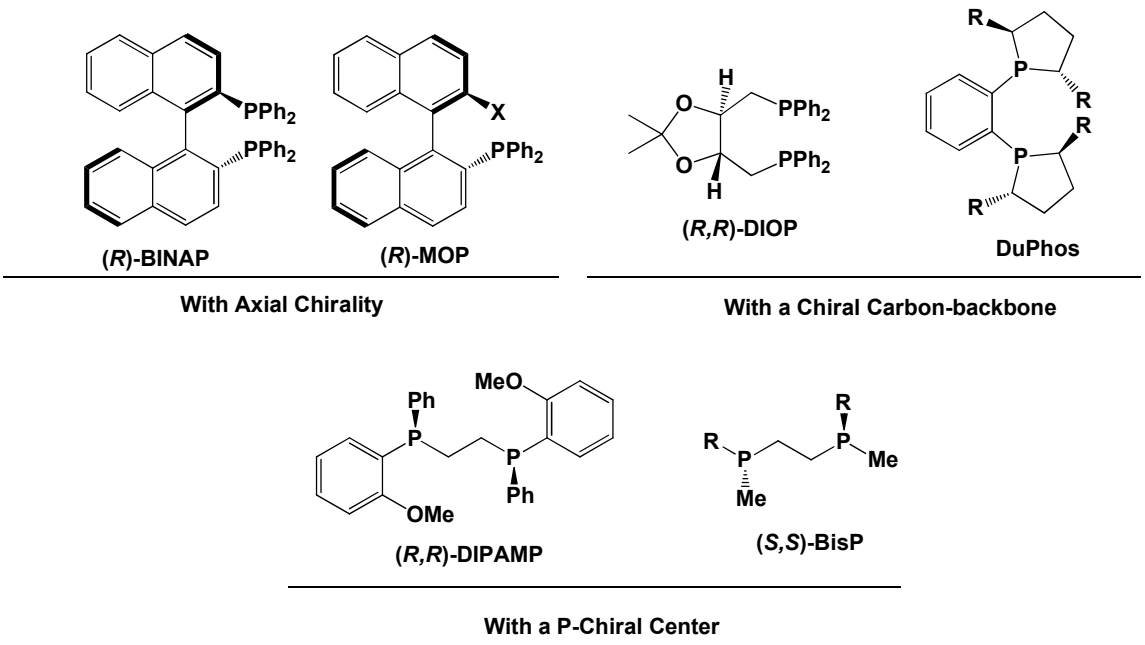
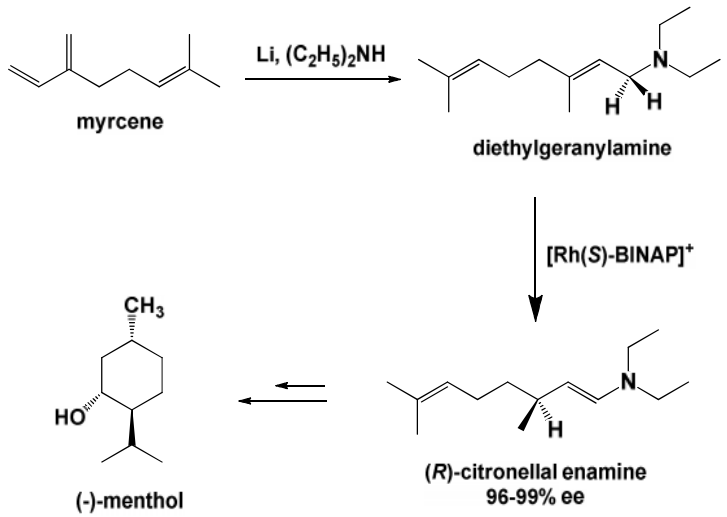


Figure 2.3. The three main categories of Phosphane chiral ligands.

Among many phosphane ligands prepared so far, a relatively small number of structural classes stand out due to their broad applicability, allowing high levels of enantioselectivity in many different metal-catalyzed reactions – ligands with C_2 symmetry (see Figure 2.3, all of the examples are C_2-symmetric ligands).[55,56] DIOP (Figure 2.3) was introduced by Dang and Kagan in 1971 and with it has emerged the concept of C_2-symmetry in ligands.[57] The main advantage of having a C_2-symmetrical axis in ligands is that it reduces the number of possible competing, diastereomeric transition states, as well as the number of different substrate-catalyst arrangements and reaction pathways, comparatively to the use of a non-symmetrical ligand. The design principles that led Dang and Kagan to this ligand had a marked influence on the course of research in asymmetric catalysis and many diphosphane ligands were reported and modeled on DIOP. For instance, Knowles[58] reported a dimeric analogue of one of his previously synthesized mono-phosphanes, which he termed DIPAMP (Figure 2.3). An

industrial catalytic process (production of *L*-Dopa) was developed using this ligand in a Rh-catalyzed hydrogenation reaction.[59] Highly efficient diphosphane ligands, such as BINAP and DuPhos (Figure 2.3) were reported previously by Noyori[60] and Burk's group,[61] respectively, and applied successfully in asymmetric catalytic reactions. One of the outstanding industrial achievements using these chiral ligands in asymmetric catalysis is the widely known Takasago's industrial synthesis of (-)-menthol starting from myrcene. The crucial step is asymmetric isomerization of diethylgeranylamine to (*R*)-citronellal enamine using a Rh-BINAP catalyst (Scheme 2.21).[62]

We decided to screen a variety of these commercial ligands in this study (Figure 2.4).



Scheme 2.21. Takasago menthol synthesis.[62]

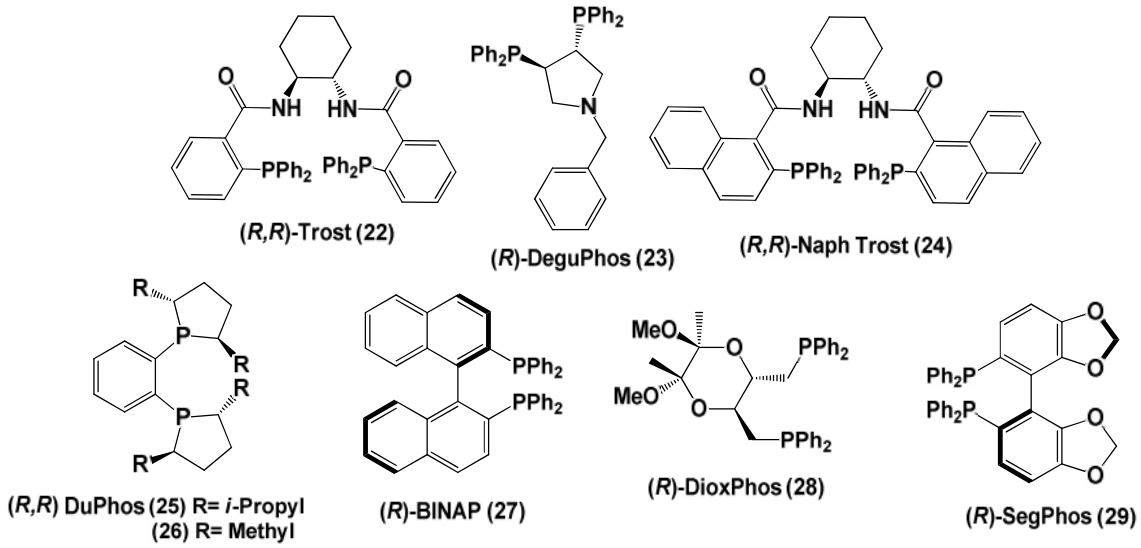
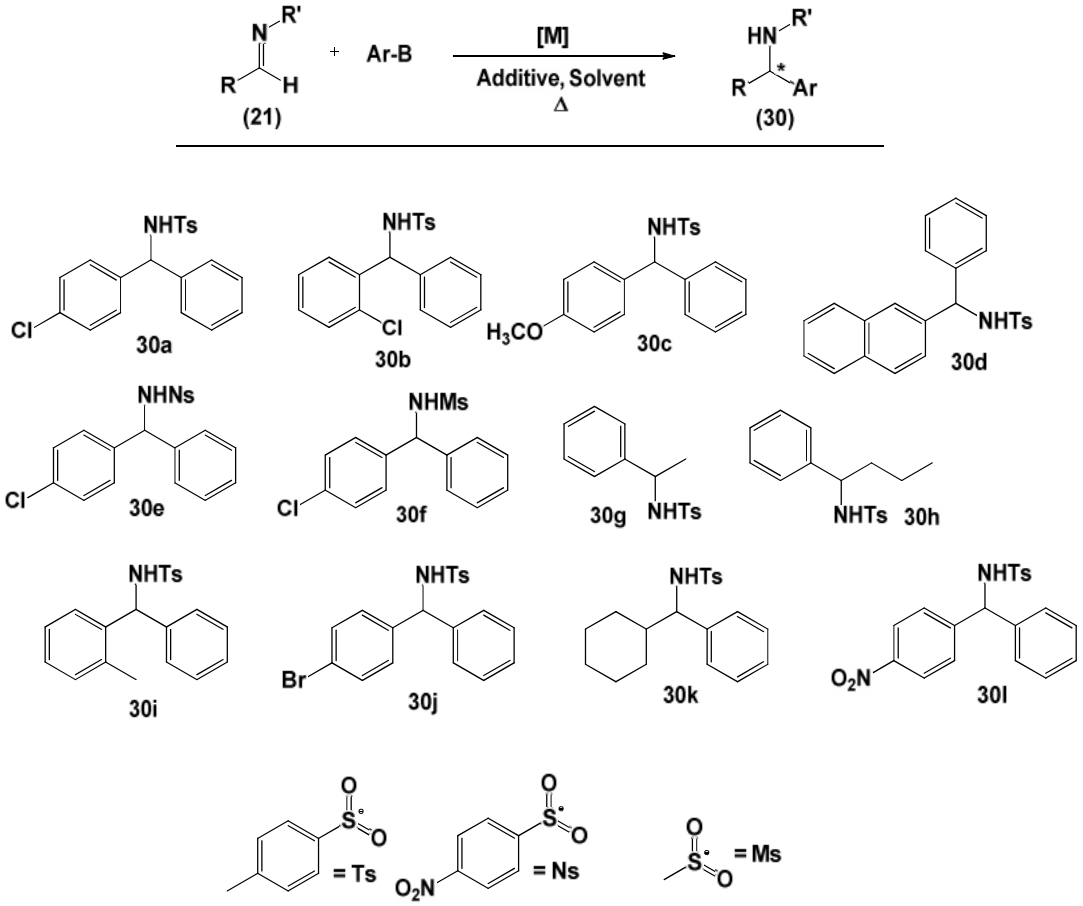


Figure 2.4. Chiral commercial phosphane ligands used in this study.

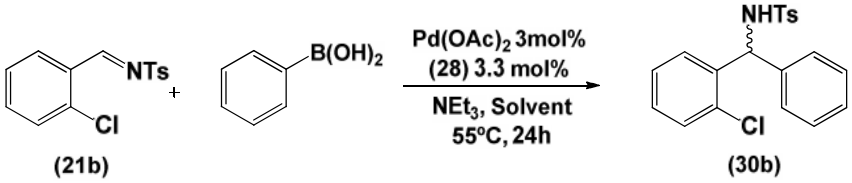
In their study, Dai and Lu[48] concluded that aldimines with strong electron-withdrawing groups, such as halogens or nitro, in the phenyl ring were very effective in the catalytic arylation using boronic acids. We decided to start our investigation by performing a test reaction with the aldimine **(21b)** (Scheme 2.19), with a corresponding *o*-chloro group in the phenyl moiety. The commercial $Pd(OAc)_2$ was used as the palladium source and (*R*)-DioxPhos **(28)** (Figure 2.4) as chiral ligand, *in situ*. As organoboron reagent, the simple phenylboronic acid was used at a loading of 2 molar equivalents. The non-polar solvent toluene was used and NEt_3 as the basic additive. The desired chiral amine **(30b)** (Scheme 2.22) was obtained with an isolated yield of 77% and an enantiopurity of 42% ee in favor of the (*R*)-enantiomer (Table 2.1, entry 1), as determined by HPLC.



Scheme 2.22. Transition metal-catalyzed addition of organoboron reagents to aldimines in the synthesis of chiral biarylarylmethylamines.

On the basis of this good result, we decided to perform a solvent screening study of the above reaction to determine if there were any solvent effects. Solvents like 1,4-dioxane, THF, CH_2Cl_2, DMF, CH_3CN, MeOH and $CHCl_3$ were screened. The results can be seen in Table 2.1.

Table 2.1. Solvent screening studies.



(21b) (30b)

Entry	Solvent[a]	Yield/%[b]	ee/%[c]
1	Toluene	77	42 (*R*)
2	1,4-Dioxane	24	10 (*R*)
3	$CHCl_3$	26	17 (*R*)
4	MeOH	13	45 (*R*)
5	DMF	<10	<5 (*R*)
6	THF	30	38 (*R*)
7	CH_2Cl_2	26	46 (*S*)
8	CH_3CN	<5	81 (*R*)

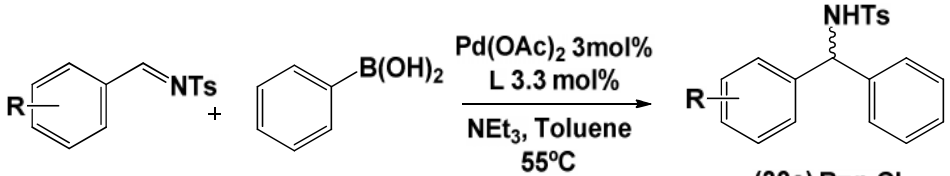
[a]All the solvents used were dried using common lab techniques.
[b]Isolated yields.
[c]Determined by chiral stationary phase HPLC.

Despite the fact that the yields obtained were lower comparatively to those obtained with toluene (Table 2.1, entry 1), an overall look at the results leads us to conclude that the reaction could be conducted in almost all the solvents described, with the exception of DMF and CH_3CN (Table 2.1, entries 5 and 8). We observed that in the case of the coordinated polar solvents like MeOH, DMF and CH_3CN the yield decreased considerably, and this might be explained by the fact that imine hydrolysis was probably more promiscuous in these cases.

The enantioselectivity decreased using these solvents. The switch in the configuration of the major enantiomer to (*S*) on using CH_2Cl_2 (Table 2.1, entry 7) was surprising and we believe that a change in the structure of the active catalyst might have been the reason. Toluene is therefore, the solvent of choice.

Enthusiastic about the results obtained, we decided to perform a screening study using all the phosphine ligands available (Figure 2.4) with the two chlorinated aldimines (**21a** and **21b**, Figure 2.19) using the methodology shown in Table 2.1. Among the ligands screened were the well-known Trost ligands (**22** and **24**, Figure 2.4), the DuPhos ligands (**25** and **26**, Figure 2.4) and the BINAP ligand (**27**, Figure 2.4), all applied with lots of success in Pd catalyzed C-C bond reactions.[63-66] The results can be seen in Table 2.2.

Table 2.2. Asymmetric arylation of *N*-tosylaldimines **(21a)** and **(21b)** with phenylboronic acid and ligands **(22)**-**(28)**.



(21a) or (21b)

(30a) R=*p*-Cl
(30b) R=*o*-Cl

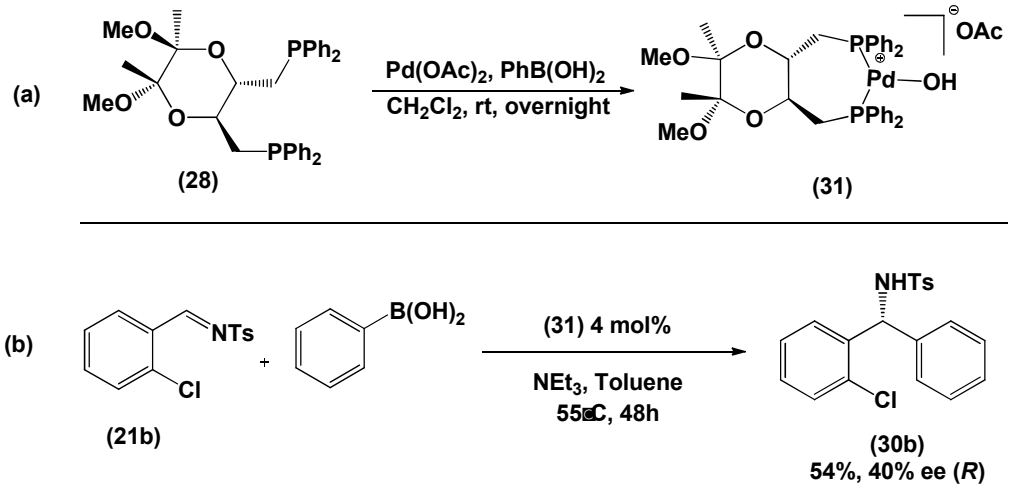
Entry	Aldimine	L	Time/h	Yield/%[(a)]	ee/%[(b)]
1	**21b**	**22**	70	27	82 (*R*)
2	**21b**	**23**	41	57	72 (*R*)
3	**21a**	**23**	40	<10	12 (*R*)
4	**21b**	**24**	70	22	69 (*S*)
5	**21a**	**24**	40	16	29 (*S*)
6	**21b**	**25**	70	21	92 (*S*)
7	**21a**	**25**	40	n.r.	n.d.
8	**21b**	**26**	70	41	>99 (*S*)
9	**21a**	**26**	40	19	11 (*S*)
10	**21b**	**27**	45	29	<5 (*S*)
11	**21a**	**27**	45	10	<10 (*S*)
12	**21b**	**28**	23	77	42 (*R*)
13	**21a**	**28**	45	22	41 (*R*)

[(a)]Isolated yields.
[(b)]Determined by chiral stationary phase HPLC. Absolute configurations determined by comparing the data with those already known in the literature.[47,48]
n.r.: no reaction.
n.d.: not determined.

The yields were moderate to good, with a highest of 77% (Table 2.2, entry 12). In fact, this result was already presented above (Table 2.1, entry 1), having been the first test reaction carried out. It is important to underline that all the yields shown in Table 2.2 (and Table 2.1 as well) represent isolated yields from silica-gel column chromatography. Upon analyzing these results in order to determine the influence of electronic effects from the aldimine substrate, we noticed that the best results were obtained using aldimines with *ortho*-substituents (e.g. **21b**). When the *para*-chlorine substituted aldimine (**21a**) was investigated, the yields were poor (see for instance Table 2.2, entries 3, 5, 7 and 11). With regard to the enantioselectivity, some very good ees were obtained. The best ee values were obtained using *ortho*-chloro aldimine **(21b)**, with the exception of (*R*)-BINAP **(27)** (Figure 2.4 and Table 2.2, entry 10). We have shown that this wasn´t a good ligand for this particular catalytic transformation, given that both the yields and ees

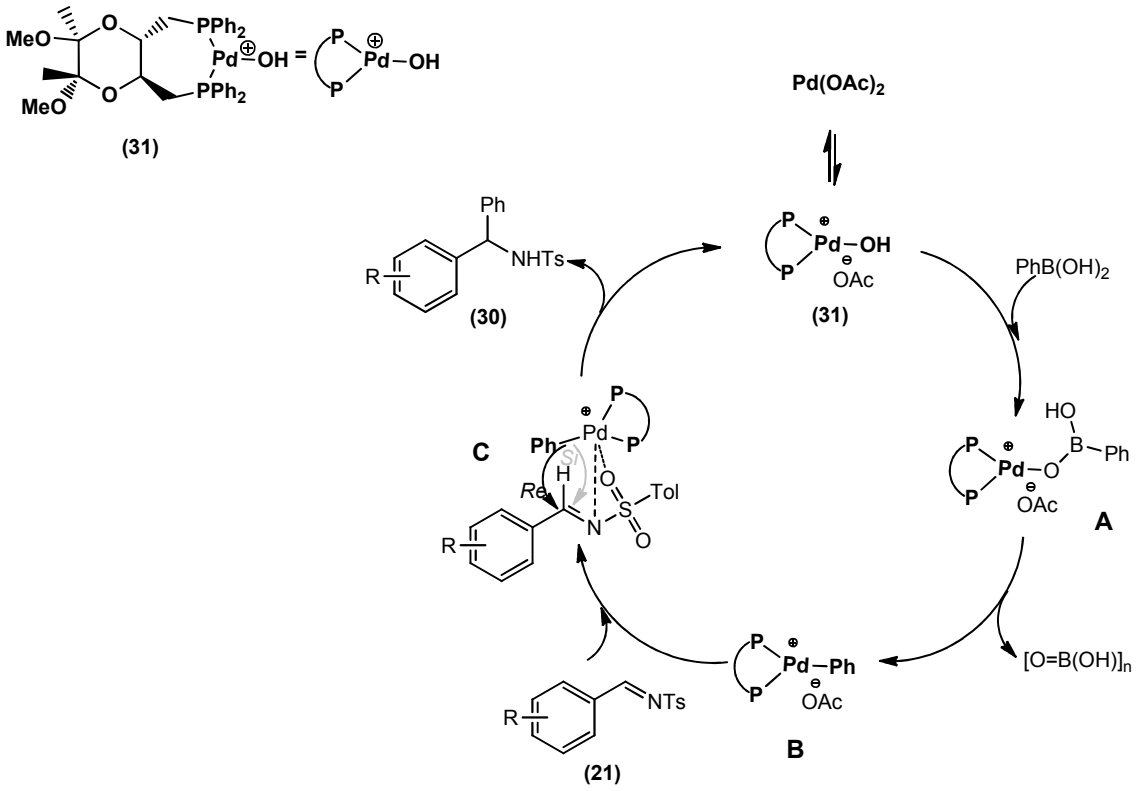
with both aldimine substrates **(21a)** and **(21b)** were quite poor. In fact, this was already confirmed by Dai and by Zhou.[48,36] The best ee values of >99% and 92% were obtained from the desired amine product **(30b)** using (*R*,*R*)-Me-DuPhos **(26)** and (*R*,*R*)-*i*Pr-DuPhos **(25)** (Figure 2.4 and Table 2.2, entries 8 and 6, respectively). The less bulky (*R*,*R*)-Me-DuPhos **(26)** gave a slightly higher ee. Both Trost ligands **(22)** and **(24)** (Figure 2.4) gave very good ees (Table 2.2, entries 1 and 2) on using *ortho*-chloroaldimine **(21b)** and (*R*)-DioxPhos ligand **(28)** (Figure 2.4) providing identical ees for both aldimines tested (Table 2.2, entries 12 and 13).

To try to understand the mechanism of the catalytic cycle of the reaction, we decided to isolate and characterize the complex formed with $Pd(OAc)_2$ and (*R*)-DioxPhos ligand **(28)**. The procedure involved the simple addition of $Pd(OAc)_2$ and (*R*)-DioxPhos ligand **(28)** in equimolar amounts, to phenylboronic acid (2 molar equivalents) in CH_2Cl_2 at room temperature (Scheme 2.23, (a)). The crude product which existed as a bright red solid, was recrystallized, and after NMR and MS analysis, it was concluded to be the ionic complex **(31)** (Scheme 2.23, (a)). The complex **(31)** was tested in the arylation of *N*-*ortho*-chloroaldimine **(21b)** with phenylboronic acid using the same conditions applied before. The corresponding biarylarylmethylamine **(30b)** was obtained with 54% isolated yield and in 40% ee, with (*R*)-**(30b)** being the major product (Scheme 2.23, (b)).



Scheme 2.23. (a) Synthesis of the possible active Pd-complex **(31)**. **(b)** Application of the Pd-complex **(31)** in the arylation of imine **(21b)** with phenylboronic acid.

From previous work by Dai and Lu[67] and Ma and Shi[47], that used a similar Pd complex, that incorporated N,N-ligands and NHCs, we propose the following mechanism for this reaction (Scheme 2.24). Starting from the previously isolated complex **(31)**, (which we thought to be the active species in the *in situ* reactions), transmetalation could occur to form the palladium boronate complex **A**, due to the high oxophilicity of boron. β-aryl elimination is expected to occur to give the palladium-aryl complex **B**. Due to the vacant coordination site on the palladium, both the nitrogen and the oxygen from the aldimine could in principle coordinate quite easily, generating the intermediate **C**. In this step, it is expected that asymmetric induction will occur. Studies presented by Ma and Shi[47] pointed out that if the delivery of the aryl group to the aldimine takes place by *Si*-face attack, it leads to the formation of the (*S*)-amine enantiomer. On the other hand, if the aryl group is delivered *via Re*-face attack, the (*R*)-amine enantiomer is preferred. Hydrolysis is the last step in the cycle, which provides the desired amine product and regenerates the catalytically active specie **(31)** to continue the catalytic cycle.



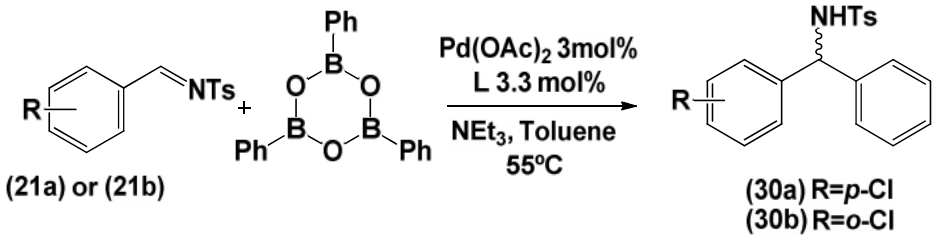
Scheme 2.24. Proposed mechanism for the catalytic asymmetric arylation of *N*-tosylaldimines with Pd catalysts **(31)** and phenylboronic acid.

According to this working model, the catalysts bearing the Trost-naphtyl ligand **(24)**, DuPhos ligands **(25)** and **(26)** and the BINAP ligand **(27)** (Figure 2.4) are expected to deliver the phenyl group to the aldimine **(21)** *via Si*-face attack, providing the corresponding (*S*)-amine product **(30)**. While in the case of the Trost-phenyl ligand **(22)**, DeguPhos ligand **(23)** and DioxPhos ligand **(28)** (Figure 2.4), the phenyl group is expected to be delivered *via Re*-face attack, resulting in preferential formation of the (*R*)-amine product **(30)** (Scheme 2.24, intermediate **C**).

In an attempt to block aldimine hydrolysis which we believe to be the main contributing factor that leads to low yields, phenylboroxine (see scheme in Table 2.3) was investigated as an alternative organoboron reagent. Phenylboroxine $(BOPh)_3$, is a 6-membered, heterocyclic compound composed of alternative

oxygen and boron atoms with the phenyl units attached to the boron. Its synthesis is achieved simply by refluxing phenylboronic acid in benzene, with a Dean-Stark trap. We tested this organoboron reagent using the aldimines **(21a)** and **(21b)** and the ligands *i*-Pr-DuPhos **(25)** and DioxPhos **(28)**. The results can be seen in Table 2.3. DioxPhos **(28)** gave the best result (Table 2.3, entry 5). Compared with phenylboronic acid (Table 2.2, entry 12), this method makes a significant difference, and, the aryl group is expected to be delivered *via Re*-face attack resulting in preferential formation of the (*R*)-amine products **(30a)** and **(30b)**, which is verified (Table 2.3, entries 1, 2, 5 and 6). When *i*-Pr-DuPhos ligand **(25)** was used, the yields improved slightly but the ees remained quite low (Table 2.3, entries 3, 4, 7 and 8). As previously noted (Table 2.2, entry 6) the aryl group is expected to be delivered *via Si*-face-attack resulting in preferential formation of the (*S*)-amine products **(30a)** and **(30b)**.

Table 2.3. Asymmetric arylation of *N*-tosylaldiminies **(21a)** and **(21b)** with phenylboroxine and ligands **(25)** and **(28)**.



(21a) or (21b)

(30a) R=*p*-Cl
(30b) R=*o*-Cl

Entry	Aldimine	L	M.S. 3Å/mg	Time/h	Yield/%[(a)]	ee/%[(b)]
1	**21b**	**28**	-	44	<10	36 (*R*)
2	**21a**	**28**	-	44	27	40 (*R*)
3	**21b**	**25**	-	44	27	38 (*S*)
4	**21a**	**25**	-	44	<10	<5 (*R*)
5	**21b**	**28**	200	64	99	64 (*R*)
6	**21a**	**28**	200	64	64	37 (*R*)
7	**21b**	**25**	200	64	38	<5 (*S*)
8	**21a**	**25**	200	64	29	<10 (*R*)

[(a)]Isolated yields.

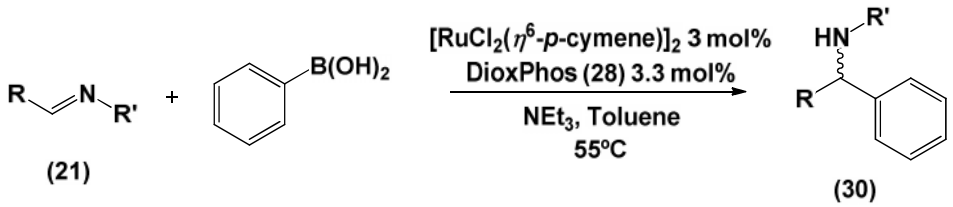
[(b)]Determined by chiral stationary phase HPLC. Absolute configurations determined by comparing the data with those already known in the literature.[47]

2.2.3. Ruthenium chemistry

2.2.3.1. Phosphane ruthenium complexes

Our interest in investigating new ruthenium catalysts for these arylation reactions was based on the fact that ruthenium is cheaper than rhodium and palladium and has an impressive application profile in organometallic chemistry.[50] The possibility of being tested for the first time in this particular transformation was the motivation for performing the following study. Starting with a test reaction, using the commercial half-sandwich ruthenium (II)-η^6-arene $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ as pre-catalyst, along with DioxPhos **(28)** (Figure 2.4), applying the same conditions as were used for the palladium catalysts (see Table 2.1). The desired biarylarylmethylamine product **(30b)** was obtained in 63% yield and 57% ee, in favor of the (*R*) enantiomer. Motivated by this result, we applied this procedure to all the aldimines previously tested (Figure 2.19) to evaluate the scope of these novel Ru catalysts. The results are shown in Table 2.4

Table 2.4. Catalytic enantioselective arylation of *N*-sulphonylaldimines with Ru catalysts and phenylboronic acid.



(21) (30)

Entry[a]	Aldimine			Time/h	Yield/%[b]	ee/%[c]
	R	R'				
1	*p*-ClC_6H_4	Ts	**21a**	48	14	90 (*R*)
2	*o*-ClC_6H_4	Ts	**21b**	72	63	57 (*R*)
3	*p*-$CH_3OC_6H_4$	Ts	**21c**	72	<5	n.d.
4	2-naph	Ts	**21d**	48	12	44 (*R*)
5	*p*-ClC_6H_4	Ns	**21e**	48	<5	n.d.
6	*p*-ClC_6H_4	Ms	**21f**	48	10	75[d]
7	CH_3	Ts	**21h**	48	0	-
8	$CH_3CH_2CH_2$	Ts	**21i**	48	13	<10 (*R*)
9	*o*-$CH_3C_6H_4$	Ts	**21j**	48	<10	14 (*S*)
10	*p*-BrC_6H_4	Ts	**21k**	48	12	69 (*S*)
11	cyclohexyl	Ts	**21l**	48	17	17 (*S*)
12	*p*-$NO_2C_6H_4$	Ts	**21m**	48	<10	<10 (*R*)
13[e]	C_6H_4	Ts	**21g**	48	<5	-
14[f]	C_6H_4	Ts	**21g**	72	0	-

[a]Reagents and conditions: aldimine (0.2 mmol), $PhB(OH)_2$ (0.4 mmol), toluene (2 ml), NEt_3 (0.4 mmol).
[b]Isolated yields after chromatography.
[c]Determined by chiral stationary phase HPLC.
[d]Preferred configuration not determined.
[e]*para*-Chlorophenylboronic acid was used.
[f]*para*-Methoxyphenylboronic acid was used.

From literature precedents,[48] the best yields were expected to be obtained using electron-poor aldimines. In general, the overall yields were poor, the majority were lower than 20% (Table 2.4, entries 1, 3 to 12). The only aldimine that afforded a good yield was the *ortho*-chloro **(21b)**, giving a yield of 63% (Table 2.4, entry 2). Electron-withdrawing substituents in the aldimine substrate gave the better ee values (Table 2.4, see entries 1, 2, 4, 6 and 10), while *N*-sulphonylaldimines with electron-donor groups, gave poor ee values (Table 2.4, entries 7, 8, 9 and 11). These observations lead us to think that steric effects had a specific role in the interaction between the active catalytic species and the substrate. Another interesting observation was that *N*-sulphonylaldimines other

than the tosyl derivatives, like nosyl (Table 2.4, entry 5) and mesyl (Table 2.4, entry 6) were very ineffective. Concerning the ee, a smooth decrease was noted. This might be attributed to the reduced steric hindrance during the aryl addition step.[68] The absolute configuration of the novel amine product **(30f)** obtained from aldimine **(21f)** wasn't determined. In the case of the nosyl substituted aldimine **(21e)**, only vestigial amounts of product were obtained. It was also possible to conduct the reaction with aliphatic aldimine substrates **(21i)** and **(21l)**, despite the poor yields and the moderate enantioselectivities (Table 2.4, entries 8 and 11). The best result was obtained using the aldimine **(21b)**, with an electron-withdrawing group substituted in the phenyl ring. The other aldimine used with an *ortho* substituted group was the aldimine **(21j)**, but, in this case low yields were observed. To try to explain these results, we referred to a study reported by Davies *et al.*[69] that described base-assisted cyclometalation reactions between an imine and a metalacycle in the presence of a stoichiometric amount of base (Figure 2.5). In our reactions, given that NEt_3 is present in the reaction media, it seems that a stable ruthenacycle might be formed (Figure 2.5), when *para*-substituted aldimines are used, blocking the normal sequence which leads to the formation of the amine product. This should not occur with *ortho*-substituted aldimines, since *ortho*-substituted aldimines will block the coordination to the metal center. This hypothesis would support the observation that the arylation of *para*-substituted arylimines occurs with low yields.

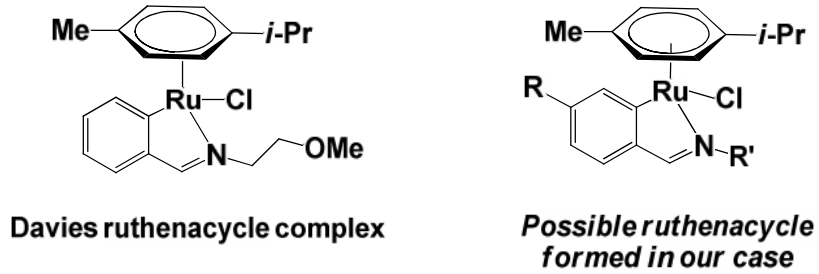
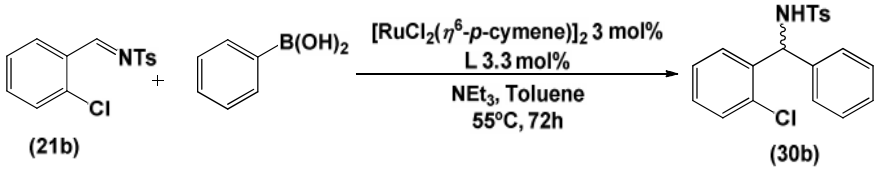


Figure 2.5. Base-assisted formation of ruthenacycle type complexes, based on work described by Davies *et al*.[69]

Interestingly in an attempt to try and gain better insight into the mechanism of the reaction, the substitution patterns of the substrate and the boronic acid compounds were reversed, i.e. we decided to apply the aldimine substrate **(21g)** with the *para*-chloride and *para*-methoxyl substituted phenylboronic acids expecting that the amine products **(30a)** and **(30c)** would be obtained. When this was investigated in fact, the reactivity was extremely poor. In both test reactions, only vestigial quantities of products were obtained. It seems as though the substituted phenylboronic acids suffer some sort of steric hindrance during the course of coordination to the Ru metal catalyst, preventing the formation of the desired amine product (Table 2.4, entries 13 and 14). To conclude this study, we decided to perform a screening of the available phosphane ligands (Figure 2.4), with the best substrate, aldimine **(21b)**. The results are shown in Table 2.5.

Table 2.5. Screening of phosphane ligands in the catalytic asymmetric arylation in *N*-tosylaldimine **(21b)** with phenylboronic acid.



(21b) (30b)

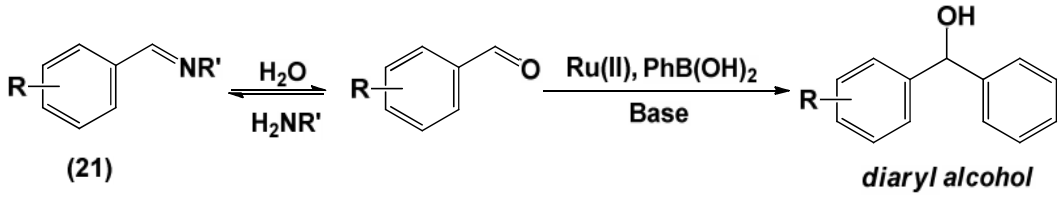
Entry[a]	L	Yield/%[b]	ee/%[c]
1	**23**	16	16 (*R*)
2	**24**	29	90 (*R*)
3	**25**	27	91 (*R*)
4	**26**	38	94 (*R*)
5	**27**	<10	98 (*R*)
6	**29**	<10	12 (*S*)

[a]Reagents and conditions: **(21b)** (0.2 mmol), $PhB(OH)_2$ (0.4 mmol), toluene (2 ml), NEt_3 (0.4 mmol).
[b]Isolated yields after chromatography.
[c]Determined by chiral stationary phase HPLC.

The other phosphane ligands tested, gave lower yields than with DioxPhos ligand **(28)** (Table 2.4, entry 2). The naphtyl Trost ligand **(24)** and the DuPhos derivatives **(25)** and **(26)** gave moderate yields (Table 2.5, entries 2 to 4).

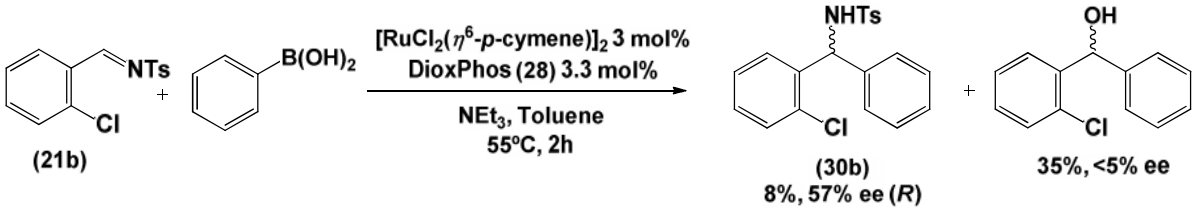
Phosphane ligands with a binaphtyl backbone, like BINAP **(27)** and SegPhos **(28)** proved inadequate for this catalytic reaction, since the yields obtained were below 10%. This was already verified using palladium catalysts (see Table 2.2, entries 10 to 13). Perhaps the bulkiness of this ligand type blocked their interaction with the corresponding aldimine substrate. Despite the moderate yields obtained, the enantioselectivities obtained were excellent (90-94% ee). In all these reactions, the product configuration was (*R*).

During the course of this study, we became aware, through TLC analysis, of a secondary diaryl alcohol side product. Yamamoto *et al.*[70,71] have previously developed an interesting Ru-catalyzed enantioselective arylation of aldehydes and α-ketoesters using arylboronic acids. As has already been discussed, these aldimine substrates **(21)** are very susceptible to hydrolysis, and since commercial arylboronic acids contain a small percentage of water, this unwanted process takes place. In fact, this was confirmed by conducting an experiment with only the aldimine substrate and the phenylboronic acid. Besides the work reported by Yamamoto *et al.*[70,71], there have been more reports of this type of catalytic arylation of aldehydes (see Chapter 3). So, in fact, the formation of the corresponding diaryl alcohol was actually reducing the yield of the desired amine product (see Scheme 2.25). It is also very likely that the alcohol side product was coordinating with the catalyst and deactivating it. Although we did not quantify the amount of secondary alcohol produced in all the reactions performed, as unfortunately this came into our attention after the reactions were carried out and analyzed, the HPLC analysis showed that there were more than vestigial quantities present. These secondary products were always obtained in almost racemic form for all of the reactions using the aldimine **(21b)** (<5% ee). The enantiopurities of all of the other secondary alcohols products were not determined.



Scheme 2.25. Formation of the secondary product in this catalytic arylation reaction.

In fact, an additional experiment was performed using the conditions shown in Tables 2.4 and 2.5. A shorter reaction time was given, using aldimine **(21b)**, giving the desired amine product **(30b)** with an isolated yield of 8% (at 57% ee) along with the corresponding secondary alcohol in a yield of 35% (racemic) (Scheme 2.26). It seems that, at the outset, the formation of the alcohol might be more rapid that of the amine, but perhaps then the alcohol concentration reaches a threshold, and then arylation of the imine proceeds for the remaining reaction time.

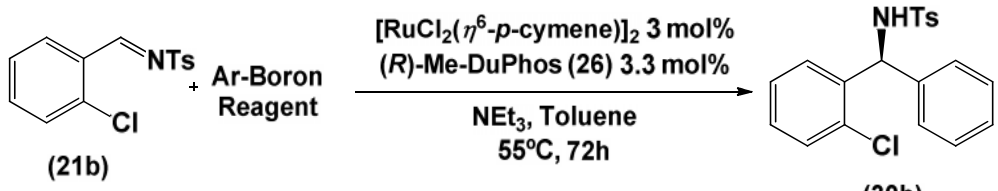


Scheme 2.26. Test study to evaluate the formation of the corresponding secondary alcohol products in the Ru-catalyzed imine arylation.

To avoid this unwanted side reaction, we implemented some countermeasures. One such strategy was to add the aldimine **(21b)** substrate slowly to the reaction mixture containing phenylboronic acid and the corresponding catalyst formed *in situ*, from complexation of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ with Me-DuPhos **(26)**. The addition was carried out over a 7 hours period, and then the reaction was left

stirring for an additional 2 hours. The isolated yield was less than 10% with an enantioselectivity of 78% ee, in favor of the (*R*)-enantiomer. Analysis of the crude product by HPLC showed that there was a vestigial quantity of the secondary alcohol formed (in racemic form) and small quantities of both the aldimine substrate **(21b)** and its aldehyde precursor. The strategy failed to improve the reaction yield. Another approach to resolve this problem was to use more anhydrous arylboron reagents, like sodium tetraphenylborate (Ph_4BNa), potassium trifluoro(phenyl)borate ($PhBF_3K$), 1,3-propanediol boronic ester ($C_9H_{11}BO_2$), Ph_3B[72] and phenylboroxine ($(PhBO)_3$). This strategy worked to some extent, as the quantity of the secondary alcohol decreased, but, unfortunately, the isolated yield of the desired amine product **(30b)** didn't improve. All of the results are show in Table 2.6.

Table 2.6. Catalytic enantioselective arylation of the *N*-tosylaldimine **(21b)** with several organoboron reagents.



Entry[a]	Ar-Boron Reagent	Yield/%[b]	ee/%[c]
1	$(PhBO)_3$	31	74 (*S*)
2	Ph_4BNa	<10	93 (*S*)
3	$PhBF_3K$	<10	68 (*S*)
4	$C_9H_{11}BO_2$	26	56 (*S*)
5[d]	$(PhBO)_3$	<10	78 (*S*)
6[d]	$PhB(OH)_2$	11	68 (*S*)
7	Ph_3B	<5	n.d.

[a]Reagents and conditions: **(21b)** (0.2 mmol), Ar-Boron Reagent (0.4 mmol), toluene (2 ml), NEt_3 (0.4 mmol).
[b]Isolated yields after chromatography.
[c]Determined by chiral stationary phase HPLC.
[d]M.S. (3Å, 200 mg) were added to the reaction vessel.
n.d.: Not determined.

Regarding the enantioselectivity, what was very surprising was the change in the absolute configuration of the amine product **(30b)** from (*R*) to (*S*) under these

conditions, even when phenylboronic acid was used (Table 2.6, entry 6, in the presence of activated molecular sieves (M.S.)). When the amount of water is reduced, there may be a change in the enantiofacial delivery of the phenyl group (see below for further discussion). The best aryl transfer reagents were phenylboroxine and 1,3-propanediol boronic ester (Table 2.6, entries 1 and 4), but nonetheless, phenylboronic acid gave the best overall results, 38% yield and 94% ee (Table 2.5, entry 4). Although, it should be noted that the use of a boronic acid ester derivative (Table 2.6, entry 4) was applied by the first time in this catalytic transformation. The only phenylboronic acid derivative that could compete successfully with phenylboronic acid in terms of enantioselectivity was Ph_4BNa, which gave an ee of 93% (compare Table 2.5, entry 4 with Table 2.6, entry 2). It is important to underline that water must play an important role in the overall mechanism, due to the difference in the results obtained when water sequestering molecular sieves were used (Table 2.6, entries 5 and 6), which led to significant decreases in the yields and enantioselectivities.

In an analogous fashion to the palladium catalysts in the previous study (see above), we tried to get a handle on the type of active catalyst involved as well as understanding the mechanism. Likewise, an attempt to isolate and characterize the complex formed *in situ* was executed. Using the enantiopode ligand (*S*)-**(28)** (due to the unavailability of the (*R*)-enantiomer at that time) attempts were made at isolating the initial catalyst by coordinating it with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ in CH_2Cl_2 at room temperature. Two complexes were isolated, existing as orange solids (Figure 2.6). These were the monomer **(32)** (10% yield) and the dimer **(33)** (82% yield).

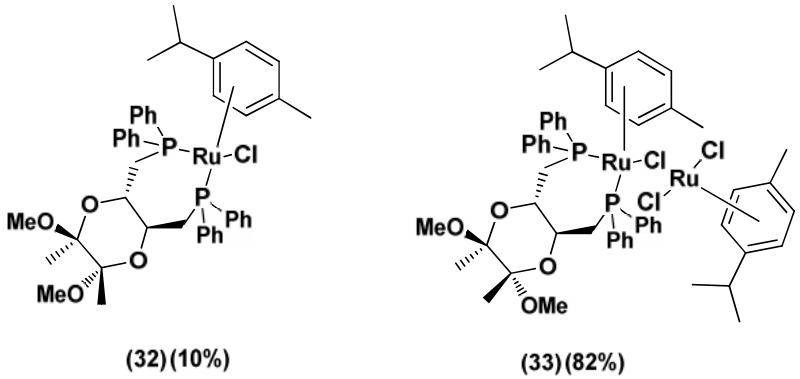
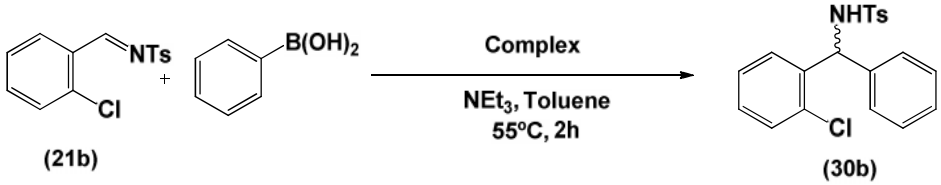


Figure 2.6. The monomeric **(32)** and dimeric **(33)** ruthenium complexes exhibiting catalytic activity.

These isolated complexes were then screened, singly, in an arylation reaction, using the aldimine **(21b)**, phenylboronic acid and the conditions shown in Table 2.5, at a loading of 5 mol% of the monomer **(32)** and 20 mol% of the dimer **(33)** (Table 2.7). Vestigial quantities of both the alcohol (in racemic form) and the aldehyde were observed.

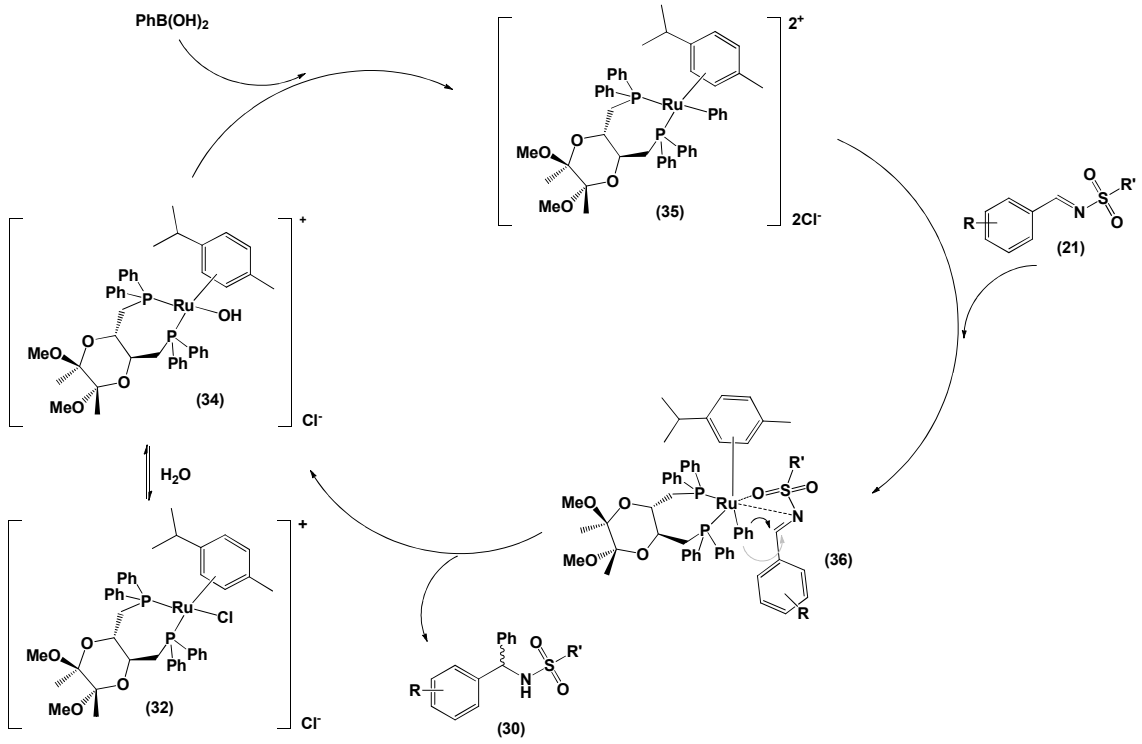
Table 2.7. Catalytic arylation of *N*-tosylaldimine **(21b)** with phenylboronic acid, with complexes **(32)** and **(33)** (Figure 2.7).



Complex	Yield/%	ee/%
(32)	41	34 (*R*)
(33)	27	54 (*R*)

These intriguing results lead us to make some crucial hypotheses on the mechanism of this particular reaction. When the absolute configuration of the ligand (used in the formation of the isolated complexes was changed to (*S*)-DioxPhos **(28)** the same major-amine enantiomer was obtained as that obtained

using the (*R*)-DioxPhos **(28)** *in situ* (Table 2.4, entry 2)). Another important observation was the fact that on reducing the amount of water in the reaction, there was a switch in its absolute configuration of the desired amine **(30b)** (see Table 2.6 and Table 2.5, entry 4 and 6, respectively). Both observations seem to imply that water could have a role in the putative catalytic mechanism, perhaps coordinating to the Ru metal center, substituting the chloride ions.



Scheme 2.27. Proposed mechanism for the catalytic arylation of aldimines with Ru catalysts.

We propose a hypothetic mechanism to explain this reaction (Scheme 2.27). We think that equilibrium is maintained between the isolated monomer specie **(32)** and the hydroxyl coordinated complex **(34)**, due to the water present[73] and the latter generated by the substitution of one of the chloride co-ligands.[74,75] the transmetalation step occurs with phenylboronic acid affording the anionic Ru(II) species **(35)** with 18 electrons. The next step is somewhat more complex in that

given that intermediate **(35)** has 18 electrons, to maintain stability during the coordination of the aldimine substrate **(21)**, there might be a change in the hapticity of the cymene unit (from η^6 to η^4 or η^6 to η^2) or and/or decoordination of one of the PPh_2 units.[76,77,78] In the case of the formation of the intermediate **(36)**, the aryl group is delivered *via Si* or *Re*-face attack, to afford the desired (*R*) or (*S*)-amine product **(30)**. Coordination of a chloride ion (from the reaction solution), affords the initial species **(32)** again, completing the cycle. This hypothesis, though very speculative, can explain some of our experimental observations. From the literature[74] it is known that bulky phosphanes favor the decoordination of the first and second chloride ions and change the *p*-cymene hapticity, whereas basic electron-rich phosphanes would stabilize the cationic complexes better. This might explain why the reactions with ligands **(23)** and **(25)** bearing electron-rich phosphanes were rather sluggish in this particular transformation, due to the generation of more stable 18-electron complexes. In the case of the reactions with the bulky ligands **(27)** and **(29)**, perhaps either coordination of the phenyl unit from the boronic acid, or the coordination of the imine substrate **(21)**, became severely limiting.[79,80]

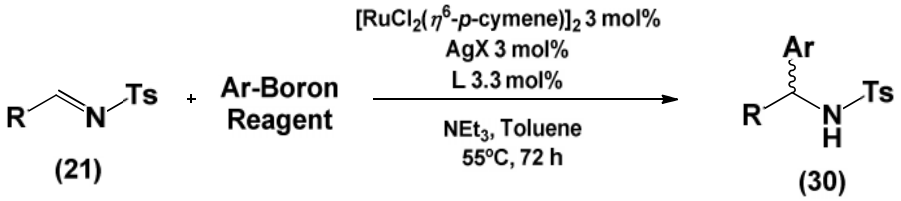
2.2.3.2. NHC-ruthenium complexes

It was conceived that perhaps NHCs, with their strong σ-electron-donating properties[81-83] and strong metal bonding[84] could be useful catalysts to test in these catalytic enantioselective reactions. We decided to investigate the NHCs synthesized in Chapter 1 in this particular reaction. To use the 1,3-diazepinium salts **(3)** and dihydroimidazolium salts **(10)** (Chapter 1) as chiral NHC ligands, *in situ*, deprotonation of the corresponding halides was required. As already discussed in Chapter 1, silver salts are often employed for the *in situ* generation of cationic transition-metal catalysts,[85-87] due to their behavior as halide scavenger agents, forming a weak Ag-NHC bond, that easily undergoes transmetalation with the metal atom.[46,88,89] We decided to perform a study with our NHC ligands and

silver salts, along with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ as pre-catalyst. The methodology used was similar to the one used so far. Starting with $AgBF_4$ as halide scavenger and using the aldimine **(21c)**, along with phenylboroxine as organoboron reagent we screened all the 1,3-diazepinium salts **(3a-c)** and **(10a)** (Table 2.8, entries 3 to 6). Disappointed by the results obtained, since none of the reactions worked, we change the silver salt to AgOTf and Ag_2O, using other aldimine substrate **(21b)** and $PhB(OH)_2$. With other reagent conditions some interesting results were obtained (Table 2.8, entries 8 to 18). It is known from the literature[90,91] that NHC-Ag(I) complexes can be used in catalysis. To determine if the silver complex was, in fact, active in this particular reaction, an experiment was performed in the absence of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (Table 2.8, entry 2), gratifyingly only substrate and phenylboronic acid were recovered, showing that the silver NHC complex derived from **(3a)** was inactive in this reaction. Just to assure us that the use of an organometallic catalyst was crucial, a test reaction was performed without pre-catalyst, chiral ligand and silver salt (Table 2.8, entry 1), and, again there was no reactivity. Returning to the study of the NHC-Ru complexes, we screened three aldimines with phenylboronic acid, using AgOTf and even though aldimine **(21b)** gave only vestigial amounts of the amine product **(30b)** (Table 2.8, entry 7), when the aldimines **(21d)** and **(21c)** were used the yields were better (15 and 27%) and accompanied by high enantioselectivities (89 and 71% ee, respectively) (Table 2.8, entries 8 and 9, respectively). The low yields obtained were probably due to the hydrolysis of the aldimines substrates, since 2-naphtaldehyde and *p*-anisaldehyde were detected in the HPLC chromatogram. Consequently, we decided to use phenylboroxine as the phenyl transfer agent,[88] maintaining AgOTf as the silver salt and the NHC precursor **(3a)**. Four aldimines **(21a-d)** were tested (Table 2.8, entries 10 to 16). In some cases, small quantities of molecular sieves (3Å, Table 2.8, entries 14 to 16) were added to determine the influence of water on the reaction yield and enantioselectivity. The yield increase significantly (Table 2.8, compare entries 12 and 16), only in case of aldimine **(21d)**. With aldimines **(21b)** and **(21a)** no significant changes in the yield were noted (Table 2.8, compare entries 10 with 14, and 11 with 15). Concerning the enantioselectivities, when molecular sieves were used, they generally dropped significantly (Table 2.8, compare for instance, entry 12 with 16). It seems that these results support the

theoretical hypothesis that water may play a significant role in the mechanism of the reaction, coordinating to the metal (see Scheme 2.27), making the catalyst more bulky and leading to greater enantiofacial discrimination at the aldimine reaction site.

Table 2.8. Catalytic enantioselective arylation of *N*-tosylaldimines with organoboron reagents and NHC precursors.

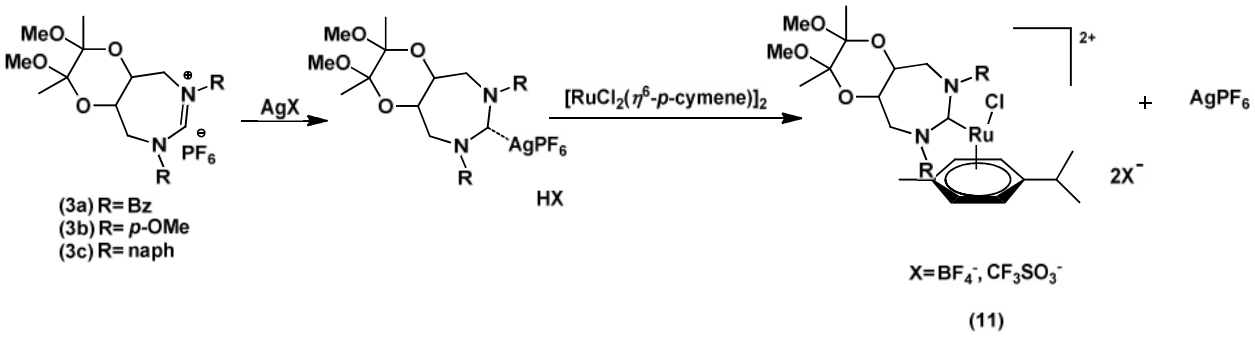


Entry[a]	R	Ar-Boron Reagent	AgX	L	Yield/%[b]	ee/%[c]
1	*o*-ClC_6H_4 **(21b)**	$PhB(OH)_2$	-	-	0	-
2[e]	*o*-ClC_6H_4 **(21b)**	$PhB(OH)_2$	AgOTf	**(3a)**	0	-
3	*p*-$CH_3OC_6H_4$ **(21c)**	$(PhBO)_3$	$AgBF_4$	**(3a)**	<10	n.d.
4	*p*-$CH_3OC_6H_4$ **(21c)**	$(PhBO)_3$	$AgBF_4$	**(3b)**	<10	n.d.
5	*p*-$CH_3OC_6H_4$ **(21c)**	$(PhBO)_3$	$AgBF_4$	**(3c)**	<10	n.d.
6	*p*-$CH_3OC_6H_4$ **(21c)**	$(PhBO)_3$	$AgBF_4$	**(10a)**	0	-
7	*o*-ClC_6H_4 **(21b)**	$PhB(OH)_2$	AgOTf	**(3a)**	<5	n.d.
8	2-naphtyl **(21d)**	$PhB(OH)_2$	AgOTf	**(3a)**	15	89 (*S*)
9	*p*-$CH_3OC_6H_4$ **(21c)**	$PhB(OH)_2$	AgOTf	**(3a)**	27	71 (*S*)
10	*o*-ClC_6H_4 **(21b)**	$(PhBO)_3$	AgOTf	**(3a)**	29	20 (*S*)
11	*p*-ClC_6H_4 **(21a)**	$(PhBO)_3$	AgOTf	**(3a)**	32	31 (*R*)
12	2-naphtyl **(21d)**	$(PhBO)_3$	AgOTf	**(3a)**	22	72 (*R*)
13	*p*-$CH_3OC_6H_4$ **(21c)**	$(PhBO)_3$	AgOTf	**(3a)**	53	80 (*S*)
14[d]	*o*-ClC_6H_4 **(21b)**	$(PhBO)_3$	AgOTf	**(3a)**	27	*rac*
15[d]	*p*-ClC_6H_4 **(21a)**	$(PhBO)_3$	AgOTf	**(3a)**	19	23 (*S*)
16[d]	2-naphtyl **(21d)**	$(PhBO)_3$	AgOTf	**(3a)**	77	<10 (*S*)
17[d]	2-naphtyl **(21d)**	$(PhBO)_3$	Ag_2O	**(3a)**	29	93 (*S*)
18	*p*-$CH_3OC_6H_4$ **(21c)**	$(PhBO)_3$	Ag_2O	**(3a)**	18	*rac*

[a]Reagents and conditions: aldimine **(21)** (0.2 mmol), Ar-Boron Reagent (0.4 mmol), toluene (2 ml), NEt_3 (0.4 mmol).
[b]Isolated yields after chromatography.
[c]Determined by chiral stationary phase HLPC.
[d]M.S. (3Å, 200 mg) were added to the reaction vessel.
[e]Reaction made without $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$.
rac: racemic.
n.d.: not determined.

As noted before, the absolute configuration of the amine product changes when water was present in the reaction vessel. This tendency is repeated here (Table 2.8, compare entries 11 with 15, and 12 with 16), supporting the conclusions made

above. The best results for the yield and enantioselectivity were obtained using the aldimine **(21c)**, providing the desired amine **(30c)** in 53% yield and 80% ee, favoring the (*S*) enantiomer (Table 2.8, entry 13). Silver (I) oxide (Ag_2O) was another alternative silver salt applied in this reaction. No improvements were noted with aldimine **(21c)**, since the yield decreased significantly and a racemic amine product was obtained (Table 2.8, entry 18). With aldimine **(21d)**, a switch in the absolute configuration of the desired amine product (*S*)-**(30d)** was achieved (Table 2.8, entry 17), initiated by the addition of molecular sieves to the reaction vessel.



Scheme 2.28. Proposed mechanism for using silver salts as halide scavengers to form the active specie of Ru-NHC.

From both literature precedent[92] and our previous synthesis of Ru-NHC complexes (Chapter 1), we established that weak Ag-NHC bonding had occured, and easily undergoes transmetalation with the Ru precursor to afford the complex **(11)** (Scheme 2.28). We assumed that this active complex, already isolated and characterized before, was formed as well *in situ* (Table 2.8). From the results obtained, it seems that the reaction runs well with triflate silver salts and silver oxide, while whith the tetrafluoroborate silver salt, there is no reaction. Tetrafluoroborate ions have a slight tendency to suffer hydrolysis and form $[BF_3OH]^-$.[93] It is believed that both $[BF_3OH]^-$ and HF are unable to act as counter ions in the final complex formation, blocking the arylation. For a successful reaction, it seems that there is certain dependence for the presence of electron-

deficient oxygen in the counter-anion, thus explaining the successful results with the bulky and extremely stable triflate ion (Scheme 2.28), with consequent precipitation of silver hexafluorophosphate ($AgPF_6$). We believe that the mechanism of the catalytic arylation takes place in a similar manner to that of the corresponding Ru-DioxPhos complex (see Scheme 2.27), since an analogous anionic active complex was formed.

The isolated complex **(11)** (5 mol %) (Scheme 2.28) was applied in a reaction test, using the aldimine **(21b)**, phenylboronic acid and the same methodology applied so far (toluene and NEt_3, 55ºC, 72 h). Curiously, the reaction doesn't occur, as only aldimine substrate **(21b)** and phenylboronic acid were recovered after the work-up. Two possibilities seem consistent with this result at this point: (i) the active complex isolated becomes unstable and decomposes upon handling, and/or (ii) the hexafluorophosphate ion (PF_6) could have an important role on the mechanism of the catalytic arylation, stabilizing the Ru-NHC species, acting as counter ion, instead of triflate ions. In our opinion, the first proposal seems to make more sense, due to the stability and bulkiness of the triflate ion (see above). It is important to point out that a test reaction was made as well with the other isolated Ru-NHC complex **(12)** (Chapter 1) coordinated with CH_3CN co-ligands, using the same methodology. Like the cationic Ru-NHC complex no reaction occurred, proving the instability of the synthesized complex.

2.3. Conclusions

Since the initial breakthrough in the field of Rh-catalyzed asymmetric arylation in 1998, distinct families of chiral ligands and several highly efficient asymmetric catalytic systems have been developed for different reaction substrates. The use of easily prepared imine substrates and commercially available, diverse arylboronic acid reagents can be applied to transform suitably activated imines to chiral primary amine products in high yields and in enantiomeric pure forms. In this Chapter we have reported the first successful application of a range of commercial chiral diphosphane ligands in the Pd-catalyzed arylation of electron-deficient *N*-tosylaldimines using phenylboronic acid and phenylboroxine.

With a large number of chiral ligands and optimized conditions available in achieving high stereoselectivity in the Rh-catalyzed asymmetric arylation, the need to exploit new possible transition metal catalysts was a goal. We have reported the first application of Ru based catalysts in the arylation of both electron-rich and electron deficient *N*-protected aldimine substrates, using boronic acids and its derivatives as the aryl transfer reagents. Commercial diphosphane ligands and our new NHC-type chiral ligands (synthesized in Chapter 1) were used for the first time in this catalytic transformation. Some very good enantioselectivities were obtained.

2.4. References

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3. Catalytic Arylation of Activated C=O bonds: Synthesis of α-hydroxyesters

"If I find 10,000 ways something won't work, I haven't failed. I am not discouraged, because every wrong attempt discarded is another step forward."
Thomas A. Edison

3.1. Introduction

The α-hydroxy ester structural function is widespread in natural products and is a convenient building block in organic synthesis.[1,2,3] For example, a group of glycosphingolipids, known as *cerebrosides* found in animal muscle and nervecell membranes, contain in their backbone an α-hydroxyester unit (Figure 3.1). Others include, Peloruside A, a secondary metabolite isolated from a marine sponge with strong cytotoxic activity at nanomolar concentrations, and (+)-wikstromol, an antitumor compound found in plants, also contain this unit (Figure 3.1).

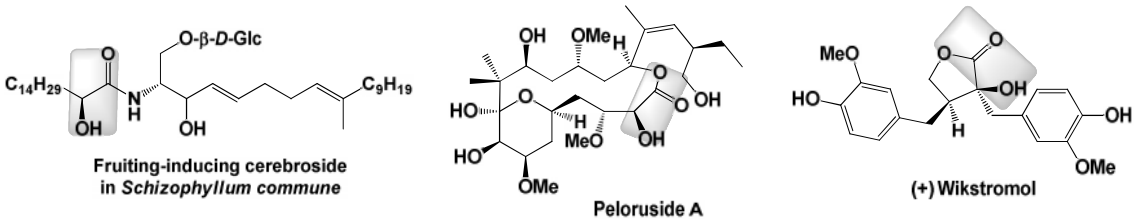
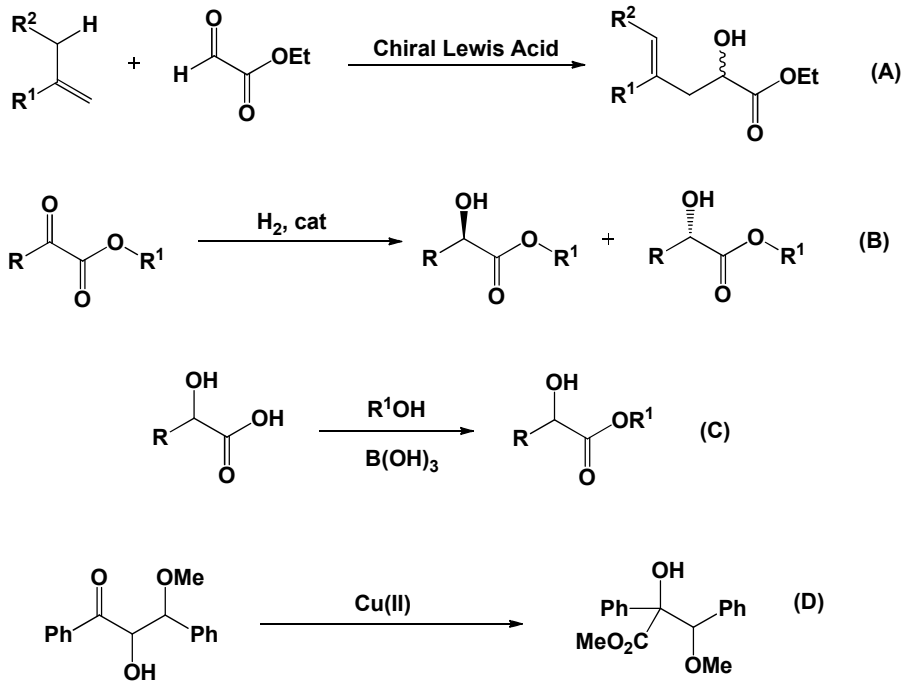


Figure 3.1. A selection of biologically active molecules containing an α-hydroxyester unit in their skeleton.

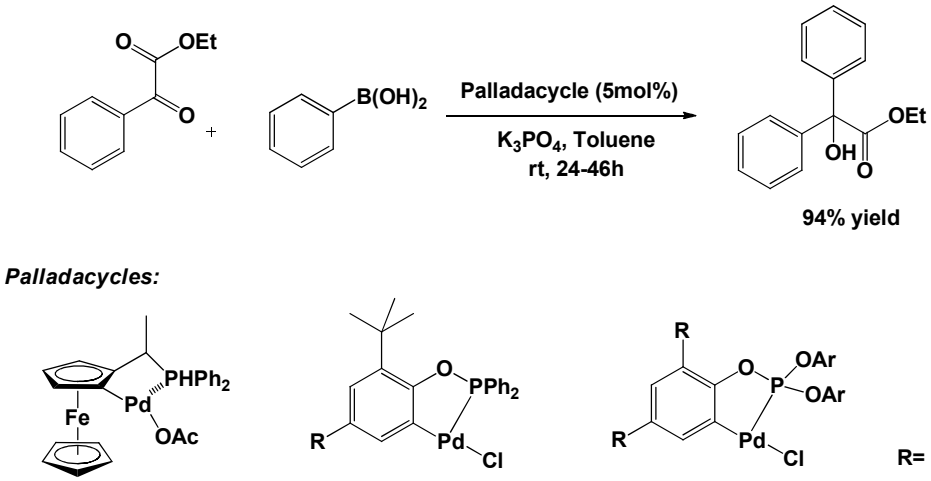
Therefore, the availability of efficient methods for accessing enantiopure α-hydroxy carbonyl compounds [RR'C(OH)C(O)Z] is of considerable current interest.[4] A number of synthetic methods exist in the literature, these include the glyoxylate-ene reaction[5-8] (A, Scheme 3.1), catalytic reduction of α-ketoesters[9-13] (B, Scheme 3.1), esterification of α-hydroxy acids[14,15] (C, Scheme 3.1) and the benzylic ester rearrangement (BER)[16,17] (D, Scheme 3.1). Due to its atom economy, the glyoxylate-ene reaction was the most widely explored. Several Lewis acids such as stannic chloride, titanium tetrachloride and ytterbium triflate have been used as the catalyst in this reaction, however, the yields of the α-hydroxyesters have not always been satisfactory.[18] In this field, the group of Mikami have made remarkable studies on mono[5] and di-substituted[8,19] olefins,

applying Pd and Ti catalysts, along with binaphthyl type ligands. Another convenient and well documented procedure is the asymmetric reduction of α-ketoesters with chiral reducing agents (B, Scheme 3.1). For example, Ghosh and Chen[20] applied indole type molecules to promote the highly stereoselective reduction of α-ketoesters with promising results, while Brown and Ramachandran[21] got full enantioselectivity (100% ee) applying a potassium organoboron reagent as the chiral auxiliary. Well known Cinchona alkaloids, are useful chiral auxiliaries for this type of reaction, as has been demonstrated by Blaser and Mtiller.[9] Recently, Mondelli and co-workers[22] published an interesting report on the application of fluorinated cinchona alkaloids. Burke and co-workers[16,23,24] have used a one pot Cu (II) oxidation/BER, with $Cu(OAc)_2$ as the copper source, to synthesize α-hydroxyesters from α-hydroxyketones, in a stereoselective manner. The main advantages of this procedure rely on the fact that it is one-pot and catalytic amounts of Cu (II) were needed (D, Scheme 3.1).



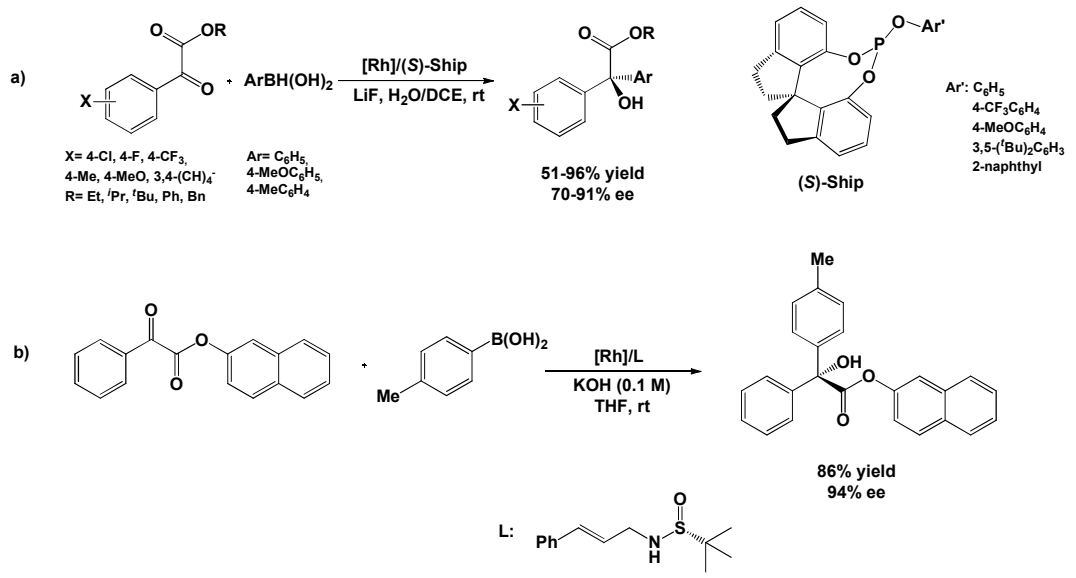
Scheme 3.1. Strategies for the preparation of α-hydroxyesters.

As an extension of our work on the development of useful methodologies to promote the catalytic asymmetric arylation in activated double bond substrates using organoboron reagents, we decided to investigate its scope, for glyoxylate esters to afford α-hydroxy esters. Some reports exist in the literature, on the use of α-ketoesters as substrates. He and co-workers[25,26] exploited the non-asymmetric version of this reaction type with phosphane, phosphinite and phosphite based palladacycles (5 mol% loading) (Scheme 3.2) to conduct the catalytic arylation of α-ketoesters, aldehydes and α,β-unsaturated compounds with phenylboronic acid derivatives. Maximum yields of 94% were achieved under mild conditions (see Scheme 3.2).



Scheme 3.2. Palladacycle Catalyzed Addition Reactions of Arylboronic Acids with α-Ketoesters.[25,26]

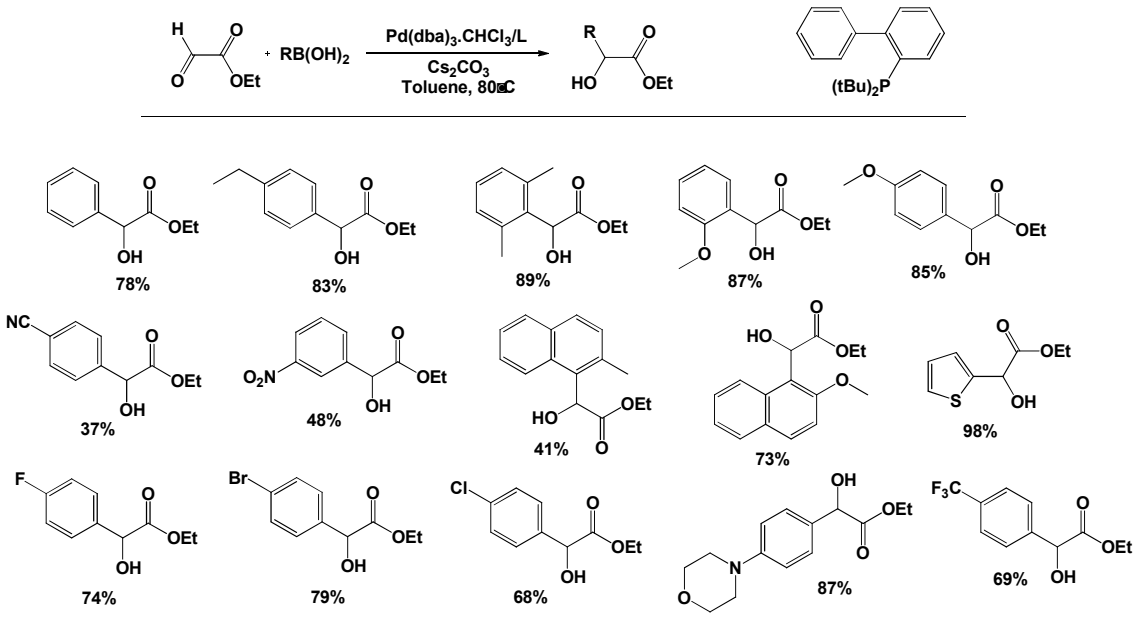
Later on, an asymmetric version of this reaction type was carried out by Duan *et al.*[27] and Zhu *et al.*[28], both applied Rh catalysts, under mild conditions, with ShiP[27] (a well-known phosphane ligand) ((a), Scheme 3.3) and a new sulfinamide/sulfoxide-based olefin ligand[28] ((b), Scheme 3.3). Good yields and enantioselectivities were achieved with both methods for a range of α-ketoester derivatives.



Scheme 3.3. Rhodium-catalyzed addition of arylboronic acids to α-ketoesters reported by **(a)** Duan[27] and **(b)** Zhu.[28]

Yamamoto and co-workers[29] showed that Ru could catalyze this reaction type, along with phosphoramidite BIPAM type ligands, under smooth reaction conditions, with a variety of electron-withdrawing and electron-donor substituents in the arylboronic acids. Good yields (41-95%) and promising enantioselectivities (86-95% ee) were achieved for the aliphatic α-ketoesters.

With regard to the arylation of glyoxylate type aldehydes, the first and only report in the literature was that from the group of Colobert[30] that employed a Suzuki-Miyaura coupling system with Pd and phosphine ligands. Thus a new catalytic system for the Pd-catalyzed coupling reaction of arylboronic acids and ethyl glyoxalate was developed. An achiral mono-phosphane ligand was used to afford a range of mandelate derivatives (Scheme 3.4). An interesting study made by these authors concerned the influence of the arylboronic acid substituents on the reaction out-come. It was observed that electron-donor substituents in the *para* and *meta* positions provided high yields but electron-donor substituents in the *ortho* position had no influence on the yield, indicating that the reaction doesn't seem to suffer from steric hindrance around the reaction center. We decided to evaluate this reaction, with our NHC type ligands (see Chapter 1).

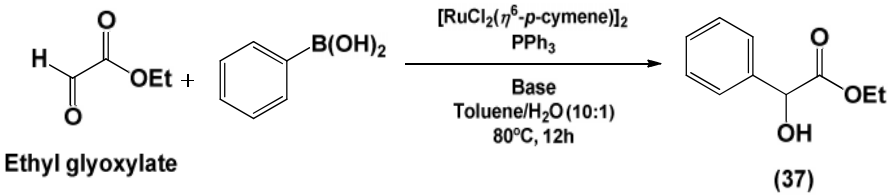


Scheme 3.4. Palladium-catalyzed addition of arylboronic acids to ethyl glyoxylate.[30]

3.2. Results and Discussion

Inspired by the work developed by Yamamoto *et al.*[29] we decided to apply a similar methodology to test the reaction scope. To evaluate the effectiveness of this metal catalyst for the phenylboronic acid arylation of ethyl glyoxylate to the α-hydroxyester **(37)** (Table 3.1), a screening study of a variety of bases was made, using $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and PPh_3 to form the catalyst *in situ*. The results can be seen in Table 3.1. In general, no significant differences were noted between the different inorganic bases. The best result, although poor, obtained for **(37)** (22% yield), was achieved with KF (Table 3.1, entries 3 and 6).

Table 3.1. Catalytic Arylation of ethyl glyoxalate with a Ru/PPh_3 based catalyst and phenylboronic acid.



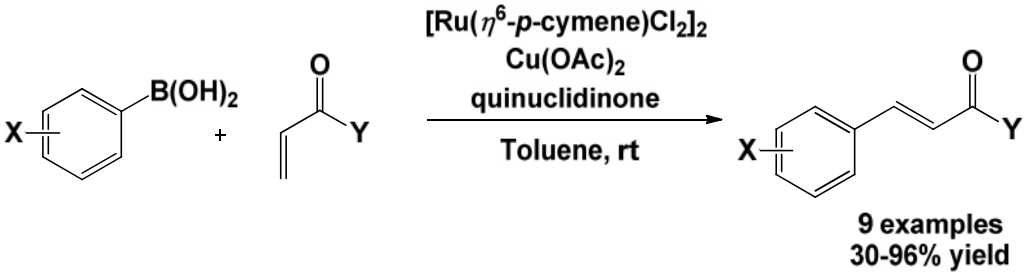
Ethyl glyoxylate

(37)

Entry[(a)]	Base	Yield/%[(b)]
1	K_2CO_3	10
2	K_3PO_4	<5
3	KF	22
4	KHF_2	7
5[(c)]	-	<5
6[(c)]	KF	22

[(a)]Reagents and conditions: Ethyl glyoxalate, 50% sol. in toluene (100 µl, 0.5 mmol), $PhB(OH)_2$ (119.2 mg, 1.0 mmol), $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (4.5 mg, 1.5 mol%), PPh_3 (3.8 mg, 3 mol%), Toluene/H_2O (10:1) (3.3 ml).
[(b)]Isolated yields after chromatography.
[(c)]Reaction without PPh_3.

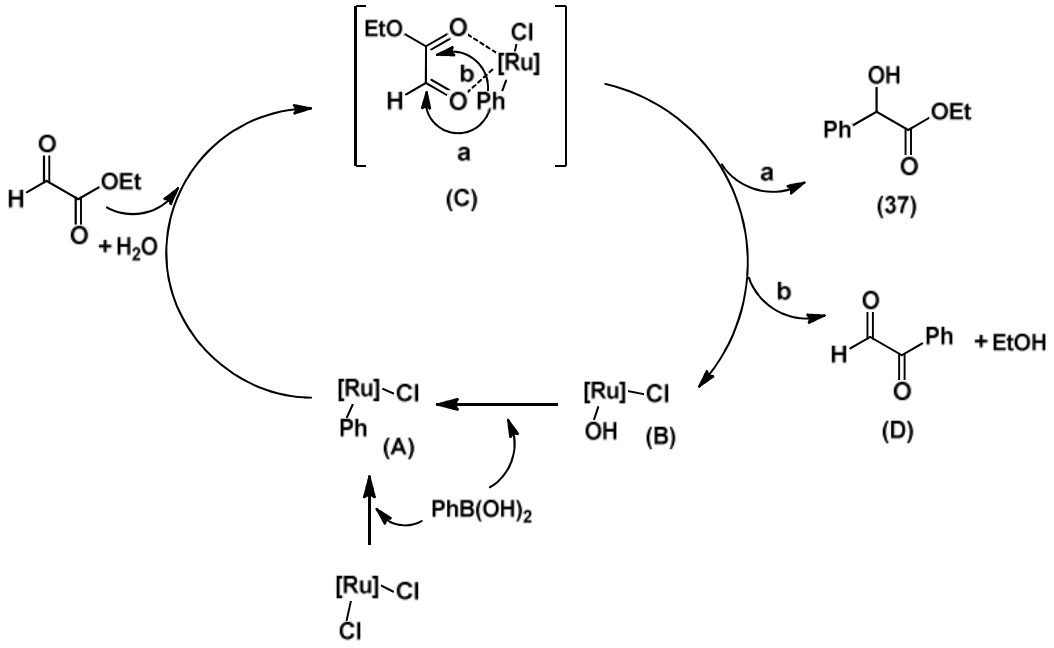
In 2005, Brown and co-workers[31] published an interesting report concerning the Heck-Mizoroki reaction of arylboronic acids with *t*-butyl acrylate catalyzed by ruthenium complexes. The use of the $RuCl_2(PPh_3)(p\text{-cymene})$ complex generated *in situ* from the commercial dimer $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ gave the desired *t*-butyl cinnamate adduct in low yield in preliminary studies. They found that the presence of a re-oxidant, such as Cu (II), was the key to catalysis (Scheme 3.5).



Scheme 3.5. Ruthenium-catalyzed Heck-Mizoroki reactions of arylboronic acids reported by Brown and co-workers.[31]

A reaction mechanism was proposed (Scheme 3.6), taking into account the studies made by Yamamoto and co-workers.[29,32] The reaction should start by transmetalation between the $RuCl_2(PPh_3)$(*p*-cymene) monomer and $PhB(OH)_2$ to yield the phenylruthenium (III) intermediate **(A)**. The two carbonyl double bonds of the substrate should coordinate with the [Ru] complex **(A)**, affording the intermediate **(C)**. Due to the existence of two C=O bonds in the substrate, we believe that the phenyl transfer could occur in both. If the phenyl transfer proceeds to the less reactive C=O bond (*via* b), in intermediate **(C)**, it will give the 2-oxo-2-phenyl acetaldehyde **(D)**. On the other hand, if migration taken place on the more active carbonyl, the desired product **(37)** will be obtained.

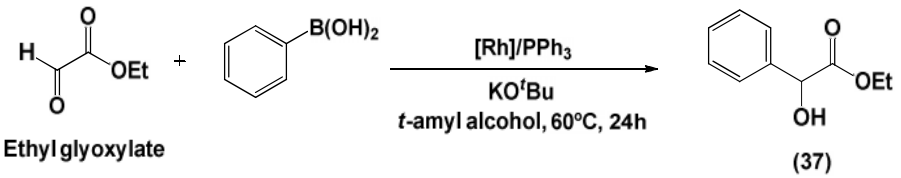
The ruthenium complex **(B)** that was formed was arylated with $PhB(OH)_2$ to regenerate the intermediate **(A)** (see Chapter 2, Scheme 2.26), restarting the cycle. In all the reactions screened (Table 3.1) the ethyl glyoxylate substrate was entirely consumed, however, other secondary products (not identified) were identified by TLC analysis. Perhaps the low yields observed (Table 3.1) could be attributed to the formation of the secondary product **(D)** (Scheme 3.6), although it was not isolated and characterized. This product itself could undergo arylation reactions.



Scheme 3.6. Proposed reaction mechanism for the Ru-catalyzed arylation of ethyl glyoxylate with phenylboronic acid.

Influenced by the work of Góis and co-workers[33-35] which concerned the arylation of aldehydes with Rh(II)-NHC complexes and phenylboronic acids, we decided to use Rh(I) metal catalysts and a number of chiral phosphanes and our NHC type ligands (Chapter 1) for the synthesis of α-hydroxyesters. The results can be seen in Table 3.2. Four different pre-Rh catalysts were tested using PPh_3 as the ligand.

Table 3.2. Screening of [Rh] catalysts for the arylation of ethyl glyoxylate with phenylboronic acid.



Ethyl glyoxylate (37)

Entry[(a)]	[Rh]	Yield/%[(b)]
1	$[Rh(COD)Cl]_2$	65
2	$[Rh(COD)OH]_2$	58
3	$Rh(acac)(C_2H_4)_2$	90
4	$Rh(COD)_2BF_4$	45

[(a)]Reagents and conditions: ethyl glyoxylate, 50% sol. in toluene (100 µl, 0.5 mmol), $PhB(OH)_2$ (119.2 mg, 1.0 mmol), KO^tBu (54.2 mg, 0.5 mmol), [Rh] (1.5 mol%), PPh_3 (3 mol%) and *t*-amyl alcohol (1 ml).[36]
[(b)]Isolated yield by silica gel chromatography.

The best result was obtained with $Rh(acac)(C_2H_4)_2$ (Table 3.2, entry 3). This less bulky catalyst, along with PPh_3 gave almost full conversion of the ethyl glyoxylate substrate to the desired ethyl mandelate product **(37)** (90% isolated yield), in racemic form. Similar moderate yields were achieved with $[Rh(COD)Cl]_2$ (Table 3.2, entry 1) and $[Rh(COD)OH)]_2$ (Table 3.2, entry 2). $Rh(COD)_2BF_4$ gave the poorest yield (Table 3.2, entry 4), probably due to the difficulty in substituting cyclooctadiene (COD) under these conditions, in order to form the active catalytic species.

In fact, $Rh(acac)(C_2H_4)_2$ has already proved its worth in enantioselective conjugate addition of arylboronic acids to enones, with monodentate phosphoramidite chiral ligands.[37] Motivated by the results obtained with rhodium metal catalysts (Table 3.2), we decided to extend this methodology to the synthesis of α-hydroxyesters with Rh(I) metal catalysts and our NHC type ligands (Chapter 1, and see Figure 3.2).

Our study commenced by screening the NHC type ligand **(3a)** (Figure 3.2) with the rhodium pre-catalysts used in Table 3.2, under the same reaction conditions. The results can be seen in Table 3.3. Comparatively to the reactions without chiral ligand (Table 3.2), the ligand effect was very significant for almost all the rhodium pre-catalysts used, with the exception of $[Rh(COD)Cl]_2$, in which the yield remained the same (compare entries 1 from Table 3.2 and 3.3). Contrary to the

racemic reactions, $[Rh(COD)OH]_2$ and $Rh(COD)_2BF_4$ provided the best yields when coordinated to the NHC type ligand **(3a)**. We assumed that NHC type ligands, with negligible π back-bonding and significant steric bulk, make them excellent ligands to apply in this catalytic reaction.[38,39] Thus, the NHC type ligands already seen in Chapter 1 and 2 were used in conjunction with $[Rh(COD)OH]_2$ and $Rh(COD)_2BF_4$. For comparative purposes, two commercial achiral NHC salts **(38)** and **(39)** (Figure 3.2) were tested as well, to evaluate the potential of this reaction. In general, the results with $Rh(COD)_2BF_4$ were quite impressive (Table 3.3, entries 10 to 14) with excellent yields obtained under very mild conditions with all the NHC type ligands tested (up to 95% yield). In the case of the use of $[Rh(COD)OH)]_2$, it seems that the bulkiness of the ligands has a detrimental effect on the reaction yield (Table 3.3, entries 5 and 6). This observation could be accounted by the fact that COD is a bulky co-ligand that can retard the reaction rate.

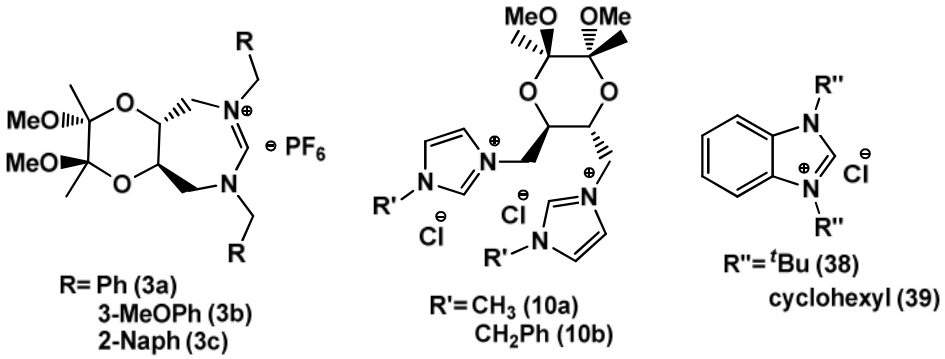
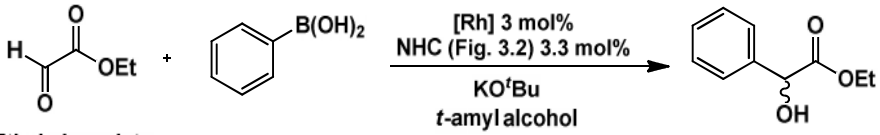


Figure 3.2. NHC-precursors used in the Rh(I)-catalytic arylation of ethyl glyoxylate with phenylboronic acid (see Table 3.3).

Table 3.3. Rh-NHC catalytic arylation of ethyl glyoxylate with phenylboronic acid.



Ethyl glyoxylate (37)

Entry[a]	Rh(I)	NHC	T/°C	tr/h	Yield/%[b]	ee/%[c]
1	$[Rh(COD)Cl]_2$	**3a**	60	7	68	27 (*S*)
2	$[Rh(COD)OH]_2$	**3a**	60	4	97	<10 (*S*)
3	$Rh(acac)(C_2H_4)_2$	**3a**	60	4	43	25 (*S*)
4	$Rh(COD)_2BF_4$	**3a**	60	4	>99	22 (*S*)
5	$[Rh(COD)OH]_2$	**3b**	60	4	73	34 (*S*)
6	$[Rh(COD)OH]_2$	**3c**	60	4	58	32 (*S*)
7	$[Rh(COD)OH]_2$	**10a**	60	4	>99	21 (*S*)
8	$[Rh(COD)OH]_2$	**10b**	60	4	<10	28 (*S*)
9	$[Rh(COD)OH]_2$	**10b**	60	16	18	26 (*S*)
10	$Rh(COD)_2BF_4$	**3b**	60	4	95	24 (*S*)
11	$Rh(COD)_2BF_4$	**3c**	60	4	>99	21 (*S*)
12	$Rh(COD)_2BF_4$	**10a**	60	4	>99	23 (*S*)
13	$Rh(COD)_2BF_4$	**10b**	60	4	30	34 (*S*)
14	$Rh(COD)_2BF_4$	**10b**	60	16	84	21 (*S*)
15	$[Rh(COD)OH]_2$	**3a**	rt	4	>99	16 (*S*)
16	$[Rh(COD)OH]_2$	**3a**	rt	0.5	>99	31 (*S*)
17	$[Rh(COD)OH]_2$	**10b**	rt	4	<5	n.d.
18	$[Rh(COD)OH]_2$	**3a**	0	4	>99	26 (*S*)
19	$[Rh(COD)OH]_2$	**3a**	-30	4	74	25 (*S*)
20	$[Rh(COD)OH]_2$	**3b**	0	4	85	13 (*S*)
21	$[Rh(COD)OH]_2$	**3c**	0	4	92	14 (*S*)
22	$[Rh(COD)OH]_2$	**10a**	0	4	<5	n.d.
23	$Rh(COD)_2BF_4$	**3a**	rt	4	66	15 (*S*)
24	$Rh(COD)_2BF_4$	**10b**	rt	4	<5	n.d.
25	$[Rh(COD)OH]_2$	**38**	rt	4	46	n.d.
26	$[Rh(COD)OH]_2$	**38**	60	4	59	n.d.
27	$[Rh(COD)OH]_2$	**39**	rt	4	12	n.d.
28	$[Rh(COD)OH]_2$	**39**	60	4	14	n.d.
29[d]	$[Rh(COD)OH]_2$	**3a**	60	4	47	<10 (*S*)
30[e]	$[Rh(COD)OH]_2$	**3a**	60	4	90	<10 (*S*)
31[f]	$[Rh(COD)OH]_2$	**3a**	60	4	21	11 (*S*)
32[g]	$[Rh(COD)OH]_2$	**3a**	60	4	>99	17 (*S*)
33[h]	$Rh(COD)_2BF_4$	**3a**	60	4	37	24 (*S*)
34[i]	$Rh(COD)_2BF_4$	**3a**	60	4	<5	n.d.
35[j]	$Rh(COD)_2BF_4$	**3a**	60	4	>99	28 (*S*)
36	$[Rh(COD)OH]_2$	-	60	4	<5	n.d.

[a]Reagents and conditions: ethyl glyoxylate, 50% sol. in toluene (100 µl, 0.5 mmol), $PhB(OH)_2$ (119.2 mg, 1.0 mmol), KO^{t}Bu (54.2 mg, 0.5 mmol), $[Rh(COD)Cl]_2$ or $[Rh(COD)OH]_2$ (1.5 mol%) or $Rh(acac)(C_2H_4)_2$ or $Rh(COD)_2BF_4$ (3 mol%), NHC (3.3 mol%) and *t*-amyl alcohol (1 ml).
[b]Isolated yield by silica gel chromatography.
[c]Determined by chiral stationary phase HPLC; Absolute configurations determined by comparing the data with those already known in the literature.[40]
[d]MeOH was used as solvent.
[e]1,4-Dioxane was used as solvent.
[f]DME/H_2O (5/1) was used as solvent.
[g]DME was used as solvent.
[h]Ph_4BNa was used as organoboron reagent.
[i]$PhBF_3K$ was used as organoboron reagent.
[j]$C_9H_{11}BO_2$ was used as organoboron reagent.
n.d.: not determined.

Nevertheless, using the di-NHC type precursor **(10a)** (Figure 3.2), the yield was >99% (Table 3.3, entry 7). Appling the bulkier NHC derivative **(10b)** (Figure 3.2), the yield dropped significantly (Table 3.3, entries 8 and 9), even when the reaction mixture was left stirring overnight at 60ºC (Table 3.3, entry 9).

We decided to evaluate the effect that temperature had on the reaction, using the less bulky NHC precursor **(3a)** (Figure 3.2), and the two rhodium pre-catalysts denoted previously. The best pre-catalyst proved to be $[Rh(COD)OH]_2$, providing the desired ethyl mandelate **(37)** in >99 % yield in less than an hour at room temperature (Table 3.3, compared entries 15 and 16 to entry 23). In fact, we showed that the reaction occurs at low temperature (Table 3.3, entries 18 to 21) with almost total conversion of the substrate within 4 hours, with the exception of using di-NHC precursor **(10a)**, in which almost no reaction occurs at 0ºC (Table 3.3, entry 22). No significant difference was verified between the different substituent groups in the NHC type ligands, at low temperature (Table 3.3, entries 18, 20 and 21). To compare the efficiency of the ligands synthesized above (Chapter 1), we conducted four test reactions using the commercial achiral benzimidazoliums **(38)** and **(39)** as NHC precursors (Table 3.3, entries 25 to 28, and Figure 3.2). These ligands had already been applied with success in the literature in the preparation of various NHC borane complexes,[41] in the synthesis of triazenes[42] and in the synthesis of dibenzimidazolylidenes and their bimetallic complexes.[43] The yields were lower than those obtained with our NHC type ligand **(3a)** (Table 3.3, compare entry 15 with entries 25 and 27). Upon increasing the temperature to 60ºC there was a slight increase in the yield (Table 3.3, entries 26 and 28). Even so, the NHCs resulting from **(38)** and **(39)** (Figure 3.2) were less efficient in this particular transformation, and it was the less bulky NHC derived from **(38)** which gave better results compared to the NHC derived from **(39)** (Table 3.3, compare entries 25 and 26 with entries 27 and 28).

We decided at this point to test for possible solvent effects. Using the optimal conditions found previously, we screened different solvents like MeOH and H_2O (polar protic, Table 3.3, entries 29 and 31) and DME and 1,4-dioxane (aprotic polar, Table 3.3, entries 30, 31 and 32). The reaction didn't work very well when

protic polar solvents were applied, since the yields were low (47 and 21%, using MeOH and DME/H_2O, respectively). When aprotic polar solvents were tested the yields were competitive with *t*-amyl alcohol (>90%, Table 3.3, entries 30 and 32). These results lead us to conclude that no solvent effects were verified in this particular reaction, since it works for a full range of solvents with different properties.

Other phenylboron derivatives were tested as well, using $Rh(COD)_2BF_4$ as pre-catalyst and the same optimized conditions applied above (Table 3.3, entries 33 to 35). Sodium tetraphenylborate (Ph_4BNa), potassium trifluoro(phenyl)borate ($PhBF_3K$) and 1,3-propanediol boronic ester ($C_9H_{11}BO_2$) were tested in the same equimolar amounts as the simple phenylboronic acid. The yields were low for sodium and potassium boronic acids salts (37 and <5% yield, respectively), but when the ester derivative was used the yield was competitive with the optimal conditions already established (Table 3.3, compare entry 4 with entry 35). As far that we are aware, this was the first application of this organoboron reagent type for this type of catalysis, whereas potassium and sodium phenylboronic salts have had several applications.[44-47] It seems that the increased nucleophilicity of the alkylboronate species due to the presence of more electron-donating groups on boron appears to play an important role.[48]

With respect to the enantioselectivity, it seems that these new NHC type salts (Chapter 1) only provide moderate values in this reaction (ca. 10-34% ee). The best enantioselectivity value (34% ee) for the corresponding ethyl mandelate product **(37)** was obtained when NHC precursor **(3b)**, along with $[Rh(COD)OH]_2$ as pre-catalyst were used (Table 3.3, entry 5) and when NHC precursor **(10b)**, along with $Rh(COD)_2BF_4$ as pre-catalyst were used (Table 3.3, entry 13), despite the low yield obtained. The best ee values were situated in the range 20 to 34% ee (see Table 3.3, last column). When the reaction time was reduced significantly to only half an hour (Table 3.3, entry 16) the ethyl mandelate product **(37)** was obtained with 31% ee. In order to study this more deeply we decreased the reaction temperature to evaluate the effect of this parameter on the enantioselectivity.[49] When the arylation of ethyl glyoxylate was conducted at low temperature (0 and -30ºC), the enantioselectivity dropped smoothly (see Table 3.3, entries 18 to 22). However, the absolute configuration of the major enantiomer of ethyl mandelate

(37) remained always (*S*) in all the reactions tested (Table 3.3, last column). We also performed a study to evaluate if racemization could occur under the reaction conditions, since it had been shown that some catalysts provoked racemization in similar reactions.[35,50] Enantiopure (*R*)-(-)-methyl mandelate (Figure 3.3) was chosen as the test substrate. Three reaction testes were made, using $[Rh(COD)OH]_2$, (*R*,*R*)-*i*-Pr-DuPhos **(25)** (Chapter 2) and our NHC type salt **(3a)**. The reactions were monitored at hourly intervals and analyzed by chiral stationary phase HPLC. The results can be seen in Figure 3.3. Series A pertains to the system with (*R*,*R*)-*i*-Pr-DuPhos **(25)**, series B pertains to the system with **(3a)**, and series C is similar to the last one, but includes $PhB(OH)_2$ as an additive. Upon analyzing all the results obtained, we observed that no racemization took place, since the enantiomeric purity remains constant during the reaction course (Figure 3.3). This suggests that there may be competing transition states in this reaction, as there is no question concerning the formation of the active Rh (I) catalysts due to the observation of pronounced ligand acceleration (see Table 3.3, entry 36), and particularly when the reaction fails without the presence of the NHC type ligand.

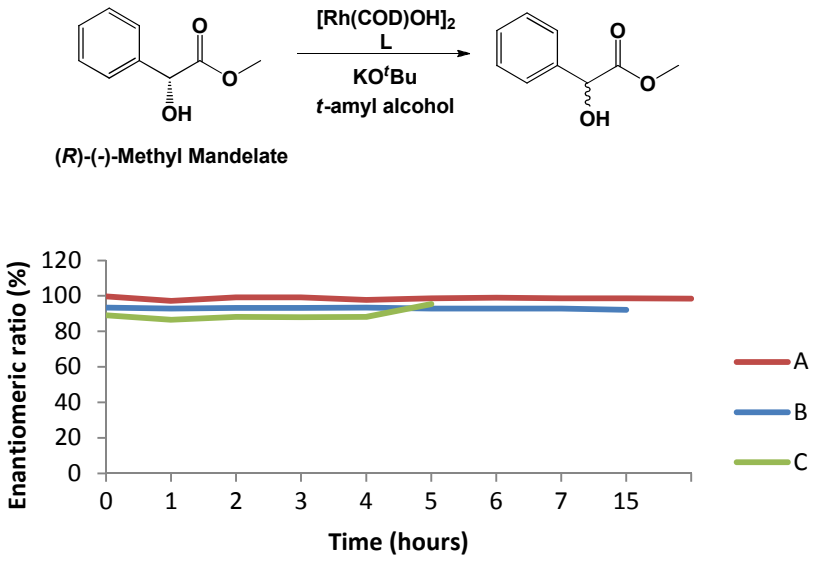
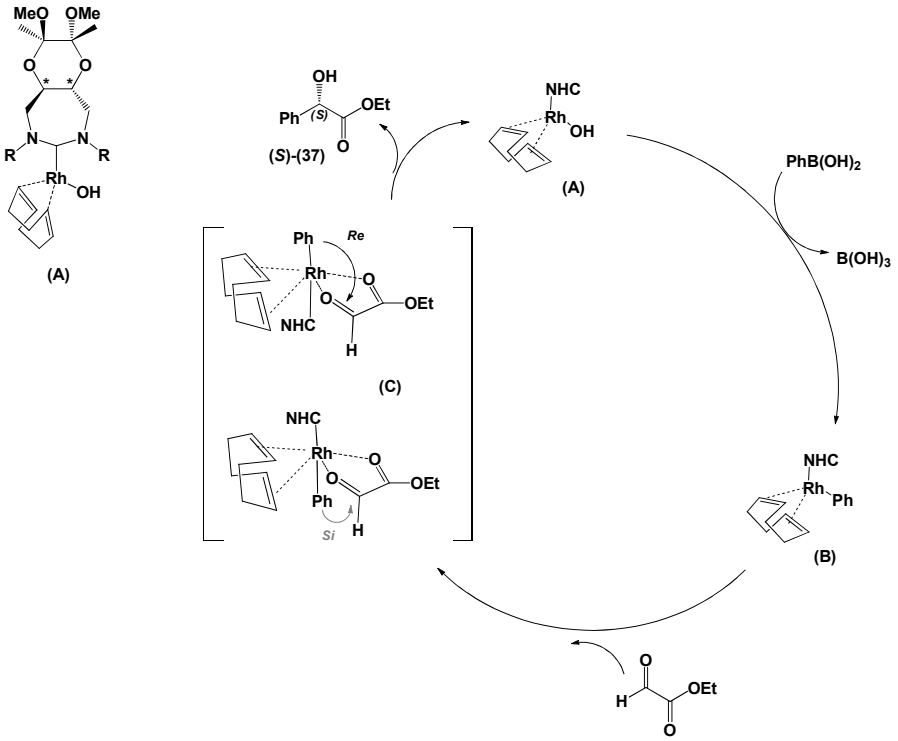


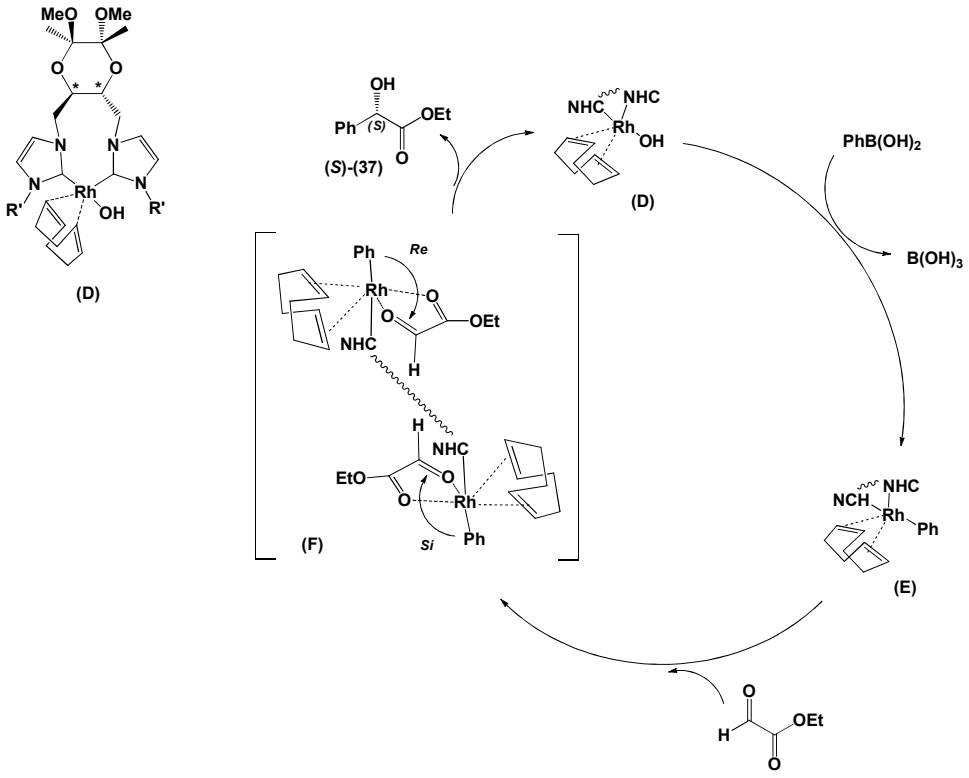
Figure 3.3. Attempted racemization studies with (*R*)-(-)-methyl mandelate and $[Rh(COD)OH]_2$.[36]

Upon analyzing all the results obtained in this study and, taking into account the studies made with certain ruthenium catalysts on this substrate type,[51,52] we propose the following mechanism (Scheme 3.7) for the mono-NHC **(3)**. From literature precedent we know that the catalytic active species are generated by transmetalation with the organoboron compound,[53] forming the Rh-aryl complex **(B)**, followed by ethyl glyoxalate insertion giving the unobserved transient di-carbonylic Rh intermediate **(C)** (Scheme 3.7). Then the key intermediate could undergo intramolecular transfer of the aryl group from rhodium to the ethyl glyoxylate substrate. Depending on this transfer step, by *Si* or *Re*-face attack, we obtained the ethyl mandelate product **(37)**, where the major enantiomer had the (*S*) configuration. We believe that the *Re*-face attack is favorable, taking into account the results obtained previously (Table 3.3). The release of the ethyl mandelate product **(37)** completes the cycle and renovates the Rh-OH complex **(A)**.



Scheme 3.7. Proposed catalytic cycle for the Rh/NHC arylation of ethyl glyoxylate.

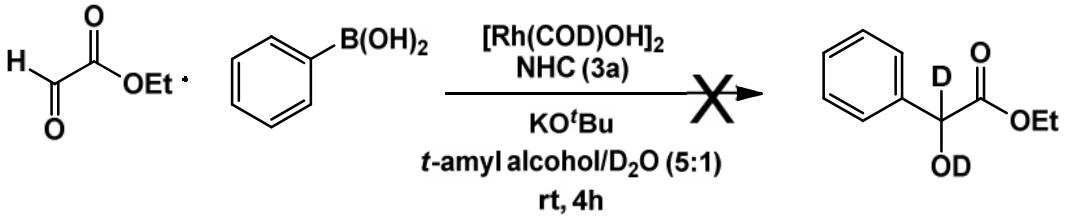
We believe that another reason behind the low enantioselectivities could be the structural nature and backbone of our NHC type ligands **(3)** and **(10)**. Both chiral centers were located far from the rhodium coordination sphere (Scheme 3.7), in all our synthetic NHC-precursors type salts. This could be answered by X-ray analysis, if we could isolate the active species, but, unfortunately, this wasn't the case. We tried to isolated the active catalytic specie, applying literature procedures[54] reacting $[Rh(COD)OH]_2$ with our 1,3-diazepinium salt **(3a)**, KO^tBu in DME at 80ºC. The green oil obtained was analyzed by NMR showing a mixture of **(3a)** and the desired complex **(A)** (Scheme 3.7). A subsequent purification by silica gel chromatography led to the decomposition of the complex. We tested a quantity of the crude mixture in a catalytic reaction, to evaluate the efficacy and potency of the formed complex **(A)** (Scheme 3.7), but the corresponding α-hydroxyester product **(37)** was obtained in a yield of only 10%. We believe that this active species is unstable so, we proceed always with the *in situ* catalytic reactions.



Scheme 3.8. Proposed mechanism for the Rh-di-NHC arylation of ethyl glyoxylate.

With regard to the di-NHC precursor **(10)**, the mechanism could be more complex. Even so, a proposed mechanism is presented (Scheme 3.8). The difference could be in the addition of ethyl glyoxylate to the intermediate Rh-di-NHC complex **(E)** (Scheme 3.8). Due to the possible instability of the complex **(F)**, we postulate that a bi-nuclear complex was formed, with further aryl transfer by *Re*-face attack, and formation of the ethyl mandelate product (*S*)-**(37)** (Scheme 3.8).

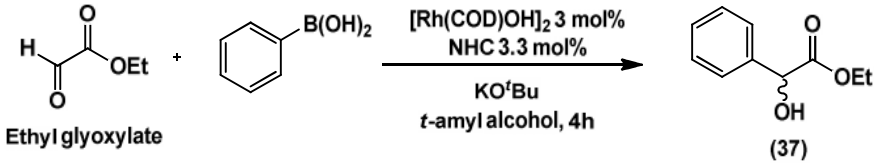
Previous literature precedent on the analogous 1,4-arylation of enones was used to support this reaction mechanism.[51,52,55,56] Water had an important role in these reactions, as it was added to promote the crucial hydrolysis step at the end of the cycle to form the desired product **(37)**. Water wasn't present in the reaction media in quantitative form (it should be noted that commercial arylboronic acid derivatives contain a small percentage of water), and when we used it with the ruthenium catalysts (see Table 3.1) the yields were very low. But to understand the exact role of water we conducted some studies with deuterium oxide (D_2O). The methodology used was the optimal one found previously (see Table 3.3, entry 15), using *t*-amyl alcohol/D_2O (5:1). The ethyl mandelate product **(37)** was obtained in 26% yield and the corresponding ^1H NMR spectrum was analyzed and compared with the original in the absence of water (Scheme 3.9). Curiously, the product showed no incorporated deuterium. We also believe that water could lead to the hydrolysis of KO^{t}Bu, leading to the formation of KOH and *t*-butanol which could coordinate with the metal to inhibit the formation of the active catalyst or even deactivate the active catalyst. So, without water present in quantitative quantities the system has the ability to regenerate itself leading to full conversion of ethyl glyoxylate to the ethyl mandelate product **(37)** (see Table 3.3 and Schemes 3.7 and 3.8).

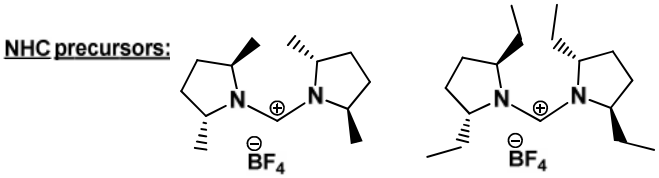


Scheme 3.9. Test reaction study using deuterium oxide.

In order to comprehend better the reaction enantioselectivity, we initiated a study with the commercial NHC chiral precursors **(40)** and **(41)**, having their center of chirality nearer the carbene carbon. The results can be seen in Table 3.4.

Table 3.4. Rh(I)-NHC catalytic arylation of ethyl glyoxylate with phenylboronic acid.





Entry[a]	NHC	T/ºC	tr/h	Yield/%[b]	ee/%[c]
1	**40**	60	4	80	24 (*S*)
2	**41**	60	4	84	20 (*S*)
3	**40**	0	4	88	22 (*S*)
4	**41**	0	4	70	23 (*S*)
5	**40**	rt	4	46	23 (*S*)
6	**41**	rt	4	94	25 (*S*)

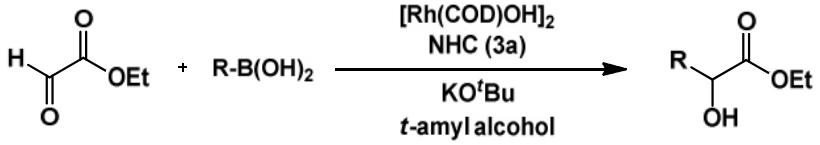
[a]Reagents and conditions: ethyl glyoxylate, 50% sol. in toluene (100 µl, 0.5 mmol), $PhB(OH)_2$ (119.2 mg, 1.0 mmol), KO^tBu (54.2 mg, 0.5 mmol), $[Rh(COD)OH]_2$ (1.5 mol%), NHC (3.3 mol%) and *t*-amyl alcohol (1 ml).
[b]Isolated yield by silica gel chromatography.
[c]Determined by chiral stationary phase HPLC; Absolute configurations determined by comparing the data with those already known in the literature.[40]

In general, no significant variations in the reaction yield were verified in the arylation of ethyl glyoxylate with phenylboronic acid using the chiral NHCs obtained from **(40)** and **(41)**, giving yields in the range 70 to 94% (Table 3.4, entries 1 to 4, and 6). When NHC precursor **(40)** was used at room temperature, ethyl mandelate **(37)** was obtained in moderate yield (Table 3.4, entry 5). Concerning to enantioselectivity, the values were similar to those obtained with our NHC type ligands (compare Table 3.4 with Table 3.3, last columns). One thing which was constant in all these reactions was the preference for the (*S*)-enantiomer of the product.

Given the assortment of boronic acid derivatives available in our laboratory we decided to investigate the scope and limitations of this reaction. These were studied using the optimized catalytic system discovered above (see Table 3.3, entry 15). The results can be seen in Table 3.5. In most cases the reaction proceeded with remarkable efficiency (up to 99% yield (Table 3.5, entries 2, 5 and 8), and over 70% yield (Table 3.5, entries 4, 6 and 10)), under mild conditions. Lower yields were observed when certain electron-donating groups were present in the arylboronic acid reagent (Table 3.5, entries 1, 11 and 12). When 3-$HOC_6H_4B(OH)_2$ was used, no reaction occurred (Table 3.5, entry 3). We believe that the strongly activating OH group hinders the arylation when coordinated to the rhodium catalyst. The same was observed when the corresponding *m*-aminophenylboronic acid was used (Table 3.5, entry 11), only vestigial quantities of the product **(42k)** were obtained. Moreover, substituents in the *ortho* position (Table 3.5, entry 4) seem to have no adverse effect on the yield, which indicates that the reaction doesn't suffer from steric hindrance around the reacting center. For instance, the bulky 1-naphthylboronic acid provides the desired product **(42j)** in high yield (Table 3.5, entry 10) contrary to the analogous 2-naphthylboronic acid that provides the desired product **(42a)** only in 36% yield (Table 3.5, entry 1). In general, it seems that this protocol was successful for the arylation of ethyl glyoxylate, showing remarkable results for electron-rich arylboronic acids. An aliphatic boronic acid derivative was also tested and the desired aliphatic product **(42l)** was obtained in poor yield (Table 3.5, entry 12), proving the requirement for an aromatic group in this reaction.

Almost all of the ethyl mandelate derivatives **(42)** were already known from the literature,[57-62] with exception of the compounds **(42e)** and **(42i**). Even so, to determine the enantioselectivity of the products **(42)**, the racemic reactions using $[Rh(COD)Cl]_2$ and PPh_3 as catalyst and the same conditions applied for the standard reactions (see Table 3.3 and 3.4) were performed and the crude products analyzed by HPLC. In general the ee values were moderate to low, with a best value achieved of 43% ee, for the product **(42i)** (Table 3.5, entry 9). As far as we know, the absolute configuration of the products **(42b)** and **(42g)** was (*S*), according to the literature.[57] For the other adducts **(42)**, the absolute configuration wasn't determined.

Table 3.5. Catalytic arylation of ethyl glyoxylate, with aryl and alkyl boronic acids.



Ethyl glyoxylate (42)

Entry[a]	R	Ethyl mandelate derivative (42)	Yield/%[b]	ee/%[c]
1	2-Naph	**a**	36	11
2	4-FC_6H_4	**b**	>99	<10 (*S*)
3	3-HOC_6H_4	**c**	n.r.	-
4	2-$MeOC_6H_4$	**d**	81	<10
5	3-$BnOC_6H_4$	**e**	>99	n.d.
6	2-Fur	**f**	71	17
7	4-ClC_6H_4	**g**	34	<10 (*S*)
8	3-$MeOC_6H_4$	**h**	>99	31
9	3-AcC_6H_4	**i**	12	43
10	1-Naph	**j**	72	<5
11	3-$NH_2C_6H_4$	**k**	trace	n.d.
12	CH_3CH_2	**l**	23	n.d.

[a]Reagents and conditions: ethyl glyoxylate, 50% sol. in toluene (100 µl, 0.5 mmol), R-$B(OH)_2$ (119.2 mg, 1.0 mmol), KO^{t}Bu (54.2 mg, 0.5 mmol), $[Rh(COD)OH]_2$ (1.5 mol%), NHC precursor **(3a)** (3.3 mol%) and *t*-amyl alcohol (1 ml).

[b]Isolated yield by silica gel chromatography.

[c]Determined by chiral stationary phase HPLC; Absolute configurations determined by comparing the data with those already known in the literature.[57]

n.r.= no reaction.

n.d.= not determined.

3.3. Conclusions

We have developed a new efficient and high yielding route to the synthesis of α-hydroxyesters, important building blocks in organic synthesis, using Rh (I) complexes formed *in situ* from $[Rh(COD)OH]_2$ and NHC ligands. Once again, the application of low cost and easily handled arylboronic acids shows their utility in this novel Rh-catalyzed arylation with ethyl glyoxylate substrates.

Our chiral NHC (Chapter 1) based catalytic systems proved more efficacious than those derived from some commercial NHC precursors, and also giving better enantioselectivities than the commercial chiral examples.

The scope of this reaction for the synthesis of ethyl mandelate derivatives was exhaustively investigated.

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4. Catalytic Arylation of di-Tosylaminoesters: Synthesis of α-Amino Acids

"Somewhere, something incredible is waiting to be known."
Carl Sagan

4.1. Introduction

Optically active α-amino acids,[1,2] the building blocks of proteins, are important biological molecules, ubiquitous to all living organisms on earth. Thereby, unnatural or non-proteinogenic α-amino acids, usually formulated as $H_2NCH(R)CO_2H$, are the most important family of carbonyl compounds and their synthesis illustrate a meaningful challenge at the academic and industrial level. Due to both their structural diversity and functional versatility, their scope of application is huge,[3-5] covering the field of organic and medicinal chemistry, biology and agrochemical science.

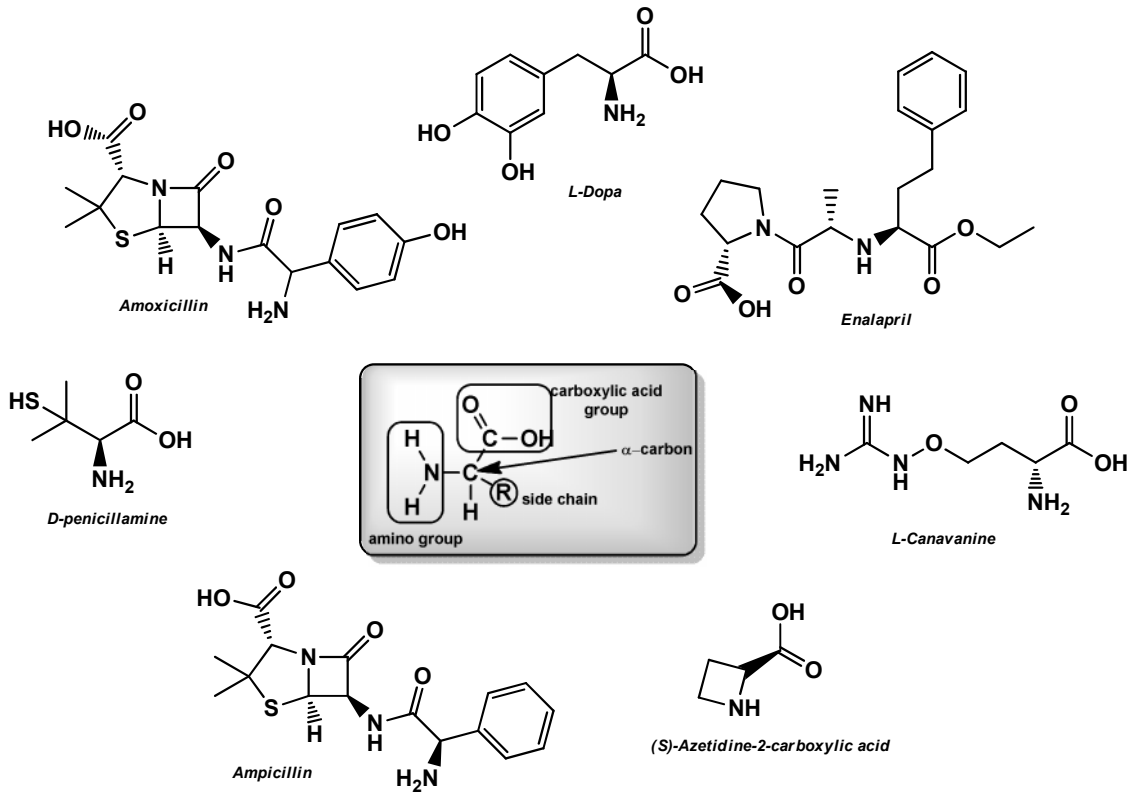
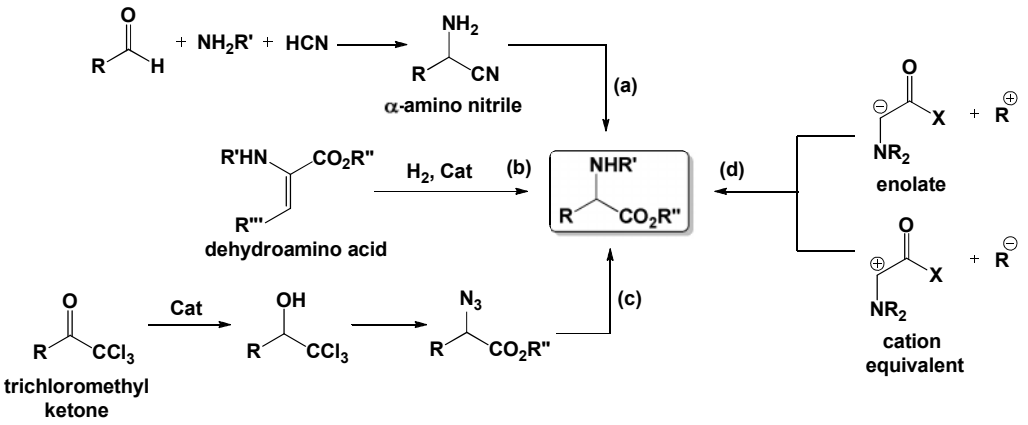


Figure 4.1. Examples of important compounds containing the α-amino acid scaffold in their skeleton: *L-Dopa* (anti-Parkinson therapeutic agent); *Enalapril* (antihypertensive therapeutic agent); *L-Canavanine* (anti-predatory agent in plants); (*S*)-*Azetidine-2-carboxylic acid* (analogue of proline); *Ampicillin* and *Amoxicillin* (antibacterial therapeutic agents); *D-Penicillamine* (anti-rheumatic therapeutic agent).

Many well-known and therapeutically relevant compounds contain unnatural amino acids in their backbones.[6] Typical examples are Amoxicillin,[7] an antibacterial agent and Enalapril,[8] an antihypertensive agent, among others (see Figure 4.1). The application of unnatural amino acids in organic chemistry has been immense, since they have been used as building blocks[9] in natural product synthesis as well as being used as chiral auxiliaries,[10,11] catalysts[12,13] and ligands.[14,15]

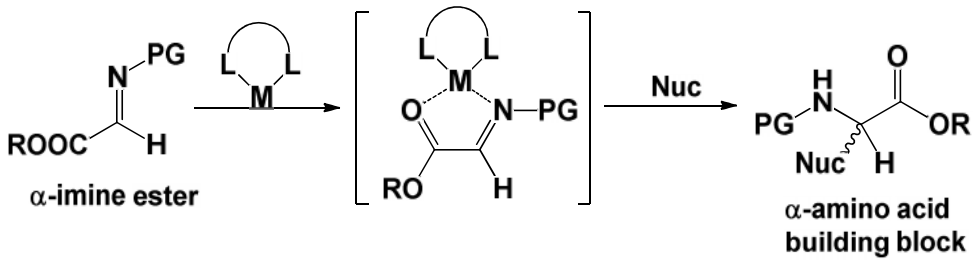
Although enzymatic synthesis and chiral resolutions are viable methods for the production of naturally occurring chiral α-amino acids,[16] they are often not useful for synthesizing non-natural *D*-amino acids or amino acids with non-natural side chains. The formation of diatereomeric salts of optically impure amino acid mixtures,[17,18] followed by chiral resolution is time consuming and therefore expensive, and thus a need to invest in alternative synthetic routes was deployed. In the literature many methods have been described,[9,19-22] among these, the Strecker synthesis, the Knowles-Monsanto asymmetric hydrogenations and the Corey-Link reaction stand out. These catalytic asymmetric methodologies (Scheme 4.1) to afford α-amino acids have clear advantages over the use of chiral reagents and auxiliaries, since a catalytic amount of chiral material can produce large quantities of enantiomerically enriched (*scalemic*) or enantiopure products. The Strecker synthesis[23-25] is a three component reaction between an aldehyde, an amide and hydrogen cyanide to form an α-amino nitrile, which is subsequently hydrolyzed to afford the free acid, resulting in an α-amino acid (path a, Scheme 4.1).



Scheme 4.1. Some common methods for the synthesis of α-amino acids; **(a)** Strecker synthesis; **(b)** Knowles-Monsanto synthesis; **(c)** Corey-Link reaction; **(d)** Types of derivatizations of glycine.

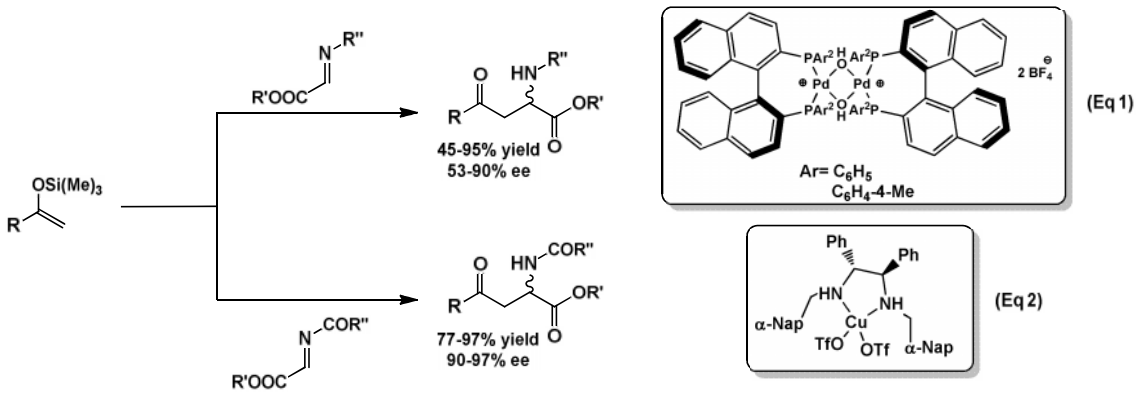
A hydrogen can be added enantioselectively to a pro-chiral α-carbon of a dehydroamino acid (path b, Scheme 4.1), as in the Knowles-Monsanto synthesis[26] and yet, several advances involving carbon-nitrogen bond forming events have emerged for the catalytic asymmetric synthesis of α-amino acids (path c, Scheme 4.1), like the Corey-Link reaction,[27] that involves first the stereoselective reduction of a substituted trichloromethyl ketone to the corresponding alcohol, which in turn can be converted to α-amino acids in four steps. Several asymmetric derivatizations of glycine involve creating a nucleophile or electrophile at the α-carbon of a glycine equivalent and subsequent asymmetric addition of an R group to that center (path d, Scheme 4.1).[28,29] There are, of course, many other routes to chiral α-amino acids, but, within the context of this work, we will only discuss the catalytic asymmetric addition of organic nucleophiles to α-imino esters or enolates, a methodology that has emerged as one of the most promising routes to optically enriched α- and β-amino acid derivatives, including β-lactams.[30] It was in the mid-1990s that α-imino esters started to be seen as excellent substrates for catalytic asymmetric reactions,[31] since a Lewis acid (as a metal catalyst) could coordinate both the imine N and the ester carbonyl O atoms to form a chelate, that was crucial during the enantioselectivity step (Scheme 4.2). Several interesting and

attractive innovative procedures were developed to exploit the electrophilic nature of α-imino esters.



Scheme 4.2. Application of α-imino esters in the synthesis of α-amino acids; M= transition metal catalyst; L= ligand; PG= protective group.

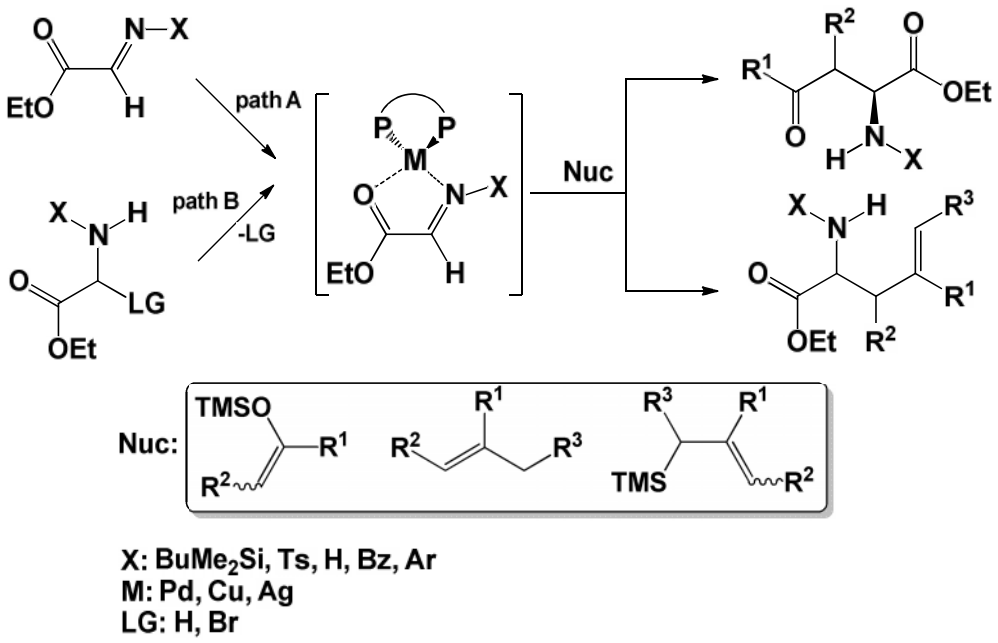
Sodeoka and co-workers[32] reported the first example of an asymmetric addition of enol silyl ethers to α-imino esters employing a hydrated Pd(II)-based chiral Lewis acid system (Scheme 4.3, Eq. 1). These so called Mannich-type reactions that involve the addition of resonance-stabilized enols to imines led to optically active γ-oxo-α-amino esters with modest to high enantioselectivity, thus proving the efficiency of the Sodeoka methodology using novel chiral binuclear μ-hydroxo palladium (II) complexes.



Scheme 4.3. Asymmetric alkylation of α-imino esters with a chiral binuclear μ-hydroxo palladium (II) complex (Eq. 1)[32] and a copper (II) bis-triflate (*S*)-(-)-Bis[bis(3,5-dimethylphenyl)phosphino]-1,1-binaphthyl catalyst (Eq. 2).[33]

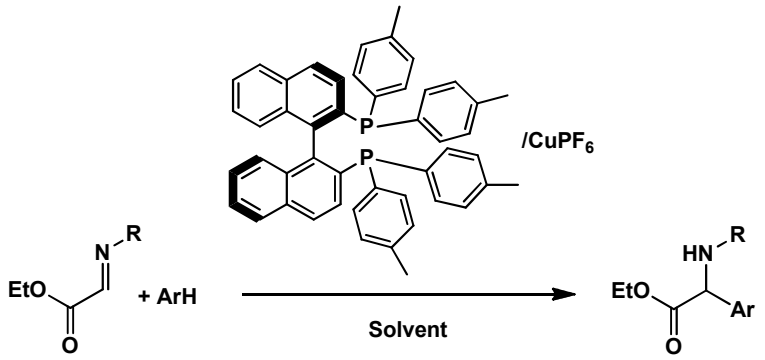
Later on, Kobayashi and co-workers reported[33] a useful extension of this methodology when they applied the reaction of *N*-acylimine esters with enol silanes to produce *N*-acylated amino acids (Scheme 4.3, Eq. 2). The application of a chiral Cu (II) catalyst led to smooth reactions affording the desired amino esters in high yields and high enantioselectivities. In fact, this new asymmetric methodology was showcased by the synthesis of a ceramide trafficking inhibitor, HPA-12.[33,34] Later on, Kobayashi developed an aqueous variant of this reaction using *N*-hydrazino imino esters and a catalyst formed from ZnF_2 and the chiral diamine ligand exploited above (Scheme 4.3, Eq. 2).[35] The desired hydrazine compounds were obtained in good yields with high stereoselectivities, using a small amount of TfOH, and after reductive deprotection with SmI_2 afforded the corresponding amino acids.

Lectka and co-workers[36] summarized and described their methods for the catalytic asymmetric alkylation of α-imino esters and *N*,*O*-acetals with enol silanes, ketene acetals, alkenes and allylsilanes, using transition metal-phosphine complexes as catalysts (Scheme 4.4). The authors were successful in accessing γ-oxo-α-amino esters (Scheme 4.4, path A) with high enantioselectivity (up to 99% ee) and diastereoselectivity (*anti*:*syn* up to 25:1), using (*R*)-tol-BINAP/$CuClO_4$ catalyst. This was the first example of a catalytic enantioselective imino-ene reaction using alkenes and allylsilanes as nucleophiles (Scheme 4.4). The corresponding kinetic study was reported with promising results. Finally in their intensive and complete study, a practical and preparative-scale synthesis of α-imino acid derivatives was described using hydrolytically stable *N*,*O*-acetals (Scheme 4.4, path B) instead of α-imino esters. There were minimal reductions in yield and selectivity.



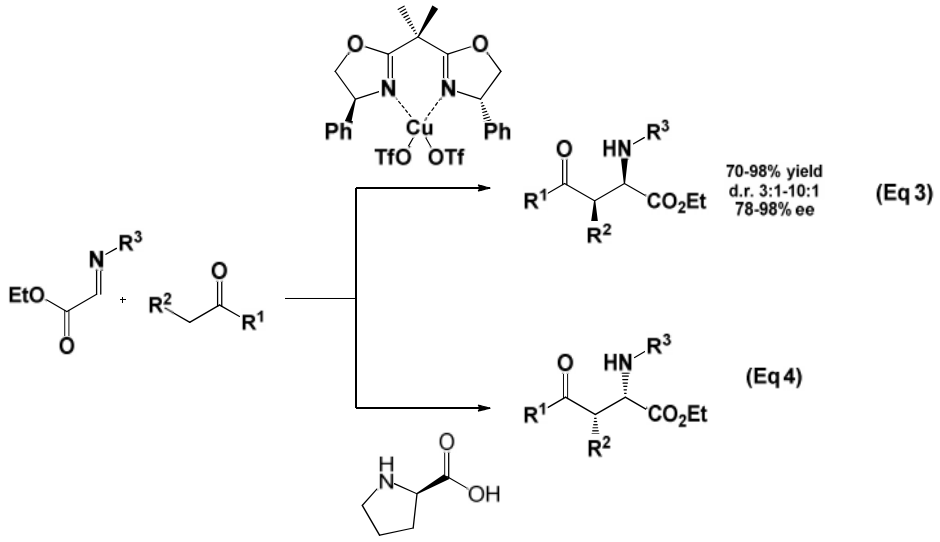
Scheme 4.4. Asymmetric alkylation of α-imino esters (path A) and *N*,*O*-acetals (path B) using copper-phosphino complexes.[36]

Jørgensen and co-workers[37,38] and Johannsen[39] independently applied the combination of $CuPF_6$ and (*R*)-tol-BINAP in the enantioselective addition of imines to electron-rich aromatic compounds. This methodology (Scheme 4.5) led to protected optically active α-aryl α-amino acid esters generally in good to high yields, and with high regioselectivity and enantioselectivity (up to 98% ee). The limitation with this approach is the restriction to electron-rich aromatic compounds. During the development of their work, Jørgensen and co-workers also employed bis-oxazolines as chiral ligands, along with copper pre-catalysts in a simple synthetic transformation of α-imino esters with activated carbonyl compounds to obtain highly functionalized γ-oxo-α-amino acid esters in high yield and diastereoselectivity.[40] The key-point advantage with this transformation (Scheme 4.6, Eq. 3) is the use of readily available carbonyl compounds rather than, often troublesome, enol silyl ethers or silyl ketene acetals.



Scheme 4.5. The catalytic asymmetric arylation of α-imino esters by Jørgensen and co-workers and Johannsen.[37-39]

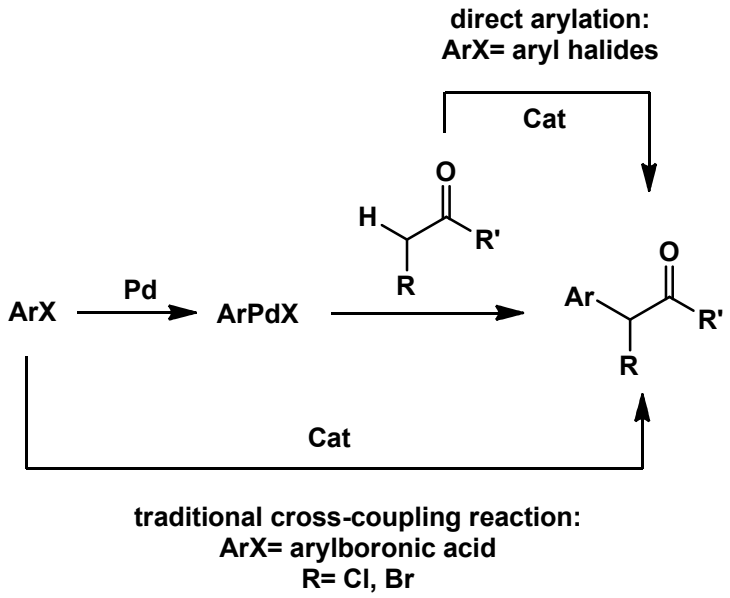
Barbas III and co-workers reported an organocatalytic version of this direct Mannich-type reaction with (*L*)-Proline, using an α-imino ester as the acceptor with a variety of unmodified aldehyde and ketone donors, to provide functionalized α-amino acid esters in moderate to high yields with excellent enantioselectivities (Scheme 4.6, Eq. 4).[40,41] A number of aliphatic aldehydes[41] (R^1=H, Scheme 4.6, Eq. 4) were tested and high diastereoselectivities (>19:1 d.r.; up to 99% ee) were achieved by increasing the bulkiness of the R^2 substituents. In the case of asymmetric ketones,[42] the predominant diastereomer was formed from the regioselective nucleophilic attack of the more substituted α-carbon atom of the ketone. This methodology opens new horizons for the enantioselective synthesis of amino acids,[43-47] since it uses readily available and rather inexpensive starting materials, doesn't require any pre-activation of substrates or metal ion assistance and can be carried out in environmentally friendly solvents under smooth conditions. In some cases, however, 20 mol% of organocatalyst needed to be used, along with six equivalents of the ketone.



Scheme 4.6. Methodology used in the synthesis of α-amino esters by Jørgensen and co-workers[37,38] (Eq. 3) and Barbas III and co-workers[41,42] (Eq. 4).

4.1.1. Palladium-catalyzed α-arylation of carbonyl compounds

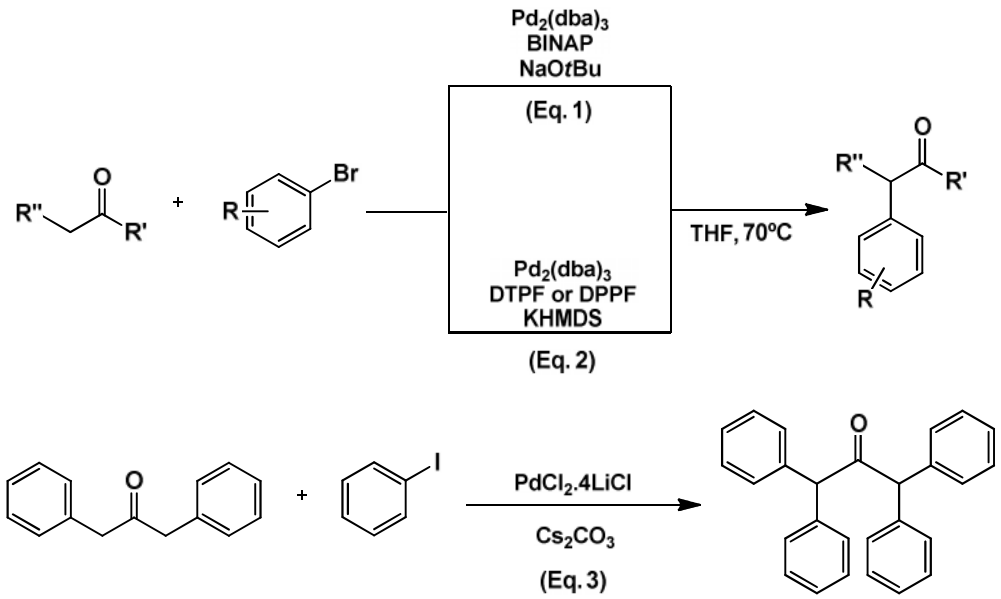
Over the last ten years, great advances have been made in the field of α-arylation of carbonyl compounds catalyzed by transition-metal complexes.[48] A large number of reactions where carbonyl compounds (ketones, esters, amides, nitriles, 1,3-dicarbonyl compounds, aldehydes, nitroalkanes, sulfoximines and sulfones) can be coupled with electron-rich, electron-neutral, electron-poor and sterically hindered aryl halides have been reported in the literature, with palladium being the metal of choice (Scheme 4.7). α-Arylation has some similarities with metal-catalyzed direct arylation chemistry of a C-H-bond,[49] but has more in common with traditional cross-coupling reactions (Scheme 4.7).[50]



Scheme 4.7. Palladium catalyzed α-arylation of carbonyl compounds; comparison between classical cross-coupling and direct arylation.

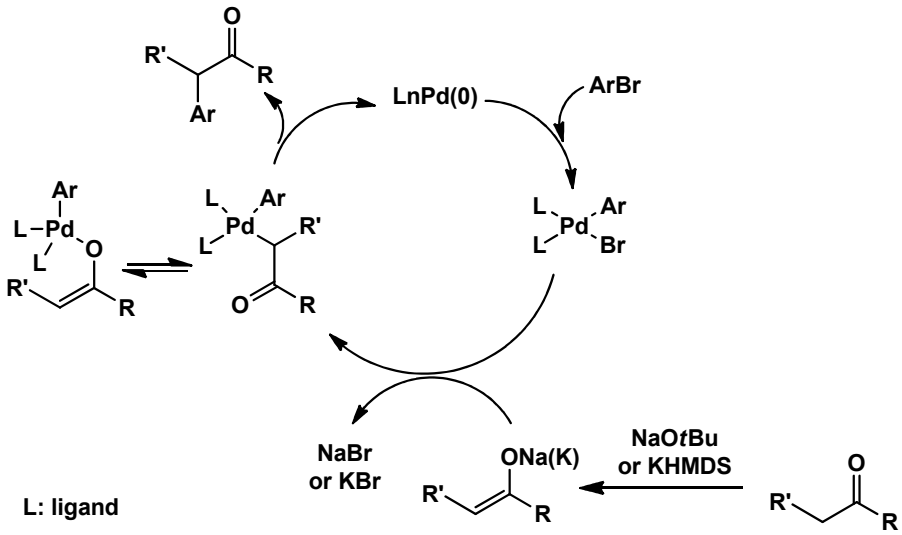
The nucleophilic aromatic substitution of enolates with aryl halides[51,52] and the transition-metal-catalyzed α-arylation of carbonyl compounds[53] are the two main methods for preparing α-arylated carbonyl compounds. Based on the requirement that good electron-withdrawing substituents in the aromatic rings (such as F or NO_2) are required for the successful nucleophilic aromatic substitution, the later method has become the one of choice for this type of transformation and many different protocols have been described to date.[54]

Buchwald and Palucki[55] reported a general method for the direct synthesis of α-aryl ketones from ketones and aryl bromides catalyzed by a Pd-BINAP complex. The mild reaction conditions - compatible with the presence of a variety of functional groups, including nitriles, ethers, imines, amides, aryl chlorides and acetals - displays high regioselectivities (Scheme 4.8, Eq. 1). Hartwig and Hamann[56] and Miura and co-workers[57], in 1997, reported, independently, a similar process using other Pd complexes (Scheme 4.8, Eq. 2 and 3, respectively). Scheme 4.9 summarizes a general mechanism for the palladium-catalyzed α-arylation of ketones using Buchwald, Hartwig and Miura methods.

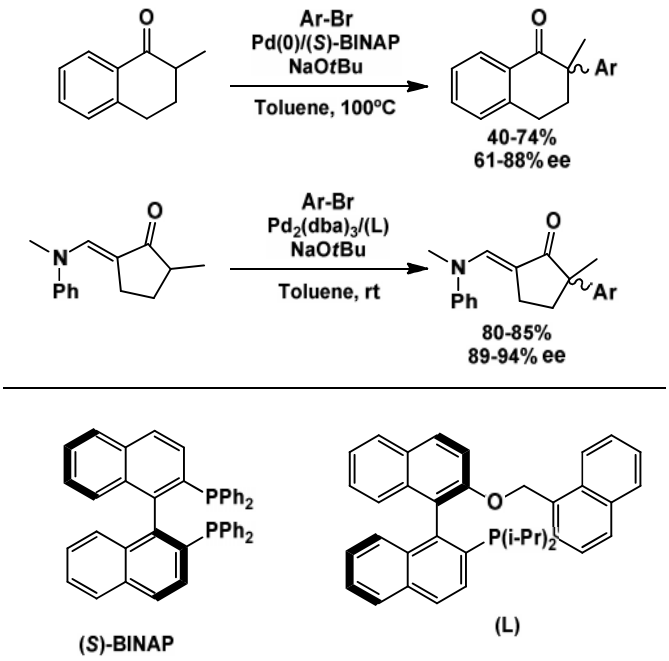


Scheme 4.8. The Buchwald and Palucki[55] method (Eq. 1), Hartwig and Hamann[56] method (Eq. 2) and the method developed by Miura *et al*.[57] (Eq. 3) for the palladium-catalyzed α-arylation of ketones.

Soon after, the first example of the direct catalytic asymmetric arylation of ketone enolates was reported by Buchwald and co-workers[58] (Scheme 4.10). Later on, Buchwald's group reported a new method for the enantioselective α-arylation of ketone enolates that gave better reactivity and higher enantioselectivities, employing only 1 mol% of the palladium species and the phosphane ligands.[59] However, this method is limited by the type of specific substrate that must be used.

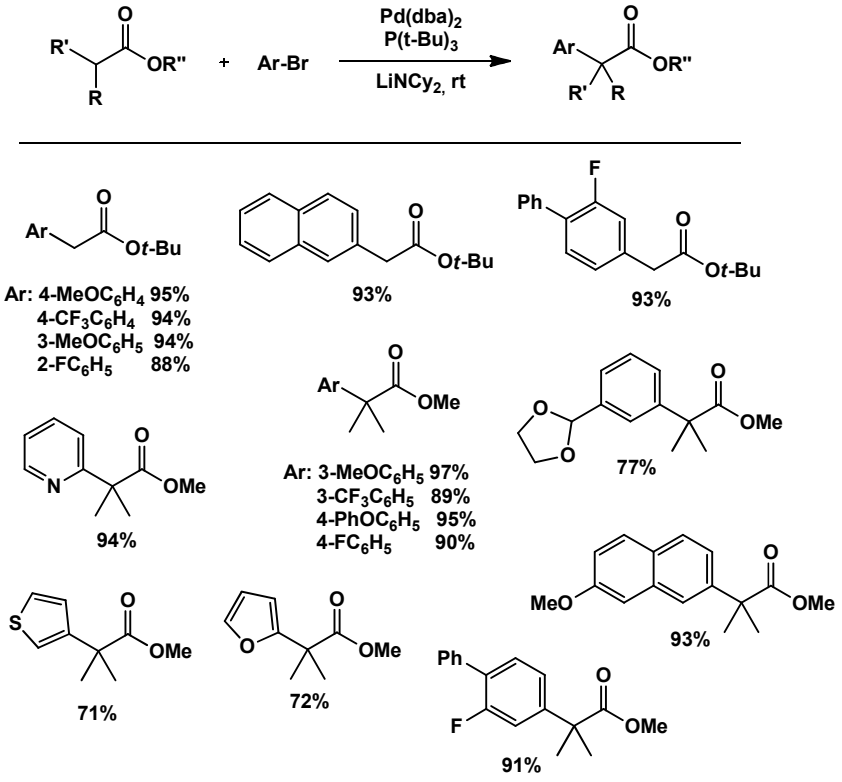


Scheme 4.9. Proposed general reaction mechanism for the catalytic α-arylation of carbonyl compounds.



Scheme 4.10. α-Arylation of ketone enolates reported by Buchwald and co-workers.[58,59]

The methods for the palladium-catalyzed arylation of ketones were extended, successfully to other carbonyl compounds like amides, esters, malonates and cyanoesters.[53] For instance, Hartwig and co-workers[60] reported an efficient synthesis of α-aryl esters by room temperature palladium-catalyzed coupling of aryl halides with ester enolates (Scheme 4.11). The development of highly active catalysts comprised of bulky, electron-rich ligands, such as the phosphane P(*t*-Bu)$_3$ proved to be highly efficient for this coupling reaction. At the outset there was some concern as regards the possibility of the ester enolates undergoing faster condensations and elimination reactions, compared with ketones or amides. However, as the coupling of ester enolates occurs with high yields, these side-reactions are negligible or don't occur at all. A stronger and hindered amide base such as lithium dicyclohexylamide (LiNCy$_2$) (in slight excess), and generation of the enolate prior to aryl halide and palladium catalyst addition provides the most efficient coupling of the ester substrate with the aryl halide to afford the substituted α-esters (Scheme 4.11).



Scheme 4.11. Synthesis of α-aryl esters by room temperature palladium-catalyzed coupling of aryl bromides with ester enolates.[60]

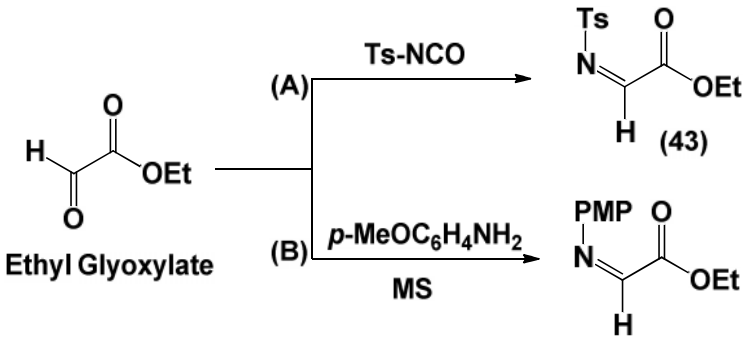
Although we had originally hoped to efficiently arylate imino-esters to amino-esters in a catalytic asymmetric fashion, with the unexpected formation of a di-*N*-tosylamine-ester adduct (see Section 4.2.1), we decided to look at the arylation of this novel substrate, in the hope that it would be its enolate that would undergo the arylation, in accordance with the above literature precedent.

Despite all the developments to date, there is still a great demand for new processes leading to α-amino acids and for the optimization of known ones.

4.2. Results and Discussion

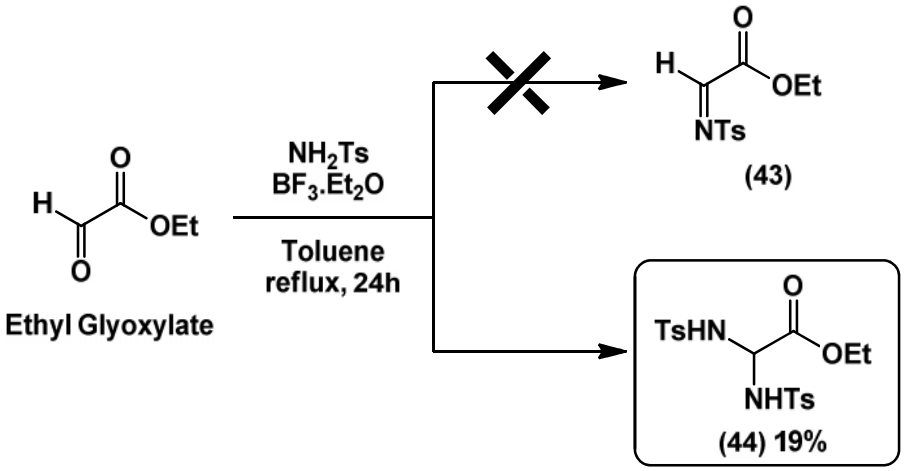
4.2.1. Attempted synthesis of an α-imino ester - Synthesis of di-*N*-tosylamine-ester (44)

Oliver's group[61] and Mikami's group[62] synthesized the α-imine ester derivative **(43)** by refluxing ethyl glyoxylate with *p*-toluenesulfonyl isocyanate (Ts-NCO) in toluene for 5 days, in 90% and 33% yield, respectively (Scheme 4.12, path A). When the *N*-protecting group is more electron rich, such as the case of *p*-methoxyphenyl (PMP), the corresponding imine ester was synthesized by Lucchini's group,[63] through condensation of ethyl glyoxylate with the free amine in the presence of a dehydrating agent, like activated molecular sieves (Scheme 4.12, path B).



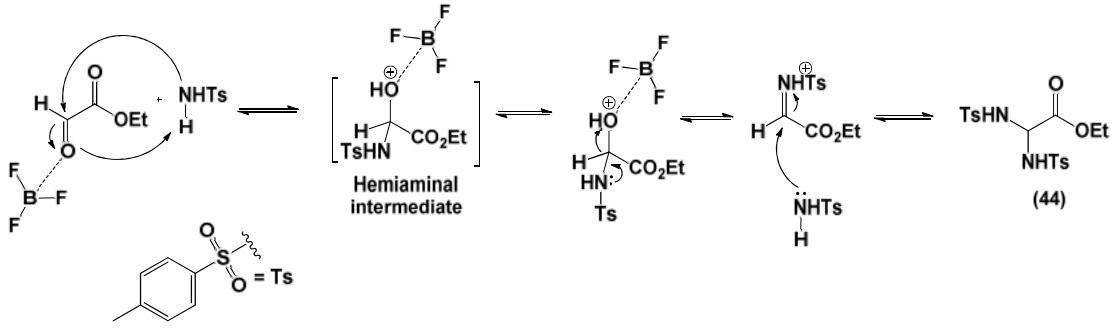
Scheme 4.12. Synthesis of α-imino esters from ethyl glyoxylate by Oliver's[61] and Mikami's[62] group (path A), and Lucchini's group[63] (path B).

Our work started with the attempted synthesis of the α-imine ester derivative **(43)** (Scheme 4.12). We decided to use the same methodology already used to synthesized the imine derivatives described throughout this thesis.[64] The commercially available ethyl glyoxylate and *p*-toluenesulfonamide, with a catalytic quantity of Lewis acid, in toluene, were refluxed in a Dean-Stark trap to collect the water formed during the reaction. Toluene was the solvent of choice for this chemical transformation, since ethyl glyoxylate was commercially available as a 50% solution in toluene, due to instability issues. Despite the fact that other procedures[30,61-63] are already known in the literature for the synthesis of the desired imine **(43)** (Scheme 4.12), we decided to apply this easier (and more familiar route to us) and more economical methodology. At the end of the reaction a white solid was obtained. After exhaustive analysis by NMR, mass spectrometry and elemental analysis, the product was identified as the *N*,*N*-di-*p*-toluenesulfonylglycine ethyl ester **(44)** and not the desired imine ester **(43)** (Scheme 4.13). In fact, a careful literature search revealed that this compound has already been prepared by Lectka's group.[65]



Scheme 4.13. Attempted synthesis of the imine ester **(43)** and synthesis of the *N*,*N*-di-*p*-toluenesulfonylglycine ethyl ester **(44)**, both using ethyl glyoxylate and *p*-toluenesulfonamide (NH_2Ts).

We propose the following mechanism to explain the formation of product **(44)** (Scheme 4.14). This condensation reaction is somewhat similar to the one presented in Chapter 2, in which ethyl glyoxylate, after being activated by the Lewis acid, is susceptible to nucleophilic attack by nucleophiles (e.g. NH_2Ts, in this case), resulting in the generation of an hemiaminal. These species are usually unstable, and, considering the activation by the Lewis acid and with the presence of NH_2Ts in solution, another nucleophilic attack occurs forming the *N*,*N*-di-*p*-toluenesulfonylglycine ethyl ester **(44)** (Scheme 4.14).[66]

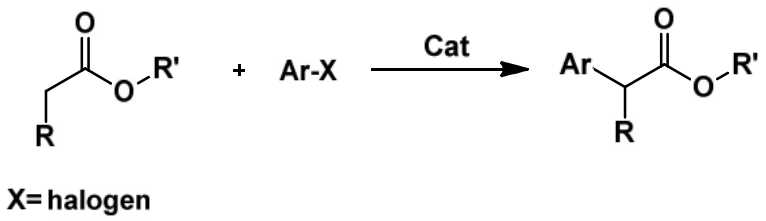


Scheme 4.14. Proposed mechanism for the synthesis of *N*,*N*-di-*p*-toluenesulfonylglycine ethyl ester **(44)** using ethyl glyoxylate and *p*-toluenosulfonamide (NH_2Ts), catalyzed by $BF_3.Et_2O$ (Lewis acid).

We used equimolar amounts of ethyl glyoxylate and *p*-toluenesulfonamide (0.1 mol), and obtained a moderate yield of 19% for product **(44)**. Taking into account that, for full conversion of ethyl glyoxylate into product **(44)**, two mole equivalents of *p*-toluenesulfonamide were required, so, this yield was to be expected for product **(44)**.

4.2.2. Arylation of the *N*,*N*-di-tosyl aminal ester (44) with arylboronic acids, catalyzed by Pd

The transition-metal-catalyzed α-arylation of enolates is a special type of cross-coupling reaction (see Section 4.1.1 and Scheme 4.15). Briefly, the α-arylation of enolates employs carbonyl compounds as nucleophiles and aryl halides or pseudo-halides ("fake" halogens of the general forms Ps–Ps or Ps–X, where Ps is a pseudo-halogen group such as cyanide, cyanate, thiocyanate and others, and X is a "true" halogen) as electrophiles. A related method involving Suzuki cross-coupling conditions employs aryl boronic acids as nucleophiles and α-halo carbonyl compounds as electrophiles.[67] Palladium and other transition metal catalysts (Cu, Ni) are able to catalyze this cross-coupling process that results in nucleophilic aromatic substitution of aryl halides and pseudo-halides by enolates. This valuable transformation, leading to the formation of C-C bonds, allows efficient construction of quaternary centers with good enantioselectivity (see section 4.1.1. for examples and further information).[68,69]

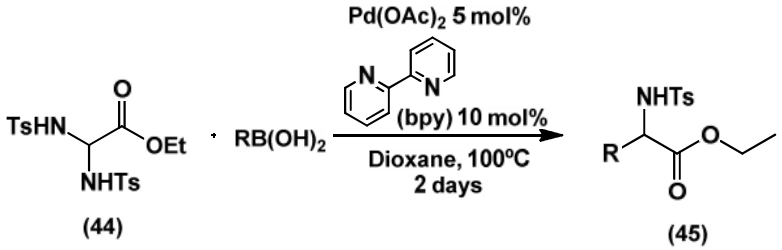


Scheme 4.15. Useful route to α-arylated esters and amino acids (if R=NH_2).

As far as we know, the arylation on aminal substrates has never been reported in the literature before.

We started our efforts with the catalytic asymmetric synthesis of a series of α-amino ester derivatives (Table 4.1), using the aminal **(44)** synthesized previously, using all the know-how acquired in the previous catalytic enantioselective arylation reactions with organoboron reagents (discussed in Chapters 2 and 3). As the first step, the racemic reactions were made, using a literature procedure[70] where $Pd(OAc)_2$ and 2,2'-bipyridine (as ligand) were used, along with an organoboron reagent and 1,4-dioxane as solvent. The results obtained can be seen in Table 4.1. In general the results were quite satisfactory, and an unexpected family of α-amino ester derivatives **(45)** was acquired in moderate to good yields. Considering the reactions with arylboronic acid derivatives, in general, the yields were moderate to good, showing good tolerance for the presence of both electron-donating and electron-withdrawing substituents in the phenyl ring of the organoboron reagent (Table 4.1, entries 1 to 11).

Table 4.1. Screening of aryl and alkylboronic acid derivatives to afford the α-amino ester derivatives **(45)** in racemic form, using the ditosylaminal **(44)** as substrate.



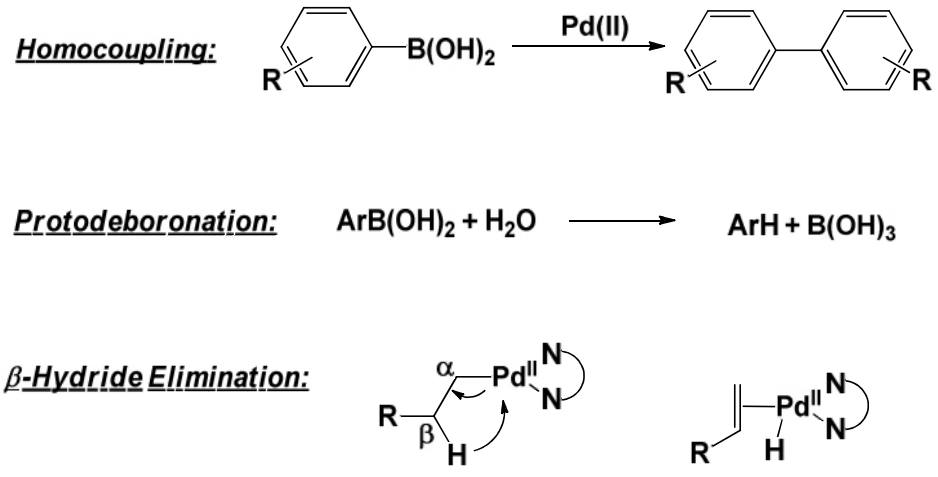
Entry[a]	R	α-amino ester (45)	Yield/%[b]
1	C_6H_5	**a**	38
2	2-Naph	**b**	28
3	2-$CH_3OC_6H_4$	**c**	58
4	4-ClC_6H_4	**d**	35
5	3-$CH_3OC_6H_4$	**e**	56
6	3-AcC_6H_4	**f**	61
7	1-Naph	**g**	79
8	4-FC_6H_4	**h**	45
9	3-$PhCH_2OC_6H_4$	**i**	30
10	3-HOC_6H_4	**j**	31
11	3-$NH_2C_6H_4$	**k**	37
12	1-Fur	**l**	0
13	CH_3	**m**	0
14	CH_3CH_2	**n**	0
15	$CH_3(CH_2)_{11}$	**o**	0

[a]Reagents and conditions: $Pd(OAc)_2$ (5 mol%), bpy (10 mol%), di-tosyl-aminal **(44)** (0.3 mmol), $RB(OH)_2$ (1.0 mmol) and dioxane (2 ml).
[b]Isolated yields after chromatography.

The exception was with 2-furanylboronic acid (Table 1, entry 12), which gave none of the desired α-amino ester product **(45l)**. There is no data in the literature on using 2-furanylboronic acid in this particular reaction. On the other hand, the reaction didn't take place either using aliphatic boronic acid derivatives (Table 4.1, entries 13 to 14). A black precipitate (which we believe was Pd black) was seen at the bottom of the flask and only aminal **(44)** was recovered. The best yield was obtained with 1-naphthylboronic acid (Table 4.1, entry 7). No significant difference was observed using an electron-donating or an electron-withdrawing group in the phenyl ring of the organoboron reagent, but apparently the reaction yield improved slightly, as expected from literature precedent,[71] when an electron-withdrawing group was present (see Table 4.1, entries 6 and 8).

Some analogies with our catalytic transformation were found with the work of Lectka and co-workers[36] on the catalyzed amination of enol silyl ethers or silyl ketene acetals (see section 4.1, Scheme 4.4). To promote the synthesis of γ-oxo-α-amino acids from acetals, the authors argued that the catalyst used could promote the elimination of the leaving group from the acetal substrate, forming the corresponding α-imino ester intermediate that would suffer the enantioselective alkylation (or amination) giving the desired acylated amino acid derivatives in high yields. Gooβen[67,72] has also made pertinent contributions on the palladium-catalyzed arylation of α-esters. It is very hard to propose a concrete mechanism at the moment for this reaction, and it will require further study outside of the scope of this thesis. We are also not certain if the initial *N*,*N*-di-p-toluenesulfonylglycine ethyl ester **(44)** undergoes transformation to the desired imino-ester **(43)** under the reaction conditions and this then undergoes the arylation process. Another possibility is that an arylated adduct of the *N*,*N*-di-tosylamine ester **(44)** is generated and that this subsequently suffers elimination of a tosylamine side-product.

In an attempt to explain the generally moderate yields of the desired α-amino ester derivatives (see Table 4.1, entries 1 to 12), we consider this reaction to be quite sluggish, leading to the possibility of the occurrence of side-reactions with the inevitable consumption of the arylboronic acid derivatives.[73,74] It was envisaged that two main side-reactions could take place under the experimental conditions at hand, namely base-catalyzed proto-deboration[75] and homocoupling[74,76] (Scheme 4.16). In the case of using aliphatic boronic acid derivatives (see Table 4.1, entries 13 to 15), like ethyl and dodecylboronic acid (Table 4.1, entries 14 and 15), the possibility of β-hydride elimination could also occur (Scheme 4.16).[77]



Scheme 4.16. Possible side-reactions.

The possibilities presented as side-reactions could block the formation of the desired α-amine ester product **(45)** or eventually decrease the rate of catalytic turnover. It seems that a protic medium is required to afford and complete this reaction, and, we believe that vestigial quantities of water present in the commercial boronic acid derivatives play that role.

4.2.3. Enantioselective arylation of *N*,*N*-di-tosyl aminal ester (44) with arylboronic acids, catalyzed by transition metals

Since $Pd(OAc)_2$/bpy catalyzes the arylation of the aminal **(44)** with arylboronic acid derivatives, giving the α-amino ester products **(45)**, obtained in racemic form, we consequently investigated an asymmetric version of this chemical transformation in order to obtain an effective route to optically active α-amino acids. Using the aminal **(44)** and phenylboronic acid, a series of test reactions were exploited using Ru, Rh and Pd catalysts, formed *in situ* with a

range of key chiral ligands. The preliminary results can be seen in Table 4.2. Starting with Pd(II) and Ru(II) catalysts, using the methods applied earlier for the enantioselective synthesis of chiral amines (see Chapter 2) only vestigial quantities of product **(45a)** were obtained (Table 4.2, entries 1 and 2). Yamamoto and co-workers[78] published recently an interesting study concerning the addition of arylboronic acids to aliphatic aldehydes and α-ketoesters using [RuCl(η^6-*p*-cymene)]$_2$ and a chiral bidentate phosphoramidite ligand. Their results were very good. Upon using the bidentate phosphine ligand **(24)** (Figure 4.2) the desired product **(45a)** was obtained in vestigial quantities (Table 4.2, entry 5).

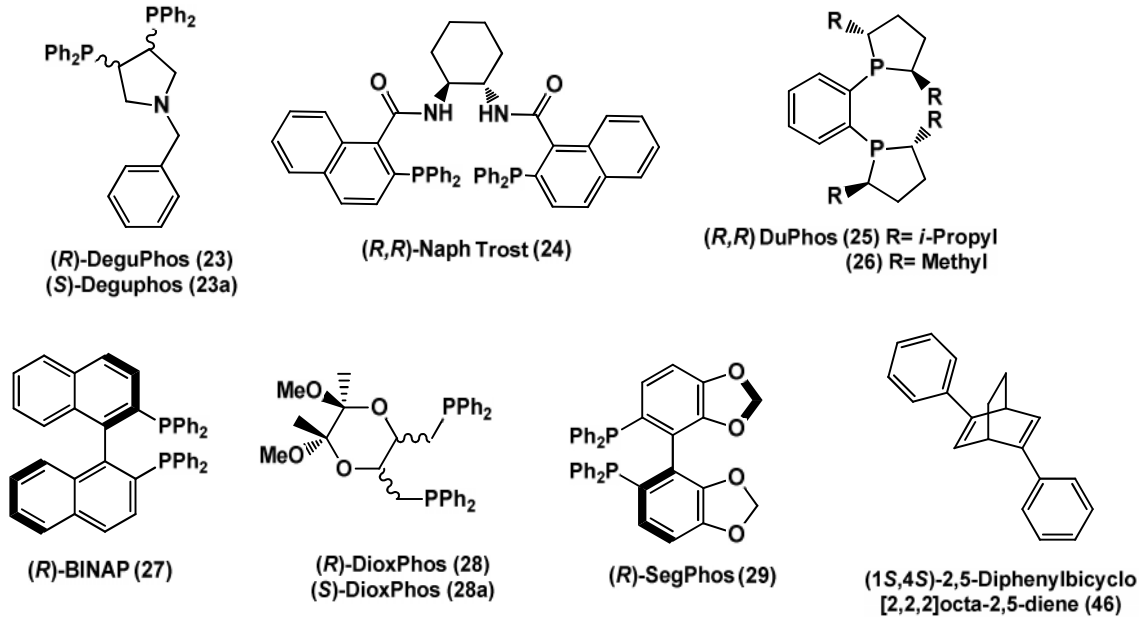
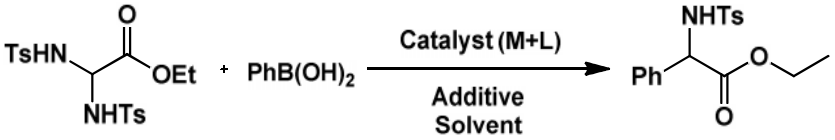


Figure 4.2. The commercial chiral ligands screened.

Table 4.2. Optimizing the reaction conditions to afford α-amino ester **(45a)** using phenylboronic acid and various catalysts.



(44) (45a)

Entry[a]	Catalyst		Additive	Solvent	T/ºC	tr/h	Yield/ %[b]	ee/%[c]
	Metal pre-catalyst (M)	L						
1	$Pd(OAc)_2$	**(26)**	NEt_3	Toluene	55	17	<10	n.d.
2	$[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$	**(26)**	NEt_3	Toluene	55	17	<10	n.d.
3	$[Rh(COD)Cl]_2$	**(23)**	KF	Toluene/H_2O	80	43	<10	n.d.
4	$[Rh(COD)Cl]_2$	**(23)**	MeOH	Dioxane	80	17	49	10
5	$[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$	**(24)**	KF	Toluene/H_2O	80	23	<10	n.d.
6	$[Rh(COD)Cl]_2$	**(46)**	MeOH	Dioxane	80	26	40	<10
7	$[Rh(COD)Cl]_2$	**(23)**	MeOH	Dioxane	100	16	52	15
8	$[Rh(COD)OH]_2$	**(46)**	3Å M.S.	Dioxane	70	15	34	30
9	$[Rh(COD)OH]_2$	**PPh_3**	K_3PO_4	Dioxane	70	18	14	*rac*
10	$[Rh(COD)OH]_2$	**PPh_3**	NEt_3	Toluene	70	18	22	*rac*
11	$[Rh(COD)Cl]_2$	**-**	$MgSO_4$	Dioxane	80	23	22	*rac*
12	$[Rh(COD)Cl]_2$	**(23)**	TMOF	Dioxane	80	17	62	<5
13	$[Rh(COD)Cl]_2$	**(23)**	KHF_2	Dioxane	80	17	96	15
14	$[Rh(COD)Cl]_2$	**(46)**	KHF_2	Dioxane	80	42	50	12
15[d]	$Rh(acac)(C_2H_4)_2$	**(46)**	KHF_2	Dioxane	55	65	14	n.d.
16[d]	$[Rh(COD)Cl]_2$	**(23)**	KHF_2	Toluene	55	21	18	18
17[d]	$[Rh(COD)Cl]_2$	**(23)**	KHF_2	Dioxane	80	18	66	<5
18[d]	$[Rh(COD)OH]_2$	**(23)**	KHF_2	Dioxane	80	18	74	<10
19[e]	$[Rh(COD)OH]_2$	**(23)**	KHF_2	Dioxane	100	24	99	<5
20[e]	$[Rh(COD)OH]_2$	**(27)**	KHF_2	Dioxane	100	24	94	<5
21[e]	$[Rh(COD)OH]_2$	**(28)**	KHF_2	Dioxane	100	24	90	<10
22[e]	$[Rh(COD)OH]_2$	**(28a)**	KHF_2	Dioxane	100	24	22	<10
23[e]	$[Rh(COD)OH]_2$	**(24)**	KHF_2	Dioxane	100	24	37	16
24[e]	$[Rh(COD)OH]_2$	**(25)**	KHF_2	Dioxane	100	24	99	<5
25[e]	$[Rh(COD)OH]_2$	**(26)**	KHF_2	Dioxane	100	24	60	<5
26[e]	$[Rh(COD)OH]_2$	**(23a)**	KHF_2	Dioxane	100	24	44	16
27[e]	$[Rh(COD)OH]_2$	**(29)**	KHF_2	Dioxane	100	24	58	13
28[e]	$[Rh(COD)OH]_2$	**(46)**	KHF_2	Dioxane	100	24	74	12
29[e]	$[Rh(COD)OH]_2$	**-**	KHF_2	Dioxane	100	24	13	n.d.

[a]Reagents and conditions: Metal pre-catalyst (3 mol% when it was the monomer and 1.5 mol% when it was the dimer), L (3.3 mol%), *N*,*N*-di-tosyl aminal **(44)** (0.12 mmol), $PhB(OH)_2$ (0.4 mmol), additive (0.4 mmol) and solvent (2 ml).

[b]Isolated yields after chromatography.

[c]Determined by chiral stationary phase HPLC. Absolute configuration not determined.

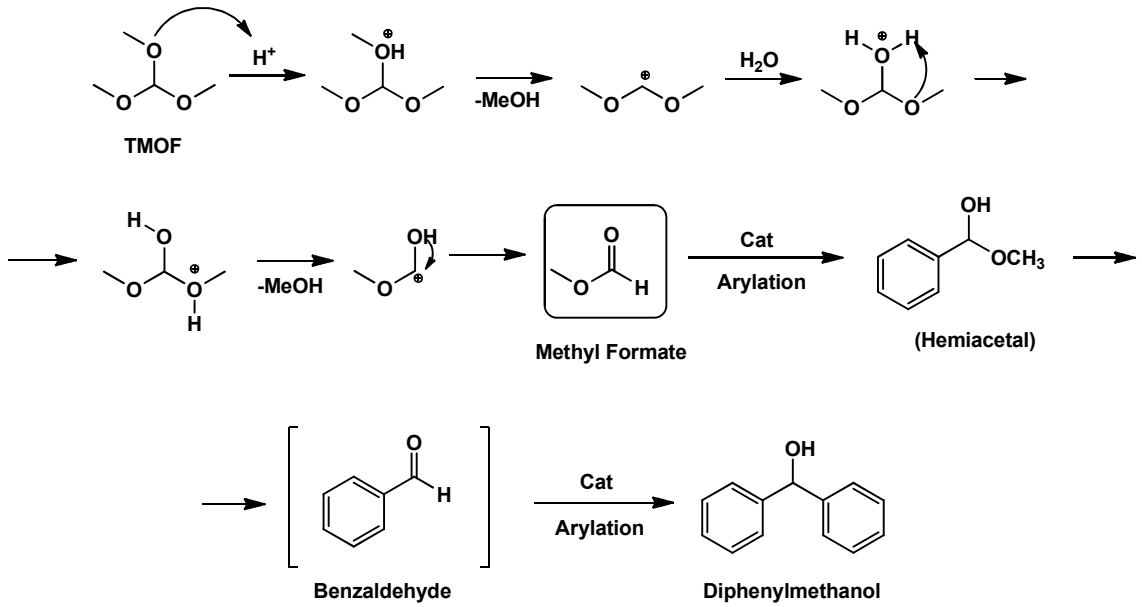
[d]KHF_2 3M (aq) was used.

[e]0.8 mmol of KHF_2 was used.

n.d.: not determined.

rac: racemic.

Discouraged by the results obtained with both Pd and Ru catalysts, we decided to use rhodium catalysts, which are highly efficient catalysts for both addition[79] and arylation[80] reactions with organoboron reagents. Upon re-adapting the literature methods of Duan[81] (Table 4.2, entry 3) and Hayashi[82] (Table 4.2, entries 4, 6 and 7) we realized that when water was used as co-solvent in combination with potassium fluoride (KF) as an inorganic base, only vestigial amounts of product **(45a)** were obtained (Table 4.2, entry 3), but, when methanol was used as the additive, moderate yields (40-52%) were obtained (Table 4.2, entries 4, 6 and 7). In the case of the use of water as co-solvent, the same effects as when using ruthenium catalysts were noted (Table 4.2, compare entries 3 and 5). Encouraged by these results we decided to study the effect of other additives in order to evaluate the reaction behavior, in the presence of water. On applying the re-adapted procedure of Hayashi, using molecular sieves (M.S.), magnesium sulfate ($MgSO_4$), trimethyl orthoformate (TMOF) and potassium diflouride (KHF_2) moderate to high yields were obtained (Table 4.2, entries 8, 11, 12 and 13, respectively). $MgSO_4$, and molecular sieves (M.S.), afforded the desired product **(45a)** in moderate yields (Table 4.2, entries 11 and 8, respectively) and the use of the water scavenger TMOF improved the reaction yield to 62% (Table 4.2, entry 12). Reducing the amount of water in the system appeared to be a priority in order to obtain good yields. On using TMOF as water scavenger, an additional problem came to our attention. As can be seen in scheme 4.17, the formation of methyl formate, which presumably gave benzaldehyde due to the instability of the hemiacetal, could in turn compete in the arylation with the aminal substrate **(44)**, to give diphenylmethanol (Scheme 4.17).[83] This possible undesired side-reaction would obviously block full conversion into the desired product **(45a)**.



Scheme 4.17. Plausible mechanism to explain the role of TMOF in lowering the reaction yield.

Potassium difluoride (KHF_2) was applied in the past by Yang and Xu[84] and Shao *et al.*[85] in the arylation of aldimines with rhodium catalysts. The use of this inorganic salt led to almost full conversion of the aminal **(44)** into the desired product **(45a)**, in 96% yield (Table 4.2, entry 13). Wang and co-workers[86] reported the arylation of nitroalkenes with boronic acids, using aqueous KHF_2 in high yields and good enantioselectivities. Despite the uncertainty of the mechanism of this reaction in the presence of water, they suggested the possibility of generating more reactive arylating reagents, like for instance potassium organotrifluoroborates[86] (see Eq. 1).

$$3\ ArB(OH)_2 + 3\ KHF_2 \xrightarrow[H_2O]{} 3\ ArBF_3K + 3\ HOF + H_2O$$

(Eq. 1)

An aqueous solution of KHF_2 (3M) was used as additive to our system (Table 4.2, entries 15 to 18). Surprisingly the yields decreased. When toluene was used as the solvent the yield of **(45a)** decrease drastically to 18%, showing a clear preference for 1,4-dioxane for this catalytic transformation (Table 4.2, compare entries 16 and 17).

$[Rh(COD)OH]_2$, a rhodium dimer pre-catalyst with many interesting applications in the literature was tested.[80,87-90] Like the other rhodium pre-catalysts, several additives were screened, among them, M.S., potassium phosphate (K_3PO_4), triethylamine (NEt_3) and potassium difluoride (KHF_2) (see Table 4.2, entries 8, 9, 10, 18 and 19, respectively). Poor yields were obtained when M.S., K_3PO_4 and NEt_3 were used as additives. Once again, KHF_2 (about 6 mol%) was the additive of choice since almost full conversion (99% yield) to the product **(45a)** was achieved (Table 4.2, entry 19). When an aqueous solution of KHF_2 (3M) was used, a decrease in the product yield was verified (Table 4.2, compare entries 18 with 19), supporting earlier speculations.

Concerning the reaction enantioselectivity, and taking an overall view of the results obtained (see Table 4.2, last column), we can conclude that they were quite disappointing (the best enantioselectivity obtained was only 30%ee!).

Basically, two important families of commercial chiral ligands were used in this study, *P*,*P*-ligands (**(23)**, **(24)** and **(26)**, Figure 4.2) and a heterocyclic diene (**(46)**, Figure 4.2). In general, the enantioselectivity values obtained (<5 to 18% ee) with the exception of 30% ee achieved using $[Rh(COD)OH]_2$, and the chiral heterocyclic diene **(46)** with no additive, beyond molecular sieves (Table 4.2, entry 8) were low. Unfortunately the yield of the reaction was only moderate (34%), perhaps due to the lack of additive, like, for example, KHF_2, or for the reasons given above. However, this result was very encouraging giving hope that high enantioselectivities could be achieved upon suitable tuning of this system. We decided to apply the optimized system (Table 4.2, entry 19) and carry out an extensive screening study of the chiral ligands (see Figure 4.2). Unfortunately, no enantioselectivity higher than 20% ee was obtained (see Table 4.2, entries 20 to 28). Moreover, almost racemic mixtures were obtained in general (Table 4.2, entries 19 to 22, and 24 and 25). Considering the fact that the reaction product **(45)** is an α-amino ester derivative, bearing a relatively acidic α-hydrogen, we

decided to run a racemization test to check if the product **(45)** was suffering racemization. The experiment was simple and consisted of carrying out the reaction with (*R*,*R*)-*i*-Pr-DuPhos **(25)** (Figure 4.2) (the experimental conditions are shown in Table 4.2, entry 24), taking samples and analyzing them by HPLC over hourly intervals for 9 hours. The results obtained are shown in Figure 4.3.

No racemization occurs on the desired product **(45)** as initially thought. So, this indicated that the low enantioselectivity was a consequence of the asymmetric induction process. The "natural" preference of a ligand for a certain coordination mode can influence the outcome of a catalytic cycle in several ways: by stabilization or destabilization of the initial, transition or final state. The flexibility of a bidentate ligand may be crucial in order to accelerate certain required transition states.

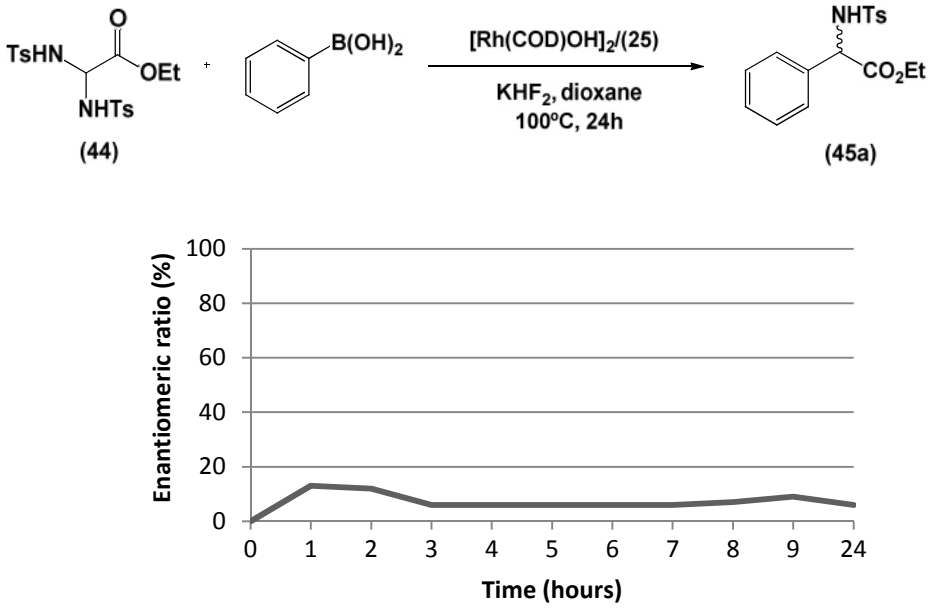
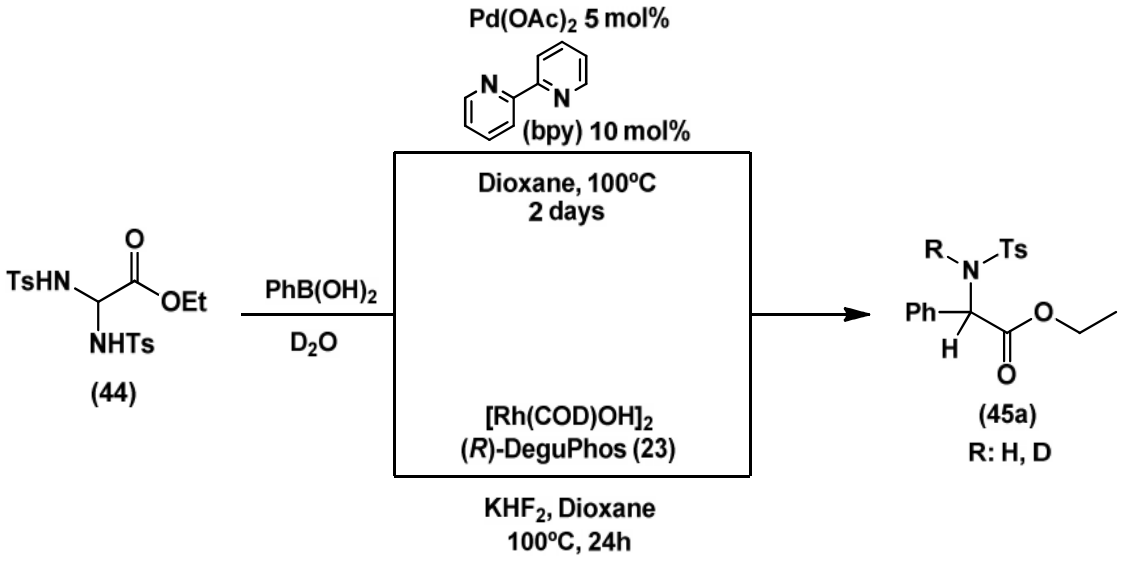


Figure 4.3. Racemization study on aminal **(44)** in the presence of $[Rh(COD)OH]_2$/**(25)** catalyst, phenylboronic acid and KHF_2 as additive.

In order to gain some insights into the mechanism of this reaction, two test reactions were made using deuterium oxide (D_2O). Using the optimized procedures for Pd and Rh catalysts (see Table 4.1, entry 1 and Table 4.2, entry

19, respectively), 3 mole equivalents of D_2O were added to the reaction vessel and left stirring for 2 days at 100ºC (Scheme 4.18). After work-up and purification by silica gel chromatography, both α-amino ester products **(45a)** were analyzed by ^1H NMR.



Scheme 4.18. Deuterium experiments conducted to probe the mechanism for the arylation of aminal **(44)** with Pd and Rh catalysts.

Despite the fact that water, in stoichiometric amounts, doesn't improve the system's efficiency, differences could be noted in the NMR spectra (Figure 4.4). We believe that, in both the Pd and Rh cases (Figure 4.4), there was no incorporation of deuterium in the α-position. But, on the other hand, there was incorporation in the N-H position, since the signal at 5.75 ppm almost disappeared.

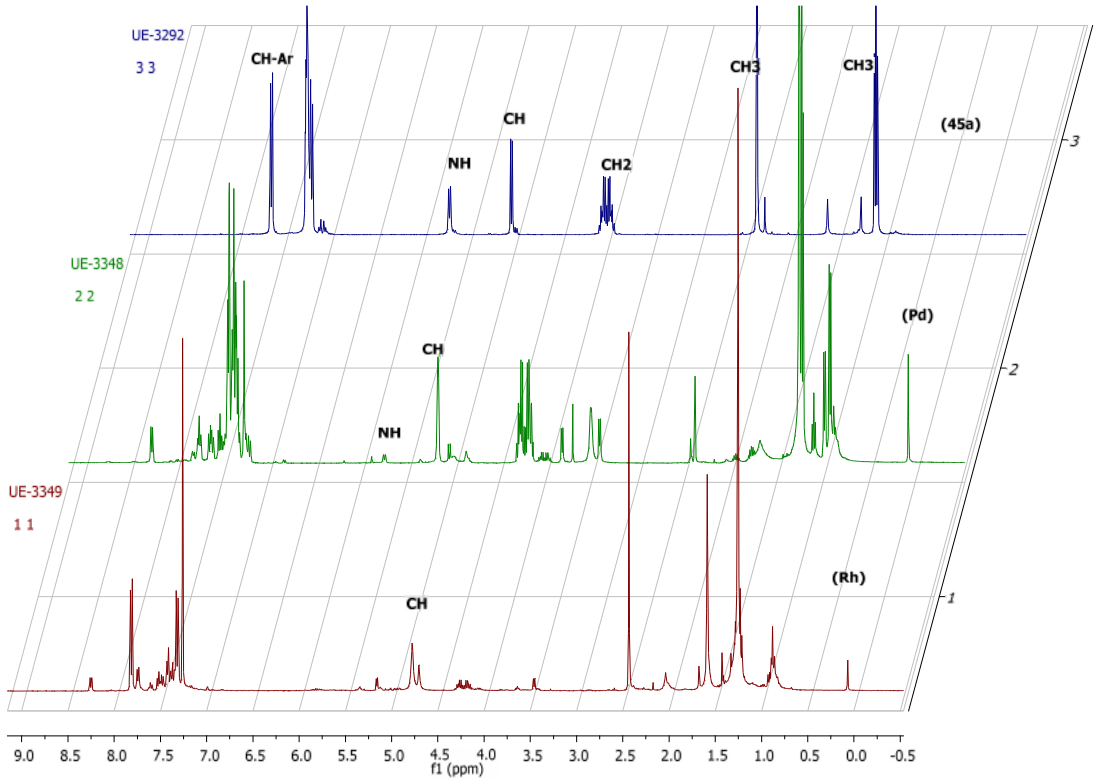


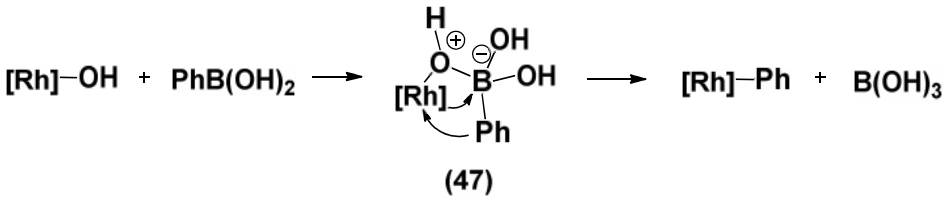
Figure 4.4. ^{1}H NMR spectra for the deuterium experiments mentioned in Scheme 4.18, made with stoichiometric amounts of D_2O using both Pd and Rh catalysts; Blue spectrum: compound **(45a)**; Green spectrum: experiment with Pd catalyst and D_2O; Red spectrum: experiment with Rh catalyst and D_2O.

It is clear, in both spectra, but more pronounced in the experiment with rhodium, that decomposition of the product ensued when there is a significant amount of water in the system.

To evaluate the scope of this reaction, we decided to conduct a screening of various phenylboronic acid derivatives, using the optimized system (see Table 4.2, entry 19). The results can be seen in Table 4.3.

Preliminary conclusions on the use of aliphatic boronic acids led us to conclude that they are ineffective in this reaction type (see Table 4.3, entries 12 to 14), and it seems to be a similar situation to when palladium catalysts were used (see Table 4.1, entries 13 to 15). The reason for this is probably explained in Scheme 4.19, where it is hypothesized that the transmetalation step is facilitated by the formation of a η^6-arene-Rh(I) complex from intermediate **(47)** (Scheme 4.19), which is not possible upon using aliphatic organoboron reagents, due to fact that

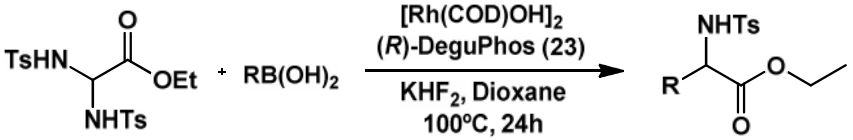
these complexes are probably less stable than the corresponding complexes containing aryl groups, and could have a propensity for β-elimination.



(47)

Scheme 4.19. Putative mechanism for the transmetalation process.[80]

Table 4.3. Screening of a variety of organoboron reagents for the transformation of the aminal **(44)** to the α-amino ester **(45)**, using a rhodium (I) catalyst.



(44) (45)

Entry[(a)]	R	α-amino ester (45)	Yield/%[(b)]
1	2-Naph	**b**	74
2	2-$CH_3OC_6H_4$	**c**	83
3	4-ClC_6H_4	**d**	61
4	3-$CH_3OC_6H_4$	**e**	0
5	3-AcC_6H_4	**f**	0
6	1-Naph	**g**	99
7	4-FC_6H_4	**h**	0
8	3-$PhCH_2OC_6H_4$	**i**	25
9	3-HOC_6H_4	**j**	0
10	3-$NH_2C_6H_4$	**k**	17
11	1-Fur	**l**	0
12	CH_3	**m**	0
13	CH_3CH_2	**n**	0
14	$CH_3(CH_2)_{11}$	**o**	0

[(a)]Reagents and conditions: $[Rh(COD)OH]_2$ (1.5 mol%), (*R*)-DeguPhos **(23)** (3.3 mol%), aminal **(44)** (0.12 mmol), $RB(OH)_2$ (0.4 mmol), KHF_2 (0.8 mmol) and dioxane (2 ml).
[(b)]Isolated yields after chromatography.

With regard to the other arylboronic acids, almost full conversion into **(45g)** was obtained using 1-naphthylboronic acid (Table 4.3, entry 6). Moderate to good yields (60 to 83%) were achieved for 2-naphthyl, 2-methoxyl and 4-chlorophenyl boronic acids (Table 4.3, entries 1, 2 and 3, respectively). We believe that the relative position of the substituents in the aromatic system had an effect on the type of yields obtained. Generally, substituents placed in the *meta*-position of the aromatic ring failed to provide the desired α-amine ester derivative (Table 4.3, entries 4, 5 and 9) and in the case of 3-benzyloxyboronic acid and 3-aminophenylboronic acid (Table 4.3, entries 8 and 10, respectively) only vestigial quantities of the relevant products were obtained. This fact, led us to assume that the transmetalation step was somewhat blocked when a *meta*-substituent was placed in the aromatic system, perhaps due to steric hindrance when rhodium coordinates with the aromatic system.

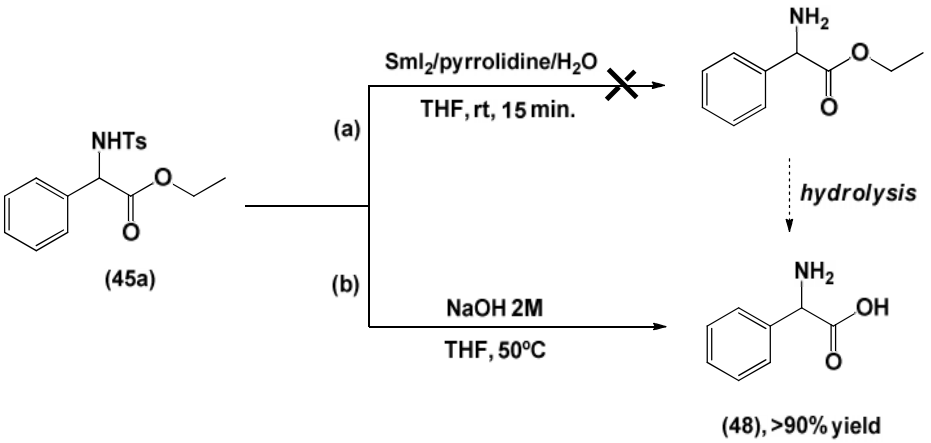
It should be noted that due to time constraints no enantioselectivities for the reactions screened in this study were measured, despite the fact that the reactions were performed using a chiral phosphane ligand (**(23)**, Scheme in Table 4.3).

4.2.4. Synthesis of an unnatural α-amino acid from an α-amino ester

Despite the low enantioselectivity values obtained using the optimized method described above, and due to the high yields obtained with this new synthetic procedure, we were interested in developing a simple and robust methodology to give amino acids, like phenylglycine[5,91,92] (**(48)**, Scheme 4.20).

Hilmersson and Ankner[93] reported an interesting method for the deprotection of tosyl amides employing SmI_2/amine/water, in near quantitative yield, under mild conditions. Aggressive protocols exist in literature,[94] which include acid hydrolysis with strong acidic reagents and the use of lithium or sodium as one-electron donors in combination with various electron carriers, but we decided to test the simple and mild protocol reported by Hilmersson and Ankner. The use of

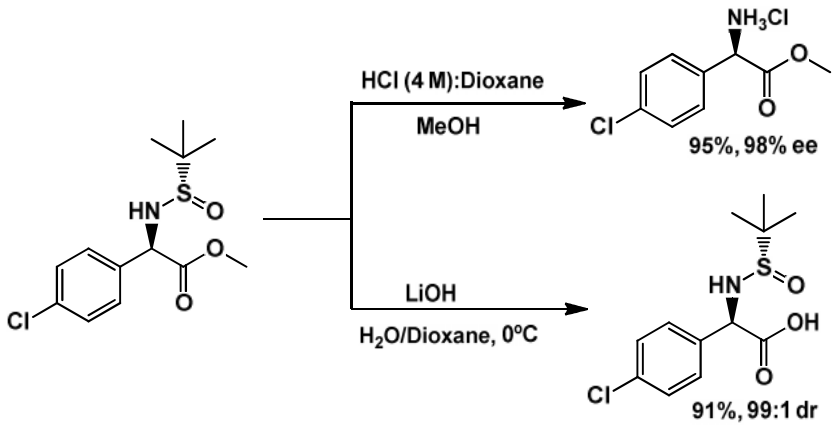
samarium iodide has already been reported in literature, as it was successfully applied for the deprotection of various tosyl protected amine groups.[81,95] Unfortunately, after purification of the crude product, only the starting material was obtained (Scheme 4.20, path a).



Scheme 4.20. The methodologies applied for the transformation of **(45a)** into **(48)**.

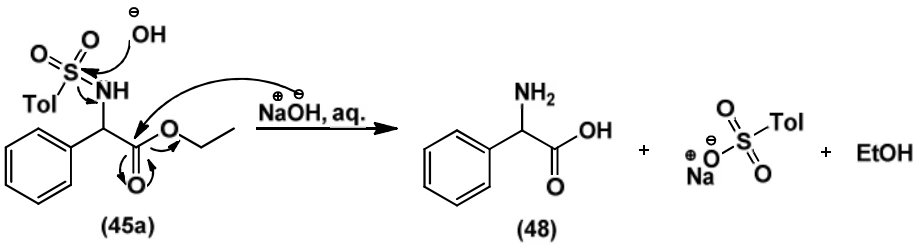
Ellman's group published an interesting report concerning the diastereoselective synthesis of protected arylglycines using rhodium catalysts and organoboron reagents, where the issues of sulfonyl group deprotection were discussed (Scheme 4.21).[96]

Selective deprotection of the sulfinyl group or of the ester group could be accomplished in high yields with no loss in stereochemical purity, applying these simple procedures (see Scheme 4.21).



Scheme 4.21. Selective amine and carboxyl group deprotection of a protected arylglicine by Ellman's group.[96]

Taking into account the work described by Ellman and co-workers, we decided to apply the basic conditions described by these workers to our 2-(4-*N*-tosyl) protected phenylglycine **(45a)** (see Scheme 4.20, path b) with the hope that we could deprotect both the amine and hydrolyze the ester in one step. Analysis of the spectral data revealed that the desired α-phenylglycine **(48)** was obtained in an excellent yield of >90%. The proposed reaction mechanism is shown in Scheme 4.22. This compound, phenylglycine **(48)**, is an important unnatural amino acid.



Scheme 4.22. Outline for the proposed mechanisms for the deprotection of the amino group and of the carboxylic acid group, using aqueous basic conditions (Note: This probably takes place in a step-wise manner).

4.3. Conclusions

In this chapter we described a new catalytic reaction, where an aminal substrate along with arylboronic acids affords α-amino esters, which are important precursors for the synthesis of unnatural α-amino acids. This new alternative and innovative method to access amino acids gave a variety of α-amino ester precursors with moderate to good yields. Some mechanistic studies were conducted to obtain key insights on the nature of this reaction. The use of aliphatic boronic acids was found to be unsuccessful for this particular transformation.

Two transition metals: palladium and rhodium, where studied. Unfortunately, in general, we couldn't obtain enantioselectivities higher than 30% ee, despite the variety of chiral ligands tested.

It was possible to easily carry out an amino and carboxyl group deprotection of the *N*-tosyl protected ethylphenylglycinate **(45a)** to give α-phenylglycine, a component of the antibiotic Ampicillin, in high yield.

4.4. References

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5. Sequential one-pot Catalytic Homogeneous and Heterogeneous Arylation: Synthesis of bi-Aryl units

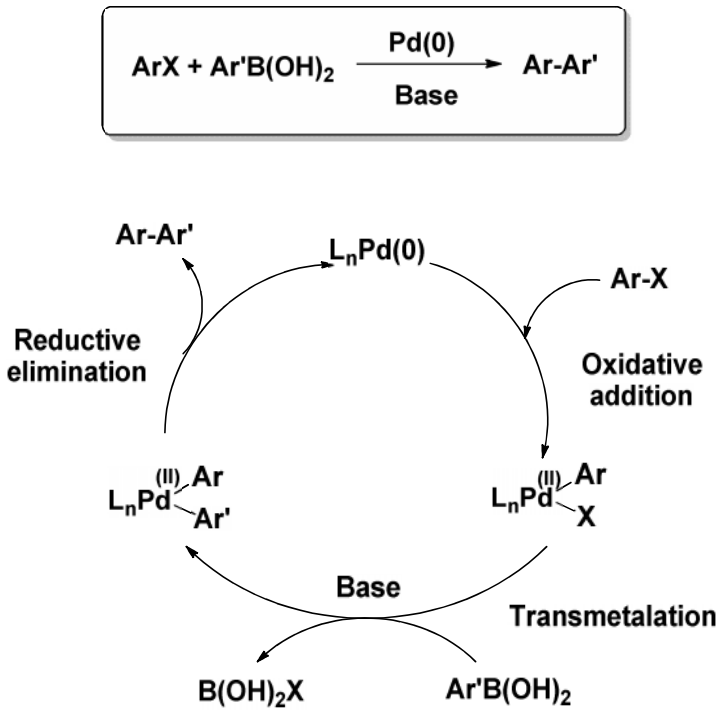
"Anyone who has never made a mistake has never tried anything new".
Albert Einstein

5.1. Introduction

Organometallic reagents play a key role in the selective and controlled formation of carbon-carbon bond forming reactions, but there is even more of a need to develop economical methods, for achieving this objective. Throughout this research work, the application of organoboron reagents in the formation of new C-C bonds using organometallic catalysts was developed, exploiting and harnessing new processes along the way. In this last chapter, which focuses on the issue of sustainable, green and atom economical processes, the application of organoboron reagents in both homogeneous and heterogeneous sequential catalytic processes is discussed.

When we think of the formation of C-C bonds using organoboron reagents, we automatically think of the Suzuki-Miyaura reaction.[1] This reaction involves coupling between an aryl or vinyl-boronic acid and an aryl or vinyl-halide catalyzed by palladium (0) complexes (see Scheme 5.1). In fact, the impact of this catalytic reaction has been immense, and it is reflected in the huge amount of publications described in the literature in the last 30 years.[2,3] This process has become arguably one of the most efficient methods for the construction of biaryl or substituted aromatic moieties, polymer building blocks,[4] ligands,[5] a plethora of natural products[6] and active pharmaceuticals.[7,8] The key advantages of the Suzuki-Miyaura coupling are the mild conditions, the high tolerance toward various functional groups and the commercial availability and stability of organoboron reagents to: heat, oxygen and water, and with the easy work-up involved, it really makes this a very desirable synthetic method.

The well-studied mechanism[9] for this catalytic transformation involves an oxidative addition of the corresponding aryl-halide to a coordinately unsaturated palladium $L_nPd(0)$ complex, forming the intermediate $L_nPd(II)(Ar)(X)$ complex. Further transmetalation between an organoboronic acid assisted by a base leads to the formation of the palladium intermediate $L_nPd(Ar)(Ar')$. Finally, a reductive elimination producing the coupled product and concomitant regeneration of the initial complex -$L_nPd(0)$- completes the cycle (see Scheme 5.1). Biaryl units, the principle products resulting from the reaction mentioned above, are essential backbones found in the skeleton of many important biologically active compounds.



Scheme 5.1. A general catalytic cycle for the Suzuki-Miyaura cross coupling; (L_n: ligands) (focusing on aryl-aryl coupling with arylboronic acids).

For example, Valsartan[10] (Diovan®) (Figure 5.1), an important angiotensin receptor blocker indicated for treatment of high blood pressure, congestive heart failure or post-myocardial infarction contains a biaryl unit in its backbone. Another interesting example is the well-known glycopeptide antibiotic Vancomycin[11] (Figure 5.1), used for prophylaxis and treatment of infections caused by Gram-positive bacteria. Boscalid[12] (Figure 5.1), a fungicide developed by BASF, and with many applications in agriculture, is another example, demonstrating the range of compounds with biaryl units in their structure.

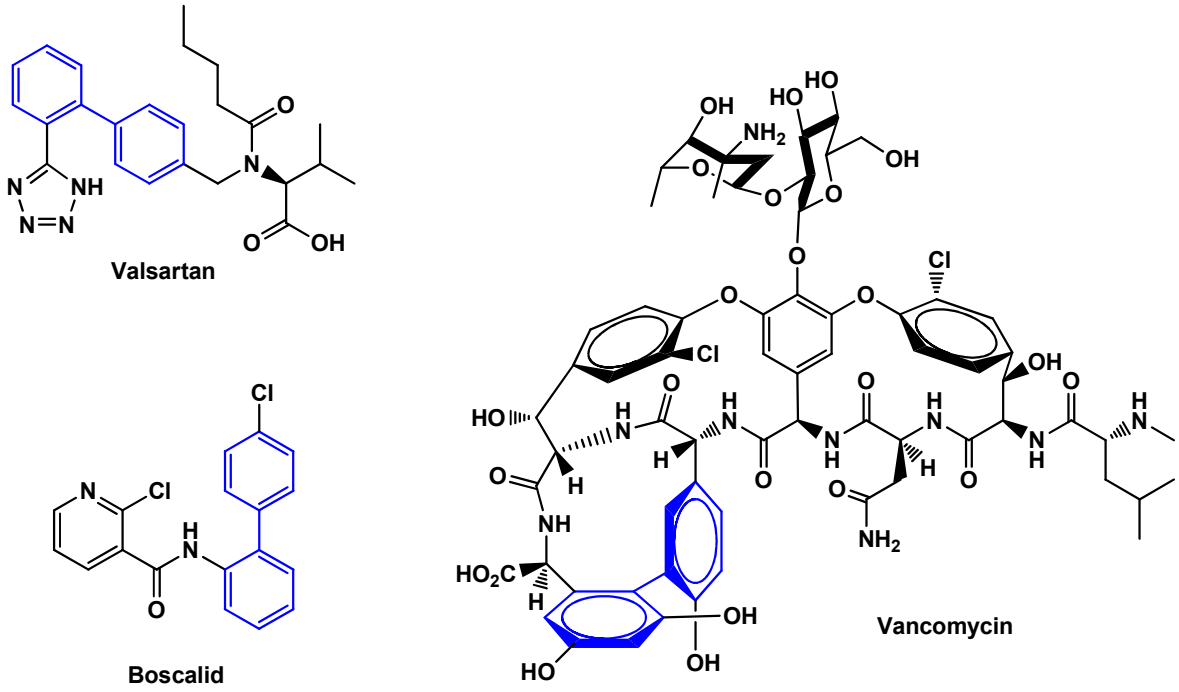
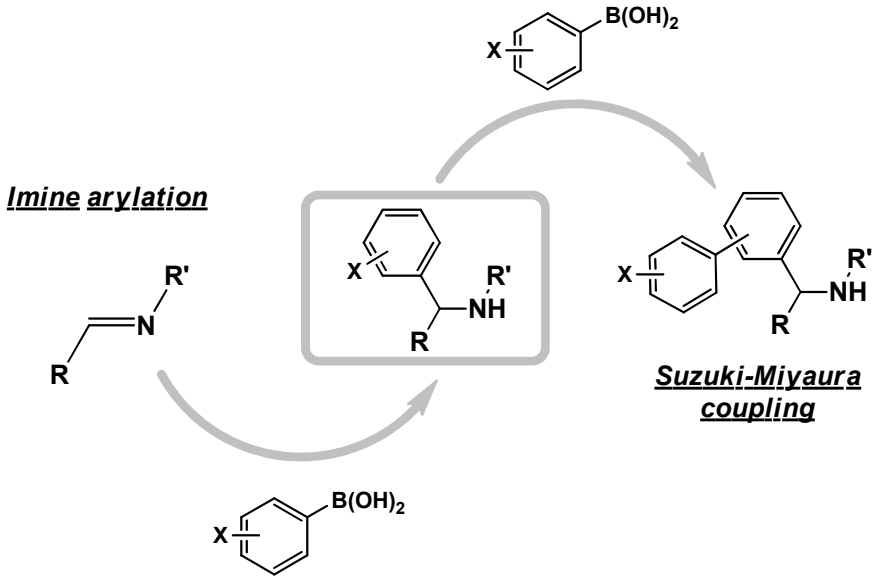


Figure 5.1. Some important biologically active compounds containing a biaryl unit in their structure.

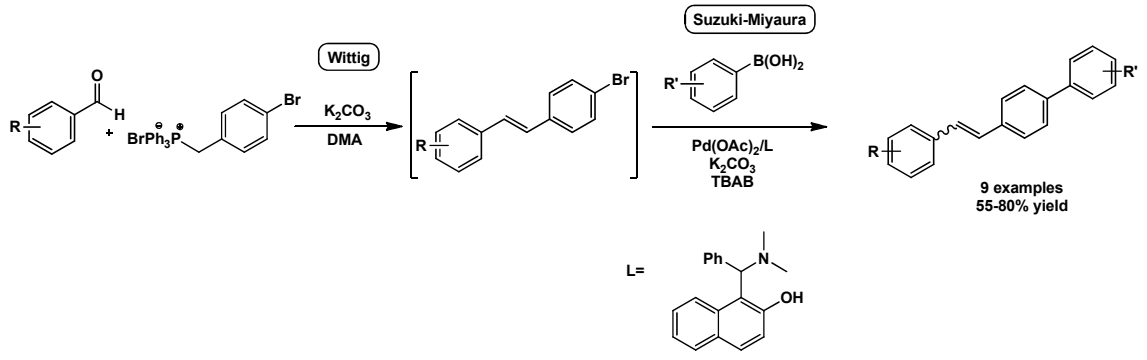
At the moment, the design of more concise, efficient synthetic methods, particularly those that involve cascade, domino, sequential or even tandem catalytic events are top priority areas of research and application.[13] Whereas most of the early work was focused on using a catalyst for one reaction at a time, currently, the goal is to employ a single catalyst for more than one transformation in a single reaction vessel.

Using our expertise in this area, our goal was to design a new synthetic method to afford biaryl units using a combination of the Suzuki-Miyaura cross coupling reaction and the arylation of the activated imine unit, with an organometallic catalyst and an organoboron reagent (Scheme 5.2). In essence this is *via* an innovative sequential catalytic process.



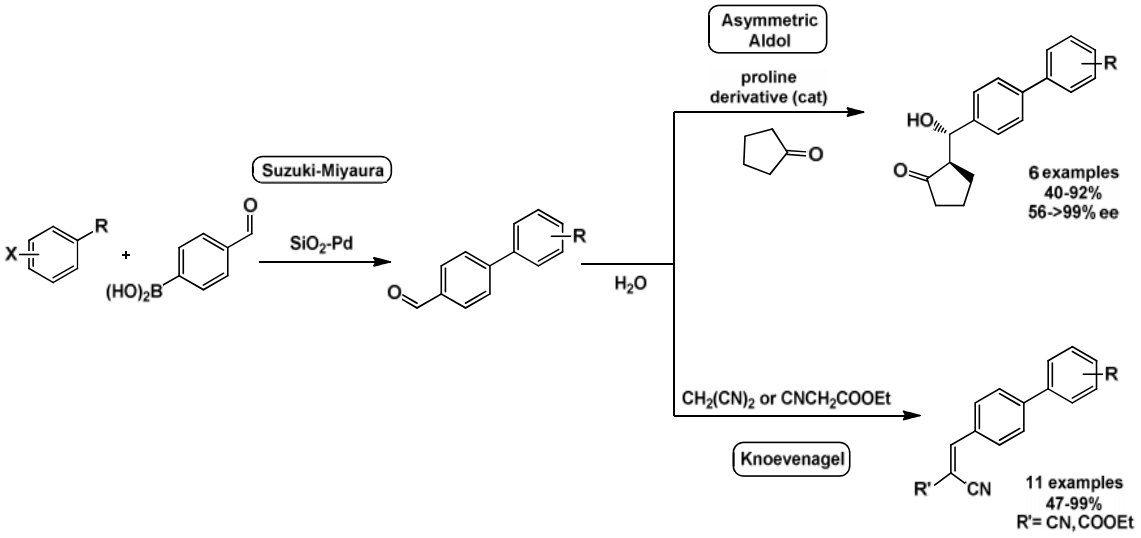
Scheme 5.2. Formation of carbon-carbon single bonds using the Suzuki-Miyaura coupling reaction and the arylation of imines.

Despite the fact that no reports were found in the literature on this one-pot methodology, important one-pot catalytic reactions have been described. For instance, Chaudhary and Bedekar[14] reported recently a novel one-pot two-step cascade reaction strategy involving Wittig and Suzuki-Miyaura reactions for the efficient synthesis of 4-styryl biphenyl units with phosphine-free Pd catalysts(Scheme 5.3). The reduced consumption of reagents, such as solvents (for the reaction and for purification) and, as well as savings in energy, offer many advantages which can make this a greener process.



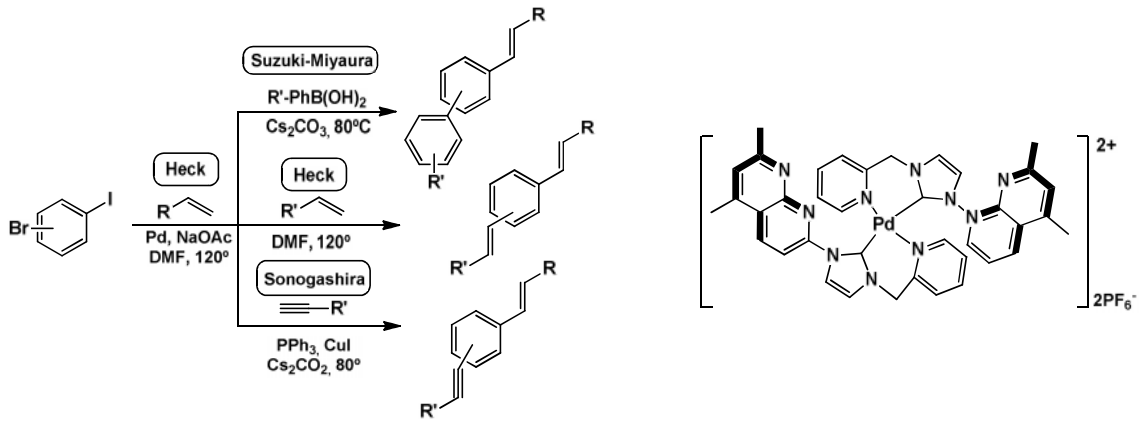
Scheme 5.3. The one-pot Wittig olefination–Suzuki-Miyaura coupling reaction reported by Chaudhary and Bedekar.[14]

Gruttadauria *et al.*[15] demonstrated the feasibility of sequential Suzuki-Miyaura/asymmetric aldol and Suzuki/Knoevenagel reactions, under aqueous conditions (Scheme 5.4). A supported palladium catalyst, along with a proline derivative was used successfully in the organocatalytic asymmetric aldol reaction coupled with the Suzuki-Miyaura reaction. The good results obtained in the case of Suzuki-Miyaura/Knoevenagel sequential reaction demonstrated the synthetic utility of this approach, taking into account the use of the same supported palladium catalyst.



Scheme 5.4. Sequential Suzuki-Miyaura/asymmetric aldol and Suzuki-Miyaura/Knoevenagel reactions with supported palladium catalysts under aqueous conditions.[15]

A successful one-pot coupling reaction requires that the catalyst is highly efficient and chemioselective towards the first coupling and maintains its catalytic activity in the subsequent coupling.[16] Through a Pd-NHC complex, Chen and co-workers reported the high yielding synthesis of unsymmetrically substituted arenes by sequential Heck/Suzuki-Miyaura, Heck/Heck and Heck/Sonogashira coupling reactions of aryl di-halides and several di-functionalized arenes (Scheme 5.5).[17] The use of a multifunctional catalyst for one-pot reactions generates less waste and also obviates the tedious separation and purification of the intermediate products.



Scheme 5.5. The Pd-NHC catalyzed one-pot sequential Heck/Suzuki-Miyaura, Heck/Heck and Heck/Sonogashira coupling reactions of aryl di-halides, developed by Zhang and Chen.[17]

5.1.1. Heterogeneous catalysis: The Palladium Situation

Due to the high cost of organometallic catalysts, particularly the chiral examples, including their potential detrimental environmental effect, improved procedures for recycling are crucial. Besides this, by immobilizing these catalysts it was envisaged that it would be possible, to fine-tune both the steric and electronic properties of the catalyst, in order to improve their efficacy. In fact, characterization of heterogeneous palladium catalysts on the molecular level is still a problem,

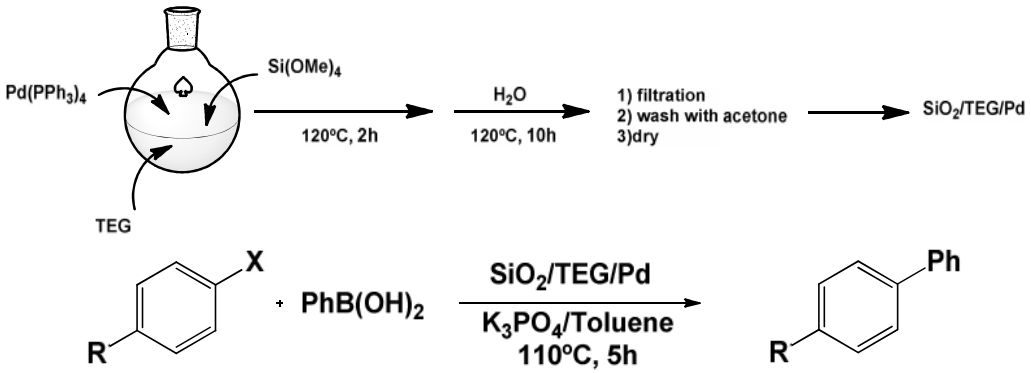
although scanning electron microscopy (SEM) or transmission electron microscopy (TEM), x-ray diffractometry, elemental analysis (EA) and infra-red (IR) spectroscopy allow important insights into the structure.[18]

A number of solid materials[19,20] such as carbon structures,[21,22] polymers,[23,24] and mesoporous silica[25,26] have been employed as supports for palladium catalysts. Regarding the Suzuki-Miyaura cross coupling reaction, useful silica-supported palladium catalysts were prepared in various ways providing different structures and activity. In general, the reaction follows the usual reaction mechanism (as for homogeneous catalysis, see Scheme 5.1) but a full understanding of the mechanism under heterogeneous conditions still remains an open question. Palladium can directly be deposited onto silica by physiosorbtion or it can be anchored as a complex,[27] depending on the type of support used. Apart from the immobilization technique, important parameters[28,29] like the loading of the active metal catalyst, its surface area, dispersion onto the solid support (typically only 10-60% of the metal atoms are exposed), the size of the particles, the oxidation state, acid-base properties, the type and suitability of the counter ions and the water content, must be taken into account. It is well known, that the support can have an impact on the activity of the catalytic system and thus a critical evaluation of these parameters should definitely be considered.[28]

Unfortunately, this technique is frequently hampered by leaching issues, including changes in the crystalline structure of the palladium or even chemical changes in the structure of the ligands complexed to the catalyst.[29-31] Congestion of the catalyst by byproducts formed during the catalytic reactions is another important issue and it inevitably leads to a decrease of activity.[32]

The first example of the Pd/C catalyzed Suzuki-Miyaura reaction was reported in 1994 by Marck and Buchecker.[33] In general Pd/C was used with[21,34] or without[35,36] additional phosphine ligands and often the application of aqueous solvents was advantageous. Several other supported palladium catalysts were applied with success in the Suzuki-Miyaura arylation. Pd can be directly deposited onto silica (physisorption) or it can be anchored as a complex, by covalent bonds to the silica (in this case grafting a ligand, by means of a spacer group could post-modify the silica spheres, thus altering their morphology). A highly active Pd catalyst on amorphous silica (SiO_2/TEG/Pd) was prepared by Kim and co-

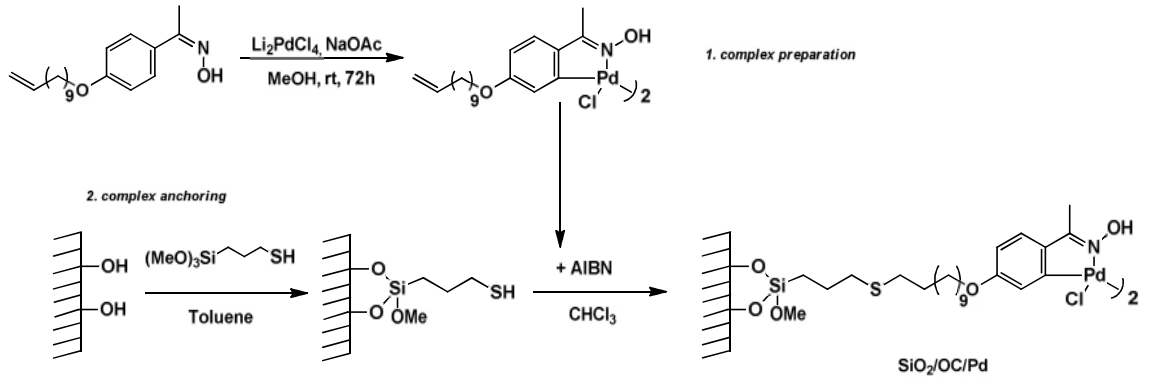
workers,[37] and this was used for Suzuki-Miyaura coupling reactions. The Pd nanoparticles were obtained from $Pd(PPh_3)_4$ in tetra(ethylene glycol) (TEG) and tetramethoxysilane (Scheme 5.6), which became encapsulated in the silica matrix. Its efficiency was established by using aryl iodides and aryl bromides as substrates, but was ineffective for aryl chlorides (Scheme 5.6). The authors determined that the catalyst could be reused three times without losing activity. The problem of using less reactive aryl chlorides was solved by Crudden and Lewis,[25] using a palladium catalyst on a thiol-modified mesoporous silica (SBA-15-SHPd). The authors showed that it could be used four times without any loss of catalytic activity. Corma and co-workers[38] developed an oxime–carbapalladacycle (OC/Pd) catalyst that was covalently anchored to silica (SiO_2/OC/Pd) and proved to be an efficient catalyst for use in the Suzuki reaction (Scheme 5.7). The catalyst gave a quantitative yield of the product with aryl chlorides in water. Leaching wasn't detected and the catalyst was reused eight times without loss of activity.



X	R	Yield/%
I	CO_2Me	100
Br	H	86 (12h)
Br	CO_2Me	100
Br	CHO	98
Br	CF_3	98
Cl	CO_2Me	<5

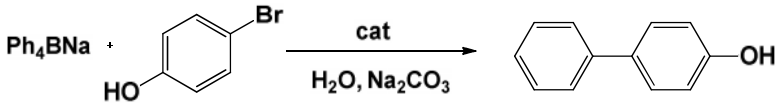
Scheme 5.6. Preparation of SiO_2/TEG/Pd and its use as a catalyst in the Suzuki-Miyaura reactions by Kim and co-workers.[37]

Palladium based catalysts supported in clays or other inorganic materials also proved their efficiency in the Suzuki-Miyaura coupling reactions. For instance Shimizu *et al.*[39] applied Pd(II)-sepiolite to the Suzuki-Miyaura coupling of 4-bromophenol with phenylboronic acid or sodium tetraphenylborate in water at room temperature in air. It provided higher yields than unsupported Pd(II) salts and some other supported-Pd catalysts (Table 5.1).



Scheme 5.7. Anchoring procedure of an oxime-carbapalladacycle onto mercaptopropyl modified high surface silica.[38]

Table 5.1. Comparison of several supported catalysts in the Suzuki-Miyaura reaction of 4-bromophenol with Ph_4BNa.[39]

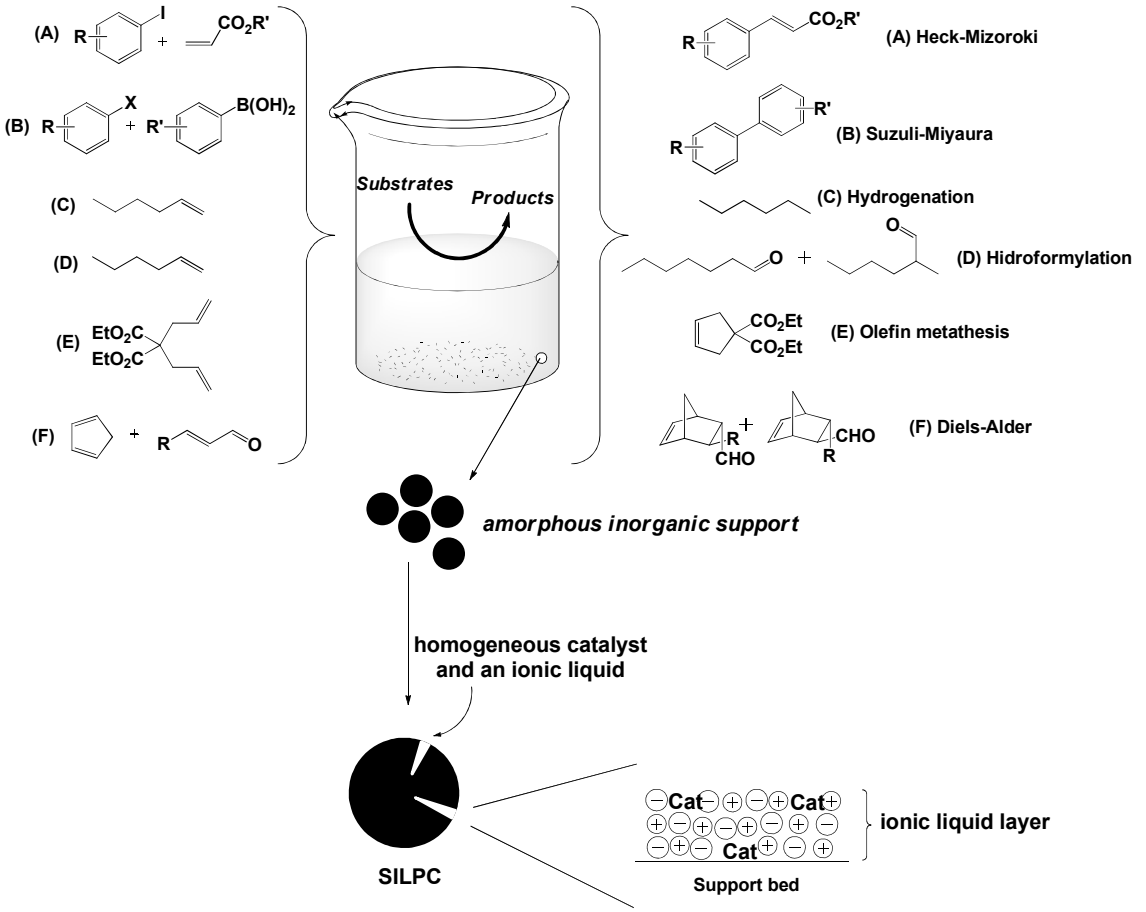


Entry	Cat (wt %)[(a)]	GC yield/%
1	Pd–sepiolite (0.5)	99
2	Pd–NaY (0.7)	83
3	Pd–mica (0.7)	73
4	Pd/C (2)	23
5	Pd–SiO_2 (0.5)	57
6	$PdCl_2$	47
7	$Pd(OAc)_2$	36
8	$Pd(OAc)_2$[(b)]	43

[(a)]Pd content of the supported catalyst.
[(b)]Catalyst loading = 1.0 mol%.

By supporting the catalyst in a thin liquid layer, adsorbed within the pores of a microporous solid it is possible to enhance the efficacy of this process.

Immobilization in a liquid support enhances the solubility of the catalyst without changing its original structure and catalytic activity. Obviously, the main requisite feature of having a liquid support is to dissolve both the substrates and catalysts without dissolving the solvents. Among many possible candidates, ionic liquids (ILs) are very suitable due to immiscibility in both water and common organic solvents.[40,41] But more importantly, Suzuki-Miyaura reactions have been performed with success in ILs.[42-45] The most notable characteristics of ILs in regard to catalysis are their stabilizing ability and propensity for recycling. In order to improve the cost and handling of the catalyst for recycling, as well as bearing in mind scale-up issues, Supported Ionic Liquid Phase Catalyst (SILPC) systems were devised. As the name suggests, a fine film of the requisite ionic liquid is coated over a relevant solid support, which is usually a porous solid such as silica[46] or molecular sieves.[47] This process combines the advantages of ionic liquids with those of heterogeneous support materials. The IL is attached either by covalent attachment to the support or by simple adsorption/deposition (physisorption), the catalytically active species is contained in the ionic liquid. This technique is a welcome alternative for the immobilization of transition metal complexes.[48] The SILPC system have been used in several catalytic reactions such as the Heck-Mizoroki reaction[49] (A, Scheme 5.8), Suzuki-Miyaura reaction[50] (B, Scheme 5.8), catalytic hydrogenation[51] (C, Scheme 5.8), hydroformylation[52] (D, Scheme 5.8), olefin metathesis reaction[46] (E, Scheme 5.8) and asymmetric Diels-Alder reaction[53] (F, Scheme 5.8). The versatility of the technique makes it possible to immobilize noncovalently a variety of homogeneous catalysts. The reactivity and stability of the SILPC is enhanced relative to that in more traditional heterogeneous supports. Due to the small amounts of the IL needed, the cost is significantly lowered. The recycling process was successful in all the reactions tested to date, with the possibility of recycling up to 6 times without loss of activity.

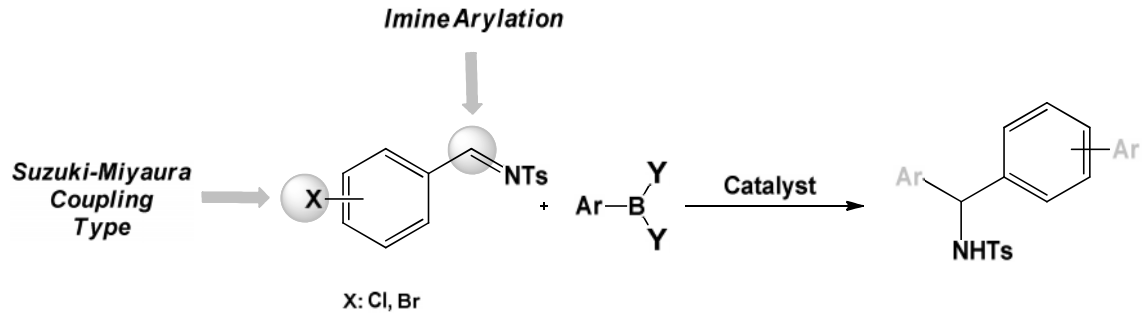


Scheme 5.8. Supported Ionic Liquid Phase Catalyst (SILPC) system and several examples of different reaction types performed, with this technique.

5.2. Results and Discussion

5.2.1. Homogeneous Catalysis

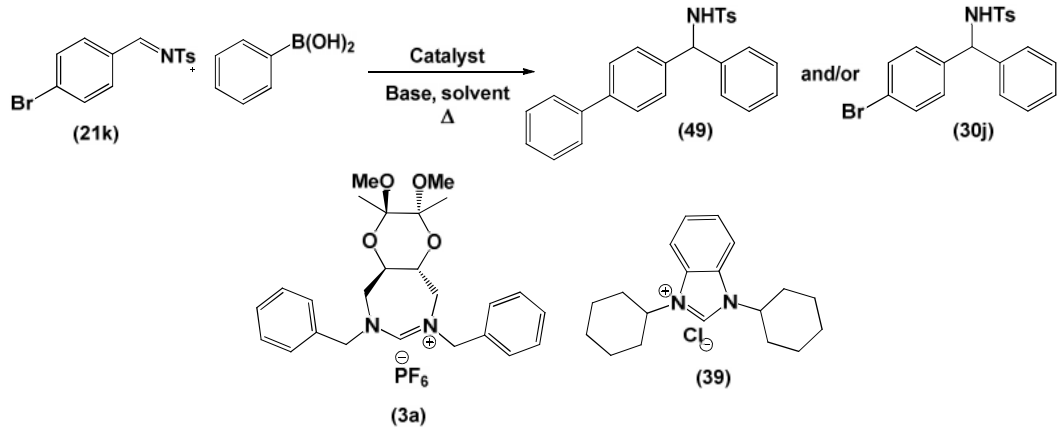
Motivated by an interest in the development of more concise, efficient synthetic methods, particularly those that involve one-pot reactions, a key catalytic study was investigated with certain aldimines having halogens in the phenyl ring (see Chapter 2) and phenylboronic acid to determine if a sequential double one-pot C-C bond-forming reaction could occur (Scheme 5.9).



Scheme 5.9. Sequential catalytic double one-pot C-C bond-forming reactions.

Starting with the aldimine previously synthesized **(21k**) (see Chapter 2), and armed with several methods from the literature[54,55] we conducted a series of reactions with palladium catalysts and phosphane and NHC ligands. The results can be seen in Table 5.2.

Table 5.2. Optimization of the catalytic reaction conditions to afford **(49)**.



Entry[a]	Catalyst	Base	Solvent	T/ºC	Tr/h	Yield (20)/%[b]	TON	TOF /h
1	$Pd(OAc)_2$/**(39)**	Cs_2CO_3	DMF	120	16	<5	<1.3	<0.08
2	$Pd(OAc)_2$/**(3a)**	Cs_2CO_3	DMF	120	16	<5	<1.3	<0.08
3	$Pd(OAc)_2/PPh_3$	NEt_3	Toluene	100	16	38	13.0	0.81
4	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	Toluene	100	40	13	4.8	0.12
5	$Pd(OAc)_2/PPh_3$	NaOMe	Toluene	100	40	58	12.5	0.31
6[c]	$Pd(OAc)_2/PPh_3$	NEt_3	Toluene	100	21	58	14.5	0.69

[a]Reagents and conditions: aldimine **(21k)** (0.5 mmol), catalyst (3 mol%), $PhB(OH)_2$ (4 mol equiv), base (4 mol equiv), solvent (2 ml).
[b]Overall isolated yield (2 steps), after purification with silica gel chromatography.
[c]Ph_3B was used instead of $PhB(OH)_2$.

Using $Pd(OAc)_2$ as pre-catalyst and the commercial NHC precursor (**39**, see Chapter 3) or our novel NHC precursor (**3a**, see Chapter 1) only vestigial quantities of the desired product **(49)** were obtained (Table 5.2, entries 1 and 2, respectively). In fact, several secondary products were visualized by TLC, by comparing with the arylated amine **(30j)** already synthesized (used as a standard) we believe that the secondary product was the arylated amine **(30j)**. It must be noted that even some alcohol traces were observed (see Chapter 2). Unsatisfied with the results obtained with these NHC type ligands, we used triphenylphosphine (PPh_3) to probe the reactivity of this reaction. The overall yields for two steps were good (Table 5.2, entries 3 to 6), with 58% the best value obtained (Table 5.2, entries 5 and 6). The use of sodium methoxide (NaOMe) as base improved the yield comparatively to the use of NEt_3, but an increased reaction time was required (compare entries 3 and 5, Table 5.2). The alternative organoboron reagent: triphenylborane (Ph_3B) was used (Table 5.2, entry 6) and the same yield of 58% was obtained with a lower reaction time. Even so, TLC analysis revealed several unidentified secondary products that we suspected to be the arylated amine **(30j)** and *p*-bromophenyl(phenyl) methanol (see Figure 5.3, diaryl alcohol – X= *p*-Br).

In Table 5.2 we show the turnover number (TON) and the turnover frequency (TOF), with the objective to compare the efficiency of the different catalysts. So far, there is no IUPAC definition for the TON, but, according to literature precedents, it could be defined as the maximum use that can be made of a catalyst for a special reaction under defined reaction conditions by the number of molecular reactions or reaction cycles occurring at the reactive center up to the decay of activity. The TOF is a measure of the instantaneous efficiency of a catalyst, calculated as the derivative of the number of turnovers (TON) of the catalytic cycle with respect to the time per active site.[56,57] TONs and TOFs of about 1000 and 500 h^{-1}, respectively, represents the ideal catalyst applied in industrial processes. In Table 5.2, the low TONs and TOFs presented give the idea that the catalysts used have low activity (high reaction time) in the catalytic reaction or decomposed quickly.

Although phosphane based ligands have been investigated most intensively in cross coupling reactions,[3,7] recently NHC ligands have received much attention due to their remarkable properties, among them the relatively high thermal stability of the Pd-C(NHC) bond.[58] So, at this point we decided to examine other options for the sequential dual-catalytic reaction. In 2005, Organ and co-workers[59] developed an elegant Pd-NHC catalyst system built around a simple concept. This family of catalysts, called PEPPSI (an acronym for *Pyridine Enhanced Pre-catalyst Preparation, Stabilization and Initiation*) (Figure 5.2) are extremely stable to air and moisture, they are commercialized on a kilo scale, are cost-competitive and a one component catalyst, with no need for additional ligands. The 3-chloropyridyl ligand functions as a "throw-away" ligand, while the bulky NHC ligand improves reductive elimination of the product, increasing their activity over other Pd catalysts. The α-donating power of the NHC ligand also binds the metal more tightly than traditional phosphanes and thus prevents metal dissociation.

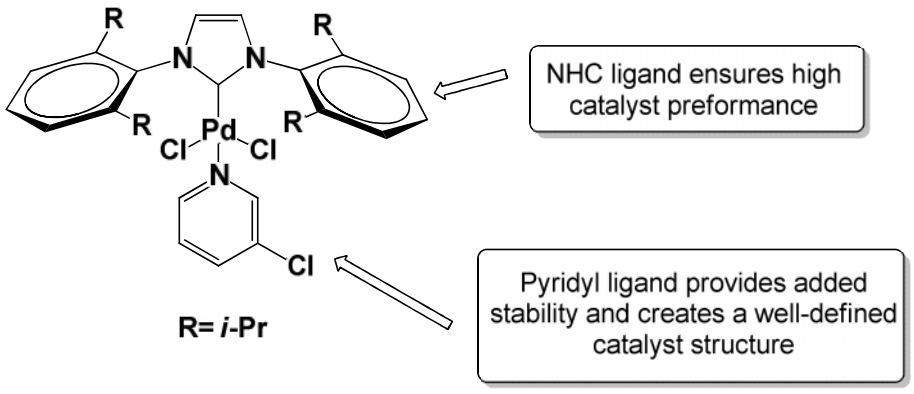


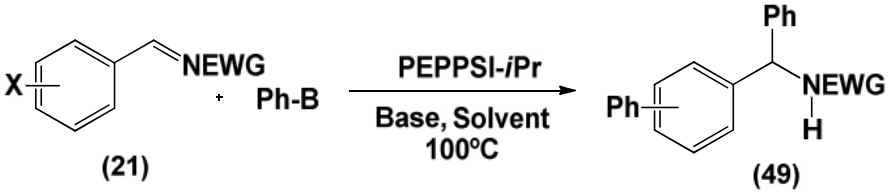
Figure 5.2. (1,3-Diisopropylimidazol-2-ylidene)(3-chloropyridyl) palladium (II) dichloride (PEPPSI-*i*Pr).

The application of PEPPSI-*i*Pr catalysts was successful in bench-mark catalytic reactions such as Negishi couplings,[60-62] Suzuki-Miyaura couplings,[59] Buchwald-Hartwig aminations,[63] Kumada-Tamao-Corriu reactions[64,65] and in a one-pot

methodology to afford indoles by sequential Aryl Amination/Heck-Mizoroki Coupling.[66]

Hereupon we decided to investigate the commercial PEPPSI-*i*Pr catalyst in this sequential catalytic reaction. Several conditions were screened (Table 5.3).

Table 5.3. Sequential dual-catalytic arylation of aldimines with PEPPSI-*i*Pr catalyst.



(21) (49)

Entry [a]	aldimine (21)			Ph-B	Base	Solvent	Tr/h	Yield/ %[b]	TON	TOF /h
	X	EWG								
1	*p*-Br	Ts	**21k**	$PhB(OH)_2$	NEt_3	Toluene	19	36	12.2	0.64
2[c]	*p*-Br	Ts	**21k**	$PhB(OH)_2$	KO^tBu	*i*-PrOH	24	0	-	-
3	*p*-Br	Ts	**21k**	$PhB(OH)_2$	Cs_2CO_3	*i*-PrOH	24	0	-	-
4	*p*-Br	Ts	**21k**	$PhB(OH)_2$	NEt_3	Dioxane	18	49	19.8	1.10
5	*p*-Br	Ts	**21k**	$PhB(OH)_2$	NEt_3	THF	18	15	5.3	0.29
6	*p*-Br	Ts	**21k**	$PhB(OH)_2$	NEt_3	DME	21	53	20.6	0.98
7	*p*-Br	Ts	**21k**	$NaPh_4B$	NEt_3	Toluene	18	95	34.9	1.94
8	*p*-Br	Ts	**21k**	$PhBF_3K$	NEt_3	Toluene	22	0	-	-
9	*p*-Br	Ts	**21k**	$(PhBO)_3$	NEt_3	Toluene	23	0	-	-
10	*p*-Br	Ts	**21k**	$C_9H_{11}BO_2$	NEt_3	Toluene	23	0	-	-
11	*p*-Br	Ts	**21k**	Ph_3B	NEt_3	Toluene	23	0	-	-
12	*p*-Br	Ts	**21k**	$NaPh_4B$	Cs_2CO_3	Toluene	18	<10	<3.3	<0.18
13	*o*-Br	Ts	**21o**	$NaPh_4B$	NEt_3	Toluene	16	0 (26)[d]	-	-
14	*p*-Cl	Ts	**21a**	$NaPh_4B$	NEt_3	Toluene	16	0 (67)[d]	-	-
15	*o*-Cl	Ts	**21b**	$NaPh_4B$	NEt_3	Toluene	16	0 (45)[d]	-	-
16	*p*-NO_2	Ts	**21m**	$NaPh_4B$	NEt_3	Toluene	21	0 (69)[d]	-	-
17	*p*-CF_3	Ts	**21n**	$NaPh_4B$	NEt_3	Toluene	21	0 (33)[d]	-	-
18	*p*-Cl	Ms	**21f**	$NaPh_4B$	NEt_3	Toluene	21	0 (48)[d]	-	-
19	*p*-Cl	Ns	**21e**	$NaPh_4B$	NEt_3	Toluene	21	0 (30)[d]	-	-
20[e]	*p*-Br	Ts	**21k**	$NaPh_4B$	NEt_3	Toluene	17	87	29.9	1.76
21[f]	*p*-Br	Ts	**21k**	$NaPh_4B$	NEt_3	Toluene	17	91	31.1	1.83
22[e]	*p*-Br	Ts	**21k**	$NaPh_4B$	NEt_3	Toluene	23	70	24.6	1.07

[a]Reagents and conditions: aldimine **(21)** (0.5 mmol), PEPPSI-*i*Pr (3 mol%), Ph-B (4 mol equiv.), base (4 mol equiv.), solvent (2 ml).
[b]Overall isolated yield (2 steps), after purification with silica gel chromatography.
[c]Reaction run at 60ºC.
[d]Corresponding yield of the intermediate amine product formed, (**30o**, **30a**, **30b**, **30m**, **30n**, **30f**, **30e**) respectively.
[e]3 mol equiv. of $NaPh_4B$ and NEt_3 were used.
[f]3.5 mol equiv. of $NaPh_4B$ and NEt_3 were used.

Upon screening a variety of solvents, it seemed that solvents, like toluene and 1,4-dioxane (Table 5.3, entries 1 and 4, respectively) gave good results. In the case of polar solvents like, dimethoxyethane (DME) a good yield of 53% was obtained (Table 5.3, entry 6), while THF gave a poor yield (Table 5.3, entry 5). The reaction doesn't work with protic solvents like *i*-propanol (*i*-PrOH) (Table 5.3, entries 2 and 3). Selecting toluene as the solvent of choice we decided to investigate the effect of the organoboron group on the reaction. We screened a variety of phenylboron reagents (Table 5.3, entries 7 to 11). Curiously, with PEPPSI-*i*Pr, only phenylboronic acid (Table 5.3, entry 1) and the corresponding sodium tetraphenylborate ($NaPh_4B$) (Table 5.3, entry 7) gave the desired product **(49)**. Gratifyingly, the $NaPh_4B$ organoboron reagent gave the desired product **(49)** in almost quantitative yield after 18 hours of reaction. Seem to be better a TON of up to 34.9 was obtained (Table 5.3, entry 7). This demonstrated the efficiency of PEPPSI-*i*Pr catalyst and also stability – last longer. In the case of the other reactions with the other organoboron reagents, analyzing the crude product by HPLC (Table 5.3, entries 8 to 11), showed the presence of *p*-bromophenylmethylamine **(30k)**. This result was supportive of a sequential catalytic event, although it was not quantified or isolated. Traces of the alcohol were detected as well, although it was not quantified (see Figure 5.3). The effect of the base was tested as well, using the conditions that provided the best yield. On replacing the NEt_3 base with Cs_2CO_3, an inorganic base already applied with success in the past for rhodium catalyzed addition reactions with organoboron reagents,[67] only vestigial amounts of the desired product **(49)** were obtained (Table 5.3, compared entry 7 with entry 12). To gain some further mechanistic insights into this particular transformation, a number of aldimines with electron-withdrawing groups in the phenyl ring were tested (Table 5.3, entries 13 to 17), using the optimized conditions already tested (Table 5.3, entry 7). For all the aldimines tested, no double-arylated product **(49)** was obtained, only the corresponding arylamines, which were now isolated by silica gel chromatography (indicated in parenthesis in Table 5.3, entries 13 to 17). The fact that the *ortho*-bromo substituted arylaldimine **(21o)** (Table 5.3, entry 13) could not afford the desired product **(49)**, may be a hint that steric effects are important in this sequential catalytic reaction. Other protecting groups such as mesyl and nosyl (on

the nitrogen of the aldimine) were tested unsuccessfully (see Table 5.3, entries 18 and 19, respectively). Only the corresponding arylamines (**30f** and **30e**) were detected and isolated by chromatography.

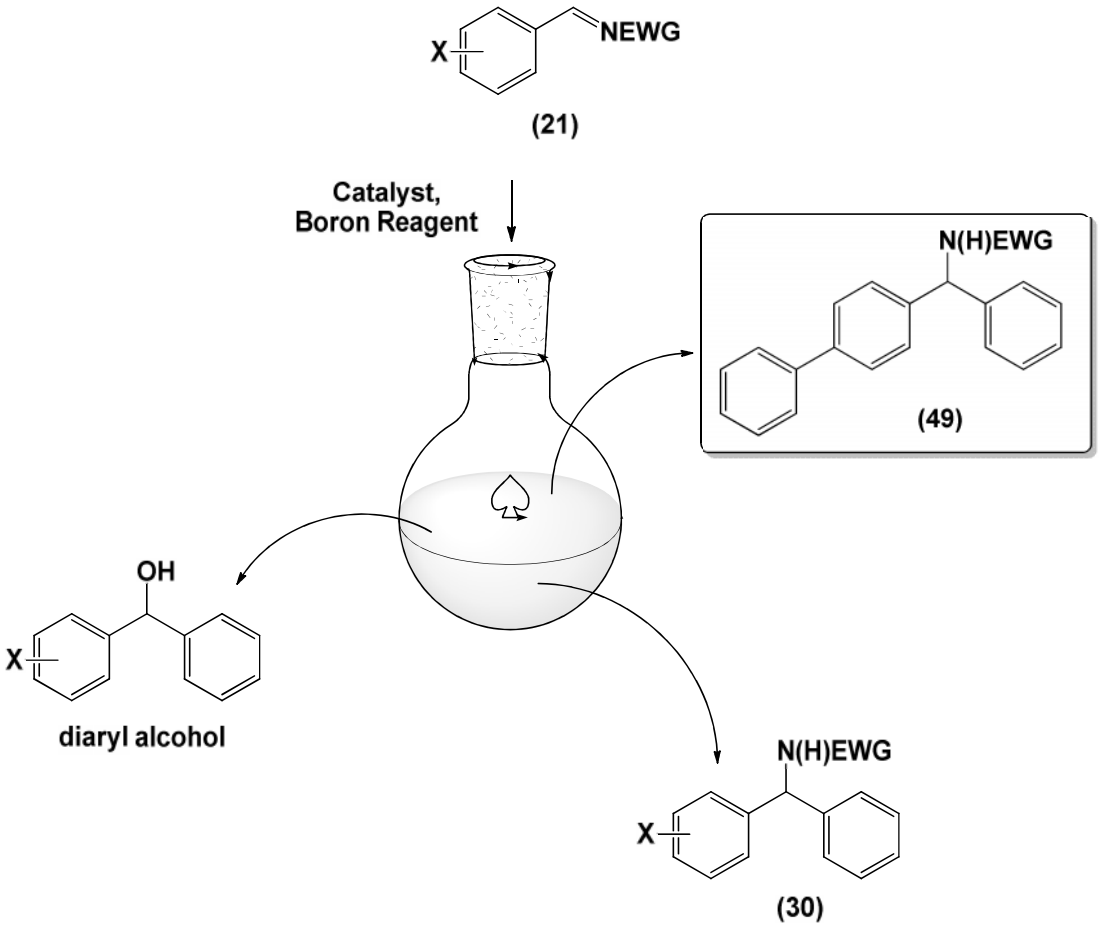
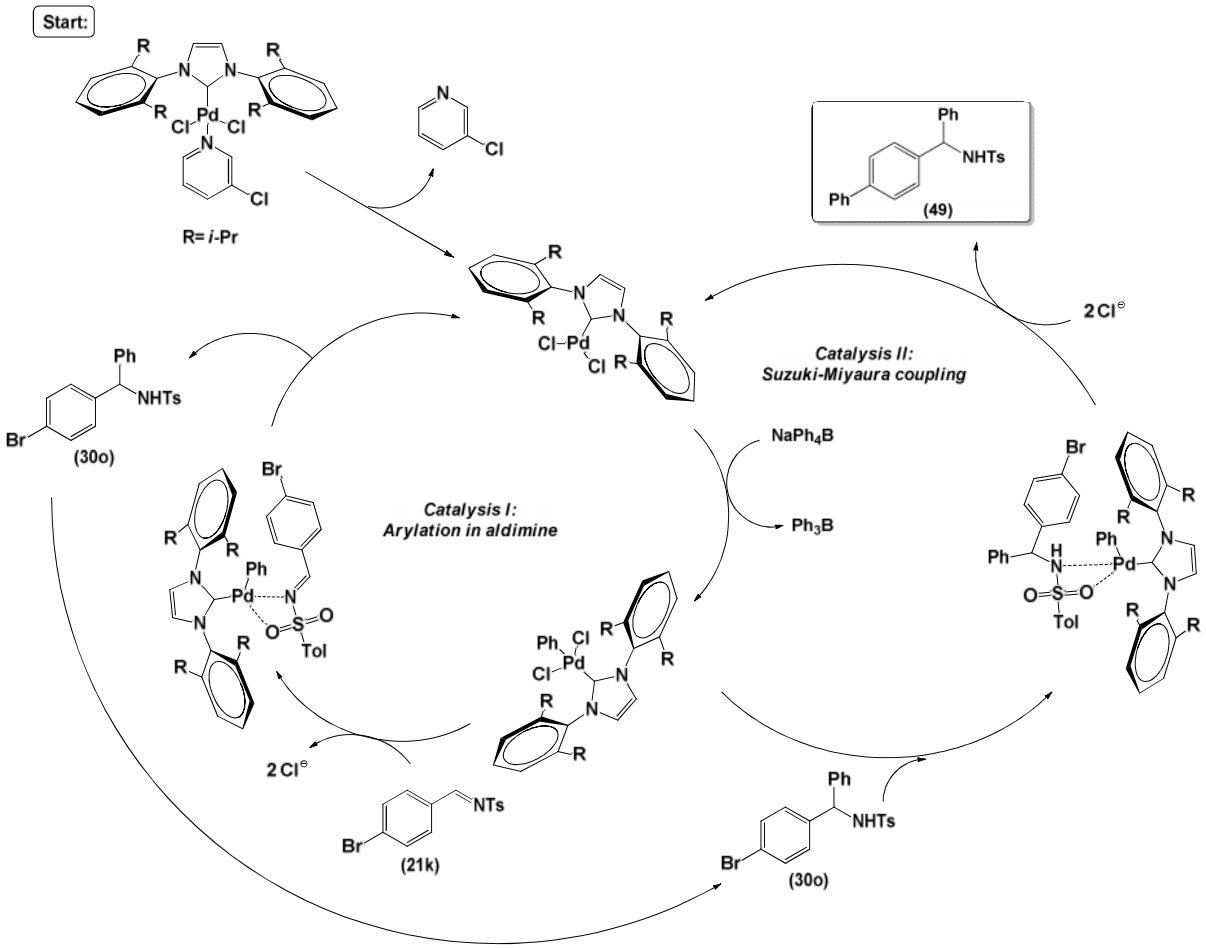


Figure 5.3. Formation of the desired biaryl product **(49)** and the corresponding secondary products **(30)** and a diaryl alcohol.

These studies were quite important as regards the mechanism, as it appears to support a sequential catalytic event and not a tandem process. It seems that first the arylation of the aldimine occurs and then the Suzuki-Miyaura reaction on the diarylamine intermediate **(30)** to afford the desired biaryl product **(49)** (Scheme

5.10). We proposed that two catalytic cycles take place in this transformation, first the PEPPSI-*i*Pr catalyst releases the pyridyl ligand and a palladium (0) complex is formed, which will be the active species in the reaction.[59] Transmetalation between boron and palladium, followed by oxidative addition of the aryl group leads to the diarylamine **(30o)** (see Chapter 2). **(30o)**, then coordinates to the active palladium species and this is followed by Suzuki-Miyaura cross-coupling to afford the desired bi-arylated compound **(49)**.

Why doesn't Ph_3B afford the desired product? Consider first the observation that the organoboron reagents that possess only one phenyl group (e.g. $PhB(OH)_2$, $PhBF_3K$ and $C_9H_{11}BO_2$) are ineffective in this dual catalytic transformation. The same goes for phenylboroxine ($(PhBO)_3$).



Scheme 5.10. Proposed mechanism for the sequential dual-catalytic reaction to afford the product **(49)** with PEPPSI-*i*Pr catalyst.

The loading of the organoboron reagent and of the corresponding base were also screened (Table 5.3, entries 20 to 22). We decided to reduce the quantity of the organoboron reagent and of the corresponding base to 3 mole equivalents, but the reaction yield decreased smoothly (Table 5.3, entries 20 and 22). Curiously upon increasing the reaction for a few hours more, the yield decreased considerably (compare entries 22 and 20, Table 5.3). We found that 3 mol% of PEPPSI-*i*Pr, along with 4 equivalents of $NaPh_4B$ and 4 equivalents of NEt_3 gives the best catalytic system (maximum TON and TOF) to obtain the desired product from this sequential catalytic process.

5.2.2. Heterogeneous Catalysis

Even though this sequential-catalytic reaction was ineffective for many aldimine substrates for reasons we do not know (despite our best efforts), we decided to develop a heterogeneous version. For simplicity and efficiency, a SILPC system was used to immobilize the PEPPSI-*i*Pr catalyst. As far we know, this was the first immobilization of a PEPPSI-*i*Pr catalyst with this procedure, as thus far only $Pd(OAc)_2$, $Pd(PPh_3)$ and Pd black have been immobilized.[46] We choose two commercial silica types to perform the immobilization of the catalyst, flash silica for liquid chromatography and silica nanopowder. The characteristics can be seen in Table 5.4. Both silicas, which are porous materials, were dried under high vacuum at 150ºC to remove any water or air molecules in the pores.

Table 5.4. Characteristics of the silica types used in this research.

	Silica flash	Silica nanopowder
Manufacturer	Merck	Aldrich
Shape	spherical	spherical
Particle size	40-63 μm	5-15 nm
Pore volume	0.74-0.84 $ml.g^{-1}$	-
Surface area	480-540 $m^2.g^{-1}$	590-690 $m^2.g^{-1}$

The immobilization of PEPPSI-*i*Pr in the amorphous inorganic oxide (silica) with the aid of an ionic liquid was conducted according to the simple procedure used by Hagiwara *et al*.[49,50] A suspension of the commercial silica in a solution of the corresponding PEPPSI-*i*Pr catalyst and the ionic liquid [Bmim]PF_6 in THF was stirred overnight at room temperature. After evaporation of the THF, the silica was washed several times with diethyl ether to wash-off the non-immobilized catalyst. Evaporation under reduced pressure gave the free powdered silica with the immobilized PEPPSI-*i*Pr catalyst (Figure 5.4).

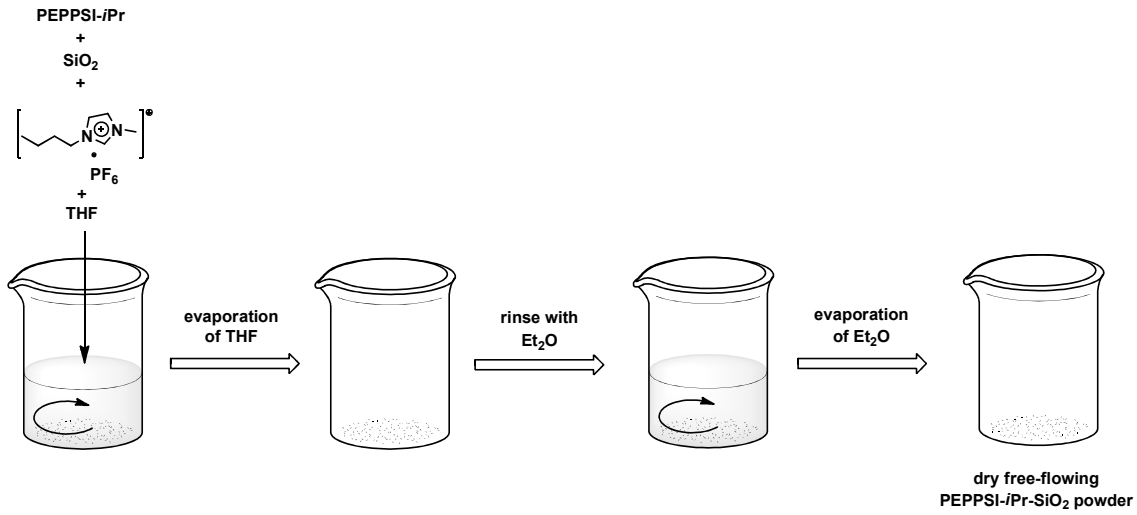


Figure 5.4. Preparation of PEPPSI-*i*Pr-SILPC.

Most of the common supported ionic liquids are based on 1,3-dialkylimidazolium cations and hexafluorophosphate (PF_6) or tetrafluoroborate (BF_4) anions.[46] Their tunable polarities[41] make them good solvents for almost all transition metal complexes. Due to such particularities, we decided to apply [Bmim]PF_6 as the ionic liquid of choice to perform this research. As far as we know, the bulky PEPPSI-*i*Pr catalyst has never been immobilized with this type of procedure before. With this SILPC strategy, the PEPPSI-*i*Pr catalyst and the ionic liquid were dissolved in THF (an organic solvent), the latter was removed under vacuum (see Figure 5.4), so that the ionic liquid remains anchored as a thin layer on the surface of the silica support. [Bmim]PF_6, a neutral ionic liquid, stays attached by physisorption.

After the PEPPSI-*i*Pr catalyst was immobilized on both silicas (flash and nanopowder), a test reaction was performed in each one to evaluate the efficiency of the solid support. The optimized conditions found in the homogeneous phase dual-catalytic reactions (see Table 5.3, entry 7) were applied in these studies. A rough calculation of the immobilized catalyst was made on weight gained in the process of immobilization, in order to estimate the reliability of the SILPC. Using flash silica gel (where the particle size was bigger) no desired biaryl product was obtained after a 24h reaction, at 100ºC. Using the nanopowder silica, the desired biaryl product was clearly visible by TLC. Thus, we decided to explore the SILPC method with the nanopowder silica (Figure 5.5).

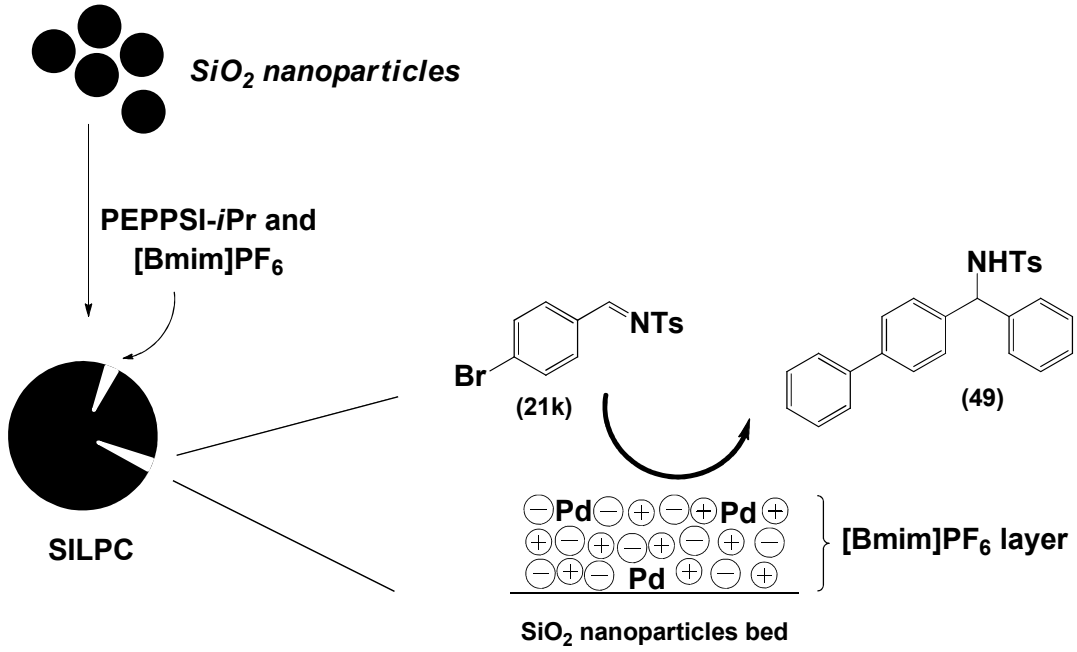


Figure 5.5. Supported Ionic Liquid Phase Catalyst (SILPC) system approach used in this research work.

Characterization of the immobilized catalyst was performed by elemental analysis (EA) particularly to determine the loading of the immobilized PEPPSI-*i*Pr. Using this technique the loading of the [Bmim]PF_6-PEPPSI-*i*Pr-SiO_2 was determined to be 0.91 mmol/g of nanopowder silica, with 0.41 mmol PEPPSI-*i*Pr/g silica nanopowder. The PEPPSI-*i*Pr immobilization yield was determined to be 76%. Scanning electron microscopy (SEM) studies were also made in order to try and establish the morphology and the surface characteristics of the supported catalyst. Unfortunately, the visualization of a single particle wasn't possible, maybe due to the small size or something in the preparation of the sample (coating by carbon evaporation). The pictures obtained do not exhibit remarkable differences, perhaps these data reveal a high dispersion of the ionic liquid on the surface without modification of the solid support. Using SEM, colored map charts were made, and this afforded interesting insights on the dispersion of the palladium (C)

on the surface (Figure 5.6), as it was observed that immobilized palladium was present on the surface and/or in the pores of the primary silica nanoparticles.

In the next step, the immobilized catalyst was tested applying our optimized protocol (see Table 5.3, entry 7), using 452 mg of *p*-bromo aldimine substrate **(21k)** and 16 mol% of PEPPSI-*i*Pr (500 mg of SILPC). The reaction was run at 100ºC for 18 hours in toluene (15 ml) with 4 equivalents of $NaPh_4B$ and NEt_3. The work-up was made, after cooling the reaction mixture to room temperature, with a simple assembly (Figure 5.7) using a kitasato flask and a plastic syringe, which was connected to a vacuum pump to separate the SILPC from the reaction product. The SILPC was washed with toluene and dried under reduced pressure for reuse in the following reaction cycle, without any pre-treatment.

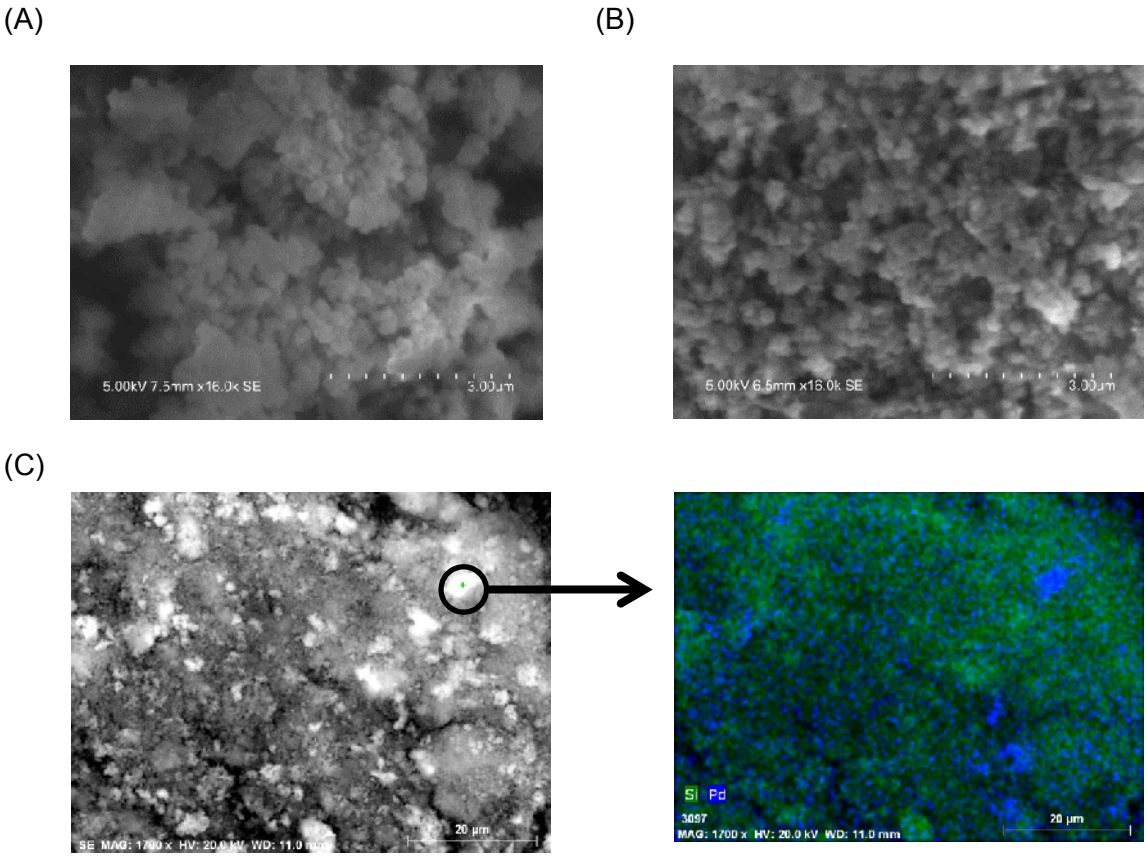


Figure 5.6. (A) SEM picture of the initial silica nanopowder (5 kV, ×16.0); **(B)** SEM picture of the [Bmim]PF_6-PEPPSI-*i*Pr-SILPC (5 kV, ×16.0); **(C)** SEM picture of [Bmim]PF_6-PEPPSI-*i*Pr-SiO_2 (20.0 kV, ×1700) and the corresponding colour map chart to detect palladium metal.

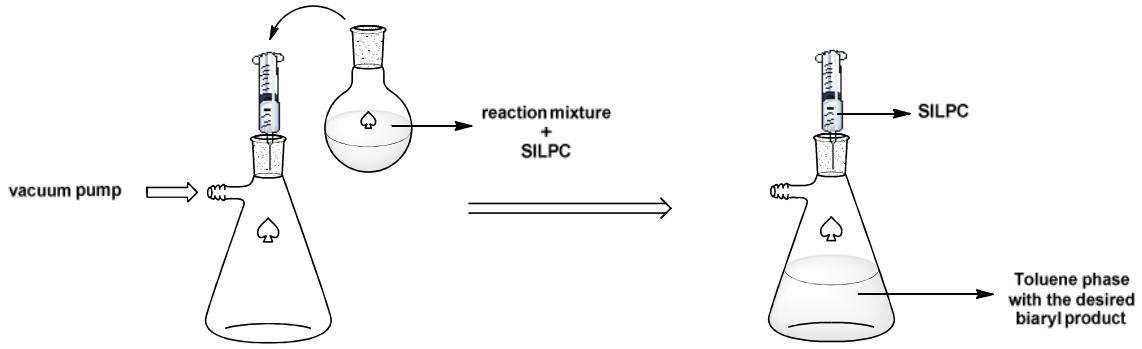


Figure 5.7. Work-up of the sequential-catalytic reaction with SILPC.

After evaporation of the crude toluene extract and further silica gel chromatography purification we obtained the desired diaryl product **(49)** in 81% yield. This was a very good result for a first run, comparatively to the 95% yield obtained with the homogeneous system (see Table 5.3, entry 7). Several other cycles were made with the reused SILPC. The results can be seen in Table 5.5.

Table 5.5. Recycling of the immobilized PEPPSI-*i*Pr catalyst.

Entry[(a)]	Cycle	Yield/%[(b)]	TON	TOF/h
1	0	81	25.2	1.40
2	1	55	17.0	0.94
3	2	54	16.8	0.93
4	3	54	16.9	0.94
5[(c)]	4	18	5.6	0.31

[(a)]Reaction was carried out under the optimized conditions as described in Table 5.3, entry 7.
[(b)]Isolated yield after liquid chromatography on silica gel (from 2 steps).
[(c)]Catalyst was washed with ethyl acetate.

An instant decrease in the catalytic activity was observed after the first cycle (Table 5.5, entry 2), in which we think that there was leaching[20] of the more weakly anchored PEPPSI-*i*Pr catalyst, perhaps those molecules attached to the surface. This has been confirmed by ICP-MS analysis, in which approximately 0.38 μg Pd/g

support was leached in washings with toluene (Table 5.5, entries 1 to 4). On carrying out the second and third cycle, the yield remained the same (Table 5.5, entries 3 and 4). Perhaps the accumulation of excess $NaPh_4B$ and its corresponding boron salts on the surface of the immobilized catalyst may have had a role in decreasing the yield. Upon testing the solubility of the $NaPh_4B$ in several organic solvents, we observed that ethyl acetate was the best solvent to wash the immobilized catalyst for $NaPh_4B$ removal. So, we decided to wash several times the immobilized catalyst with ethyl acetate, and after drying well under reduced pressure, a fourth cycle was carried out (Table 5.5, entry 5). The yield dropped significantly, and we concluded that the PEPPSI-*i*Pr catalyst (along with the ionic liquid layer) suffers significant leaching with ethyl acetate. This was in fact confirmed by ICP-MS analysis where 3.35 µg Pd/g support was recovered in the ethyl acetate phase.

Similar to the homogeneous phase reactions, vestigial amounts of secondary products (see Figure 5.3) were detected by TLC analysis, but the corresponding isolated yields weren´t determined.

With regard to the mechanism of this dual-catalytic reaction using a SILPC system we, at this juncture, believe that it is similar to the one proposed for the homogeneous phase reaction (see Scheme 5.10).

A TON as high as 25.2 could be obtained, but then they started to deteriorate due to catalyst deactivation or leaching.

5.3. Conclusions

We reported a rapid, efficient and innovative method to synthesize biphenyl units, through a one-pot sequential catalytic procedure, which involves the arylation of an activated imine (presumably first) followed by a Suzuki-Miyaura coupling reaction. Electron-withdrawing substituted aldimines were tested, but *p*-bromotosylaldimine **(21k)** was the only one that afforded the desired diaryl product! Despite this lack of reaction scope, optimized conditions which include

the use of sodium tetraphenylborate ($NaPh_4B$), triethylamine and a well-known Pd-catalyst (PEPPSI-*i*Pr) were found. The clear advantage of this process is the use of a commercially available single catalyst, without the need for additional external ligands and, one that is, extremely stable to air and moisture.

After these optimal conditions were found, a heterogeneous version of this new reaction was successfully developed, using a SILPC protocol. PEPPSI-*i*Pr was immobilized noncovalently as a SILPC nanopowder silica with the aid of $[Bmim]PF_6$, an IL. The reactivity and the stability of the SILPC remained comparable to the original homogeneous counterpart. Due to the need for only small quantities of the IL, this technique is cost effective. The immobilization procedure is simple, employing commercially available catalysts and reagents, and the fact that there is no need to modify a known catalyst chemically, makes it highly advantageous. This is the first method for the immobilization of the PEPPSI-*i*Pr catalyst in a SILPC system for use in such a sequential multi-catalytic one-pot transformation.

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6. Experimental Section

"Men are haunted by the vastness of eternity. And so we ask ourselves: will our actions echo across the centuries? Will strangers hear our names long after we are gone and wonder who we were, how bravely we fought, how fiercely we loved?"
Odysseus, Troy

6.1. General remarks

6.1.1. Solvents:

All the solvents used in this work were purified and dried under an inert atmosphere using common laboratory techniques.[1]

a) Dichloromethane was distilled over CaH_2;

b) *N*,*N*-Dimethylformamide was distilled over magnesium sulphate under reduced pressure;

c) 1,2-Dichloroethane was distilled over CaH_2;

d) Diethyl ether was distilled over sodium and benzophenone;

e) Methanol was distilled over CaH_2;

f) Tetrahydrofuran was distilled over sodium and benzophenone;

g) Toluene was distilled over $LiAlH_4$;

h) Triethylamine was distilled over $LiAlH_4$;

i) Acetonitrile was distilled over CaH_2;

j) Distilled water was used;

k) *t*-Amyl alcohol was distilled over CaH_2;

l) 1,2-Dimethoxyethane was distilled over CaH_2;

m) Carbon tetrachloride was kept over 3Å M.S. and then distilled.

n) 1,4-Dioxane was distilled over sodium and benzophenone.

Note: When Dioxane was citing in the course of this work, only 1,4-Dioxane was used.

6.1.2. Reagents:

All of the reagents were purchase from Sigma-Aldrich, Fluka, Acros and Alfa Aeser, and used as received.

The intermediates 1,2-diacetals derived from *L*-tartaric acid (see Chapter 1, Scheme 1.8) were obtained from ChiraTecnics, Lda.

Ionic liquid [Bmim]BF_4 was obtained from Solchemar, Lda.

The commercial chiral and achiral ligands used were obtained from Strem Chemicals, Inc.

1-Methyimidazole was distilled under reduce pressure.

6.1.3. Detection, characterization and purification of the synthesized compounds:

Thin layer chromatography (TLC) was carried out on aluminium backed Kieselgel 60 F_{254} plates (Merck). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol after heating with a hot air gun. The eluents were described in each experimental procedure.

Column chromatography was carried out on silica gel (SDS, 70-200 μm) and silica gel flash (SDS, 40-63 μm).

Melting points were determined on a Barnstead/Electrothermal 9100 capillary apparatus.

Infrared spectra (IR) were carried out in a Perkin-Elmer Paragon 1000 instrument.

The NMR analysis were recorded in the Faculdade de Ciências e Tecnologia/Universidade Nova de Lisboa, on a Bruker Avance instrument (400 MHz), using $CDCl_3$, DMSO-d_6 or D_2O as solvents and the signal from the residual $CHCl_3$ used as an internal standard. All ^{1}H and ^{13}C NMR chemical shifts were reported in ppm. ^{31}P NMR chemical shifts are reported in ppm relative to H_3PO_4 (external standard). All coupling constants are expressed in Hz.

Mass spectra were recorded in the C.A.C.T.I. – Universidade de Vigo, on a Waters- Micromass (MicroTOF, ESI) or FAB Focus (Bruker Daltonics) using the TOF technique.

Specific rotation measurements were recorded in the LNEG – Laboratorio National de Energia e Geologia, on a PerkineElmer 241 polarimeter.

Scanning electron microscopy (SEM) was recorded in the Centro Hércules – Universidade de Évora, and was made with a HITACHI 3700N instrument, coupled with an energy dispersive spectrometer (Bruker Xflash X-ray detector) at 20kV in high vacuum, in which the samples were analyzing after coating by carbon evaporation.

Elemental analysis (EA) was recorded in the C.A.C.T.I. – Universidade de Vigo and was performed using a Carlo Erba 1108 Elemental Analyser accompanied by combustion chromatography.

Inductively coupled plasma mass spectrometry (ICP-MS) was recorded in the C.A.C.T.I. – Universidade de Vigo, and was determined in acidic aqueous samples collected from the filtrates in a Thermo X series II ICP-MS instrument.

All the reactions were performed under an inert atmosphere (nitrogen) unless otherwise indicated.

When schlenk flasks were employed, the usual schlenk techniques were used in the handling, namely: vacuum and nitrogen cycles, including the use of well dried and deoxygenated solvents.

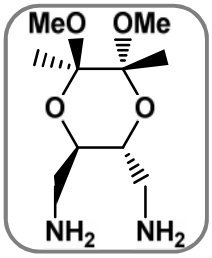
In the cases where silica gel deactivation was required, the following procedure was employed: 1% NEt_3 was added to a known volume of the desired eluent and left stirring with the desired amount of silica. After the column was packed and prepared, the proper eluent was passed through the column, to remove NEt_3 residues.

Brine solution consisted of a solution of aqueous NaCl.

6.2. General Procedures

6.2.1. Synthesis of New Ligands and Catalysts

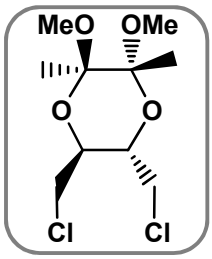
6.2.1.1. Synthesis of ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine (1):[2,3]



(2*R*,3*R*,5*R*,6*R*)-5,6-Bis(azidomethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (0.73 g, 2.5 mmol) was added to a round-bottom flask containing Pd/C (0.7 mmol) and EtOH (10 ml). The flask was then fitted with a ballon full of hydrogen gas and the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered through a porous filter with *celite* and the solvent removed under reduced pressure. ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl) dimethanamine **(1)** was obtained as a viscous colorless oil (0. 50 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.32 (s, CH_3, 6H), 1.83 (s br, NH_2, 4H), 2.76 (d, CH_2, 4H), 3.28 (s, OCH_3, 3H), 3.59 (m, CHO, 2H).

6.2.1.2. Synthesis of (2*R*,3*R*,5S,6*S*)-5,6-bis(chloromethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (9):[4]



The following reagents were added sequentially to a round-bottom flask: ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanol (0.33 g, 1.4 mmol), PPh_3 (1.50 g, 5.5 mmol), pyridine (0.5 ml, 5.5 mmol) and CCl_4 (0.5 ml, 5.5 mmol) with CH_2Cl_2 (10 ml) as the solvent. The mixture was stirred at room temperature in the dark. The solvents were evaporated under reduced pressure and the crude product purified by silica gel chromatography (Hex/AcOEt (1:1)). (2*R*,3*R*,5*S*,6*S*)-5,6-bis(chloromethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **(9)** was obtained as a white solid (0.38 g, 99 %).

m.p.: 67.4-68.6ºC.

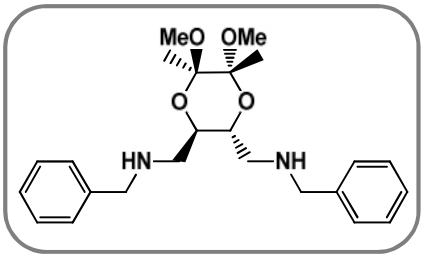
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (s, CH_3, 6H), 3.29 (s, OCH_3, 6H), 3.55-3.67 (m, CH_2Cl, 4H), 3.94-3.96 (m, CHO, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.35 (CH_3), 43.48 (CH_2), 48.08 (OCH_3), 69.68 (CHO), 99.31 (C-O).

Micro-TOF MS (m/z): 295.05 (M^+).

$[\alpha]_D^{20}$: -196.7 (c 1.33, $CHCl_3$).

6.2.1.3. Synthesis of *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-phenylmethanamine) (2a):[3,4]



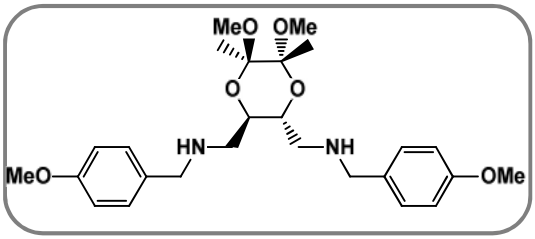
In a round-bottom flask equipped with a reflux condenser was added ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine **(1)** (1 g, 0.4 mmol), benzaldehyde (1.1 ml, 10 mmol) and MeOH (35 ml). The mixture was stirred for 12 h under reflux. Toluene (50 ml) and $NaBH_4$ (21 mmol, added in small portions over a 20 minutes period) were added to the cooled reaction mixture (cooled to room temperature). The mixture was stirred for 2 h and then the solvents were removed under reduce pressure. H_2O (50 ml) and AcOEt (50 ml) were added to the crude mixture and extracted. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and the solvent was again evaporated under reduced pressure. The crude product was purified using silica gel chromatography (Hex/AcOEt (1:1)), giving *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-phenylmethanamine) **(2a)** as a colorless oil (0.64 g, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (s, CH_3, 6H), 2.46 (s, C*H*$_2$NH, 2H), 2.63 (s, CH_2NH, 2H), 3.22 (s, OCH_3, 2H), 3.68-3.81 (m, CHO+C*H*$_2$Ar, 6H), 5.25 (s, NH, 2H), 7.22 (m, Ar, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.30 (CH_3), 47.81 (CH_2N), 49.30 (OCH_3), 53.54 (CH_2Ar), 68.93 (CHO), 98.17 (C-O), 126.66 (Ar), 127.87 (Ar), 139.49 (Ar).

ESI-TOF MS (m/z): 415.27 (M+1).

6.2.1.4. Synthesis of *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-(4-methoxyphenyl)methanamine) (2b):[4]



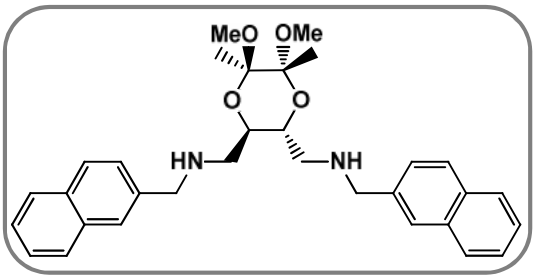
The same procedure was applied as previously (see 6.2.1.3) using *p*-anisaldehyde (0.3 ml, 2.1 mmol) and 0.2 g (0.85 mmol) of ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine **(1)**. The crude product was purified using silica gel chromatography (Hex/AcOEt (1:1)) giving *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-(4-methoxyphenyl)methanamine) **(2b)** as a yellow oil (0.22 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.28 (s, CH_3, 6H), 2.04 (s, CH_2NH, 2H), 2.65-2.67 (m, CH_2NH, 4H), 3.26 (s, OCH_3, 3H), 3.69-3.77 (m, CH_2Ar, 4H), 3.79 (s, OCH_3, 6H), 4.08-4.16 (m, CHO, 2H), 6.83-6.86 (d, Ar, 4H), 7.20-7.23 (d, Ar, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.10 (CH_3), 48.29 (CH_2N), 49.58 (OCH_3), 53.08 (CH_2Ar), 55.42 (OCH_3), 69.41 (CHO), 98.80 (C-O), 113.95 (Ar), 129.84 (Ar), 134.18 (Ar), 158.99 (Ar).

ESI-TOF MS (m/z): 475.30 (M+1).

6.2.1.5. Synthesis of *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-(naphthalen-2-yl)methanamine) (2c):[4]



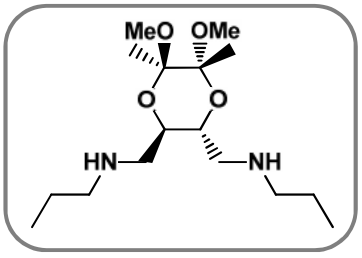
The same procedure was applied as previously (see 6.2.1.3) using 2-naphtaldehyde (0.33 g, 2.1 mmol) and 0.2 g (0.85 mmol) of ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine **(1)**. The crude product was purified using silica gel chromatography (Hex/AcOEt (1:1)) giving *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl) bis (methyl ene))bis(1-(naphthalen-2-yl)methanamine **(2c)** as a colorless oil (0.21 g, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (s, CH_3, 6H), 1.92 (s, CH_2NH, 2H), 2.69-2.70 (m, CH_2NH, 4H), 3.28 (s, OCH_3, 6H), 3.91-3.93 (m, CH_2Ar+CHO, 6H), 7.42-7.48 (m, Ar, 2H), 7.72-7.74 (m, Ar, 2H), 7.77-7.82 (m, Ar, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.78 (CH_3), 48.26 (CH_2N), 49.63 (OCH_3), 54.06 (CH_2Ar), 69.55 (CHO), 98.83 (C-O), 125.80 (Ar), 126.22 (Ar), 126.82 (Ar), 126.90 (Ar), 127.74 (Ar), 127.85 (Ar), 127.94 (Ar), 128.28 (Ar), 128.64 (Ar), 132.82 (Ar), 133.52 (Ar), 138.73 (Ar).

ESI-TOF MS (m/z): 515.30 (M+1).

6.2.1.6. Synthesis of *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(propan-1-amine) (2d):

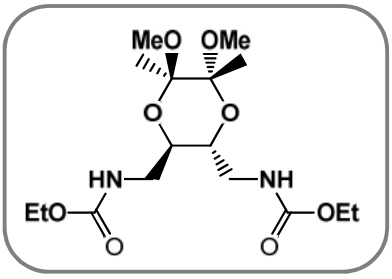


The same procedure was applied as previously (see 6.2.1.3) using propionaldehyde (0.15 ml, 2.1 mmol) and 0.2 g (0.85 mmol) of ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine **(1)**. The crude product was purified using silica gel chromatography (Hex/AcOEt (1:1)) giving *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)) bis(propan-1-amine) **(2d)** as a yellow oil (0.10 g, 31%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (m, CH_3, 6H), 1.28 (s, CH_3, 6H), 1.63 (m, CH_2, 3H), 1.96-2.04 (m, CH_2, 4H), 2.42 (s br, NH, 2H), 3.28 (s, OCH_3, 6H), 3.48 (m, CH_2N, 4H), 3.80 (m, CHO, 2H).

ESI-TOF MS (m/z): 355.26 (M^+).

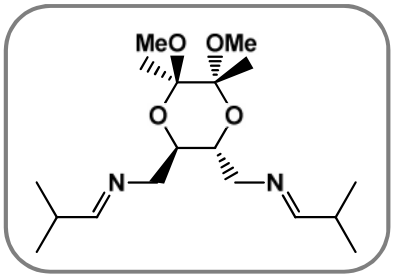
6.2.1.7. Synthesis of diethyl (((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))dicarbamate (4):



((2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl) dimethanamine **(1)** (0.2 g, 0.84 mmol), NEt_3 (0.4 ml, 2.5 mmol) and Et_2O (10 ml), in a round-bottom flask were stirring at 0ºC. Ethyl chloroformate (0.2 ml, 2.1 mmol) was added slowly. The mixture was left stirred at 0ºC for 2 h. The reaction was quenching by the addition of HCl 1M (10 ml). The organic phase was washed with sat. $NaHCO_3$ (5 ml), *brine* (5 ml) and dried with $MgSO_4$. The solvent was evaporated under reduced pressure, giving diethyl (((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))dicarbamate **(4)** as a colorless oil (0.18 g, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.22-1.28 (m, CH_3+OCH_2CH_3, 12H), 3.22 (s, OCH_3, 6H), 3.41-3.60 (m, CH_2N, 4H), 3.64-3.66 (m, OCH_2CH_3, 4H), 5.13 (s br, NH, 2H).

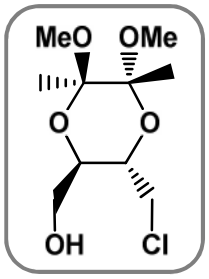
6.2.1.8. Synthesis of (*NE*,*N'E*)-1,1'-((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(*N*-(2-methylpropylidene)methanamine) (7):



To a round-bottom flask equipped with a Dean-Stark trap were added, ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine **(1)** (0.5 g, 2.1 mmol), iso-butyraldehyde (1 ml, 10.7 mmol) and toluene (10 ml). The mixture was refluxed until the theoretical quantity of water (2.1 mmol) was collected. The solvent was removed under reduced pressure, giving (*NE*,*N'E*)-1,1'-((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(N-(2-methyl propylidene)methanamine) **(7)** as a yellow oil (0.65 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08-1.13 (dd, CH_3, 12H), 1.24-1.28 (m, CH, 2H), 1.29 (s, CH_3, 6H), 3.19-3.28 (m, CH_2N, 4H), 3.31 (s, OCH_3, 6H), 3.80 (m, CHO, 2H), 7.6 (m, NCH, 2H).

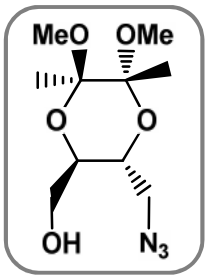
6.2.1.9. Synthesis of ((2*R*,3*S*,5*R*,6*R*)-3-(chloromethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol (13):[2]



The same procedure as previously used was applied (see 6.2.1.2.) using ((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanol (0,5 g, 2.1 mmol), PPh_3 (1,1 g, 4.2 mmol), pyridine (0.35 ml, 4.2 mmol) and CCl_4 (0.1 ml, 1.1 mmol) in CH_2Cl_2 (5 ml). The desired ((2*R*,3*S*,5*R*,6*R*)-3-(chloromethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol **(13)** was obtained as a white solid (0.26 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.31 (s, CH_3, 3H), 1.33 (s, CH_3, 3H), 2.06-2.10 (s br, OH, 1H), 3.26 (s, OCH_3, 3H), 3.29 (s, OCH_3, 3H), 3.58-3.79 (m, CH_2+CHO, 5H), 3.97-3.99 (m, CHO, 1H).

6.2.1.10. Synthesis of ((2*R*,3*R*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol (14):[2]

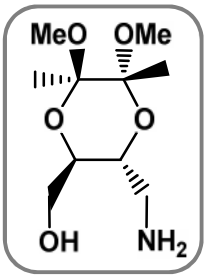


((2*R*,3*S*,5*R*,6*R*)-3-(Chloromethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol **(13)** (0.71 g, 2.8 mmol), NaN_3 (0.72 g, 11.0 mmol) and DMF (14 ml) were added to a round-bottom flask and stirred at 80ºC for 4 days. Et_2O and H_2O were added to quench the reaction. The organic phase was separated and the

aqueous phase extracted with Et_2O (2×10 ml). The organic phase was washed with H_2O (4×10 ml) to remove the DMF. After drying with $MgSO_4$, it was filtrated and then evaporated under reduced pressure. The crude product was purified by silica gel chromatography (Hex/AcOEt (3:2)), to afford the desired ((2*R*,3*R*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol **(14)** as a white solid (0.47 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30 (d, *J*= 2Hz, CH_3, 3H), 1.32 (d, *J*= 2 Hz, CH_3, 3H), 2.13 (s br, OH, 1H), 3.26 (d, *J*= 2 Hz, OCH_3, 3H), 3.29 (d, *J*= 2.4 Hz, OCH_3, 3H), 3.38 (dd, *J*=1.6 and 2Hz, CH_2N_3, 2H), 3.60 (m, C*H*$_2$OH, 1H), 3.67 (m, C*H*$_2$OH, 1H), 3.74 (m, CHO, 1H), 3.95 (m, CHO, 1H).

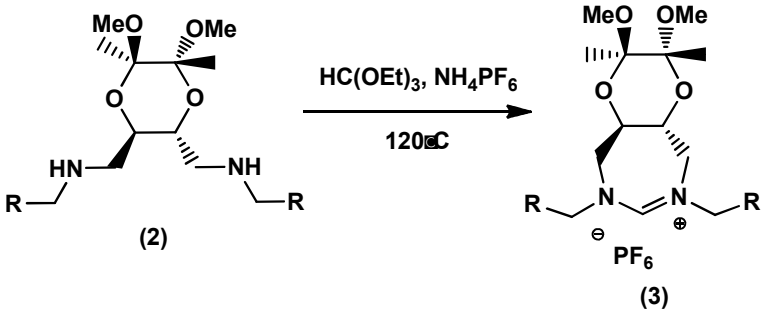
6.2.1.11. Synthesis of ((2*R*,3*R*,5*R*,6*R*)-3-(aminomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol (15):[2]



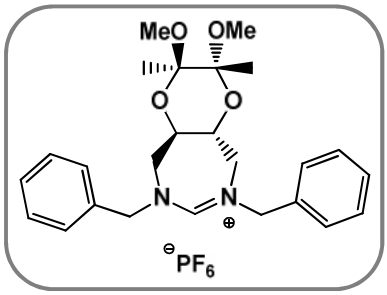
The same procedure was applied (see 6.2.1.1.) using ((2*R*,3*R*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol **(14)** (0.45 g, 1.8 mmol), Pd/C (46 mg, 10 mol%) and EtOH (20 ml) with a rubber balloon filled with hydrogen. The desired ((2*R*,3*R*,5*R*,6*R*)-3-(aminomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol **(15)** was obtained as a white solid (0.33 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30 (s, CH_3, 6H), 2.85-2.91 (m, CH_2N+NH_2, 4H), 3.27 (s, OCH_3, 6H), 3.61-3.65 (m, CH_2O+CHO, 4H).

6.2.2. Synthesis of mono-NHC-type salts



6.2.2.1. Synthesis of (2*R*,3*R*,4a*R*,9a*R*)-6,8-dibenzyl-2,3-dimethoxy-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) (3a):[3,4]



In a round-bottom flask equipped with a reflux condenser was added *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-phenylmethanamine) **(2a)** (0.11 g, 0.26 mmol), NH_4PF_6 (43 mg, 0.26 mmol) and triethyorthoformate (44 µl, 0.26 mmol). The mixture was heated with stirring at 120ºC for 3 h. The EtOH formed was evaporated under reduced pressure and the crude product recrystallized from hot EtOH to afford the desired (2*R*,3*R*,4a*R*,9a*R*)-6,8-dibenzyl-2,3-dimethoxy-2,3-dimethyl-3,4a,5,8,9,9a-

hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) **(3a)** as white crystals (0.82 g, 57%).

m.p.: 193.5-195.0ºC.

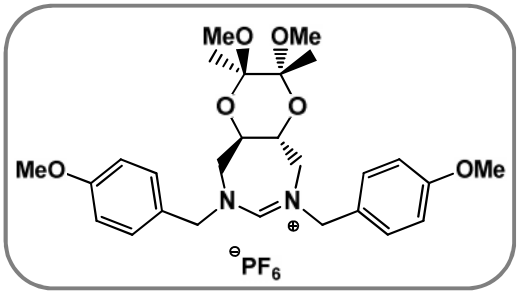
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.14 (s, CH_3, 6H), 3.02 (s, OCH_3, 6H), 3.20-3.28 (m, CH_2N, 2H), 3.37-3.42 (m, CH_2N, 2H), 3.55-3.56 (m, CHO, 2H), 4.67-4.79 (q, *J*=12 Hz, CH_2Ar, 4H), 7.33-7.38 (m, Ar, 10H), 8.37 (s, CH=N, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.10 (CH_3), 48.04 (OCH_3), 51.21 (CH_2Ar), 63.12 (N*C*H_2C), 67.20 (CHO), 99.08 (C-C), 128.78 (Ar), 129.18 (Ar), 129.28 (Ar), 132.63 (Ar-C), 159.06 (C=N).

Micro-TOF MS (m/z): 425.25 (M^+), 426.26 (M+1), 427.26 (M+2).

$[\alpha]_D^{25}$: -67.8 (c 0.96, $CHCl_3$).

6.2.2.2. Synthesis of (2*R*,3*R*,4a*R*,9a*R*)-2,3-dimethoxy-6,8-bis(4-methoxybenzyl)-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) (3b):[4]



The same procedure as reported above was applied (see 6.2.2.1.) using *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-(4-methoxyphenyl)methanamine) **(2b)** (0.18 g, 0.38 mmol). After recrystallization with hot EtOH, the desired (2*R*,3*R*,4a*R*,9a*R*)-2,3-dimethoxy-6,8-bis(4-methoxybenzyl)-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) **(3b)** was obtained as yellowish crystals (0.14 g, 59%).

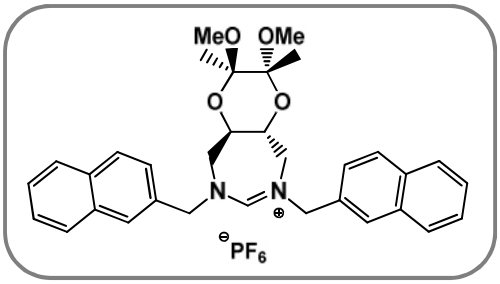
m.p.: 148.7-150.3ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.16 (s, CH_3, 6H), 3.07 (s, OCH_3, 6H), 3.18-3.26 (m, CH_2N, 2H), 3.37-3.42 (m, CH_2N, 2H), 3.50-3.60 (m, CHO, 2H), 3.80 (s, OCH_3, 6H), 4.66 (m, CH_2Ar, 4H), 6.86 (d, Ar, 4H), 7.22-7.26 (d, Ar, 4H), 8.23 (s, CH=N, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.26 (CH_3), 48.24 (OCH_3), 51.22 (CH_2), 55.43 (OCH_3), 62.91 (CH_2), 67.32 (CHO), 99.17 (CHO), 114.76 (Ar),124.58 (Ar),130.50 (Ar),158.21 (Ar), 160.38 (C=N).

ESI-TOF MS (m/z): 485.26 (M^+), 486.27 (M+1), 487.27 (M+2).

6.2.2.3. Synthesis of (2*R*,3*R*,4a*R*,9a*R*)-2,3-dimethoxy-2,3-dimethyl-6,8-bis(naphthalen-2-ylmethyl)-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) (3c):[4]



The same procedure as reported above was applied (see 6.2.2.1.) using *N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-(naphthalen-2-yl)methanamine **(2c)** (0.19 g, 0.37 mmol). After recrystallization with hot EtOH, the desired (2*R*,3*R*,4a*R*,9a*R*)-2,3-dimethoxy-2,3-dimethyl-6,8-bis(naphthalen-2-ylmethyl)-3,4a,5,8,9,9a-hexahydro-2H-[1,4] dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) **(3c)** was obtained as yellow crystals (0.19 g, 78%).

m.p.: 200.6-202.4ºC.

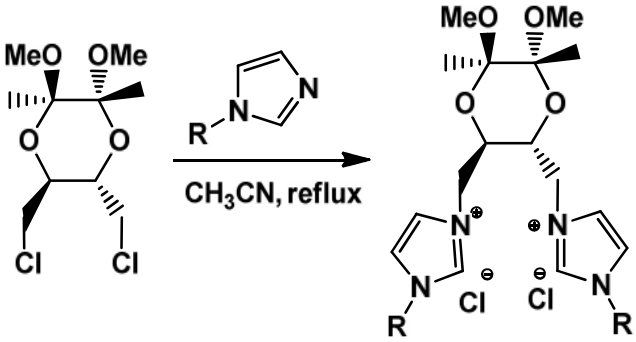
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.06 (s, CH_3, 6H), 2.94 (s, OCH_3, 6H), 3.27-3.35 (m, CH_2N, 2H), 3.45-3.49 (m, CH_2N, 2H), 3.63-3.64 (m, CHO, 2H), 4.86-

4.97 (m, CH_2Ar, 4H), 7.36-7.39 (m, Ar, 4H), 7.46-7.49 (m, Ar, 4H), 7.72-7.79 (m, Ar, 6H), 8.47 (s, CH=N, 1H).

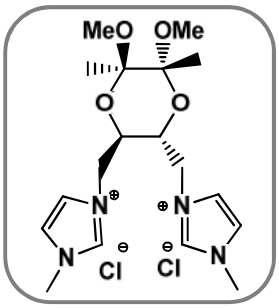
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.15 (CH_3), 48.13 (OCH_3), 51.42 (CH_2), 63.56 (CH_2), 67.37 (CHO), 99.20 (CHO), 125.37 (Ar), 126.75 (Ar), 126.88 (Ar), 127.79 (Ar), 128.23 (Ar), 128.68 (Ar), 129.53 (Ar), 130.03 (Ar), 133.28 (Ar), 133.49 (Ar), 159.14 (C=N).

ESI-TOF MS (m/z): 525.27 (M^+), 526.28 (M+1), 527.28 (M+2).

6.2.3. Synthesis of di-NHC-type salts



6.2.3.1. Synthesis of 3,3'-(((2R,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-methyl-1H-imidazol-3-ium) chloride (10a):[4]



To a round-bottom flask fitted with a reflux condenser was added (2*R*,3*R*,5S,6*S*)-5,6-bis(chloromethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **(9)** (2.0 g, 7.32 mmol), 1-methylimidazole (2.9 ml, 37.0 mmol) and CH_3CN (50 ml).

The mixture was stirred for 2 days at 90ºC. The solvent was evaporated under reduced pressure and the crude brown oil was washed several times with pentane. The pentane fractions were evaporated under reduced pressure, to afford 3,3'-(((2R,3R,5R,6R)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis (methylene))bis(1-methyl-1H-imidazol-3-ium) chloride **(10a)** as colorless crystals (1.53 g, 47%).

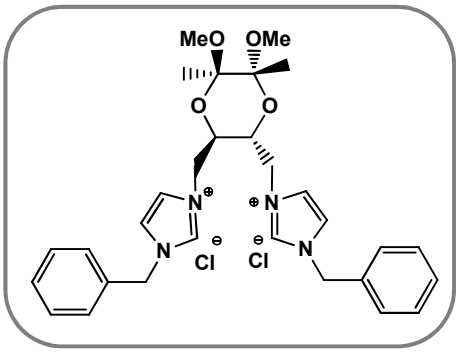
m.p.: 54.7-56.0ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.28 (s, CH_3, 6H), 3.24 (s, OCH_3, 6H), 3.55-3.63 (m, CH_2N, 4H), 3.65 (s, CH_3, 6H), 3.90-3.91 (m, CHO, 2H), 6.84 (s, NHC, 2H), 7.01 (s, NHC, 2H), 7.39 (s, NCHN, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.31 (CH_3), 33.20 (CH_3), 43.47 (CH_2), 48.01 (OCH_3), 69.56 (CHO), 99.24 (CHO), 120.02 (NC), 129.44 (NC), 137.77 (NCN).

FAB^{+} MS (m/z): 365.0 (M^{+}).

6.2.3.2. Synthesis of 3,3'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(1-benzyl-1H-imidazol-3-ium) chloride (10b):



The same procedure reported above was applied (see 6.2.3.1.) using (2*R*,3*R*,5*S*,6*S*)-5,6-bis(chloromethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane **(9)** (0.2 g, 0.73 mmol) and 1-benzylimidazole (0.23 g, 1.5 mmol). The pentane fractions afforded 3,3'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-

2,3-diyl)bis(methylene))bis(1-benzyl-1H-imidazol-3-ium) chloride **(10b)** as an orange solid (0.45 g, 98%).

m.p.: 44.0-45.6ºC.

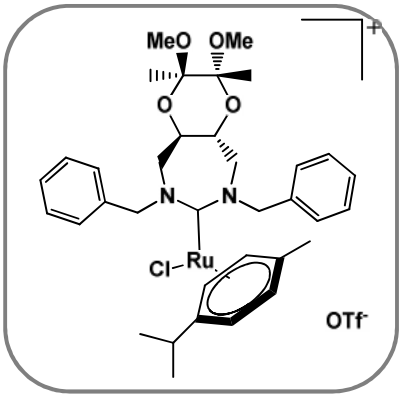
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (s, CH_3, 6H), 3.29 (s, OCH_3, 6H), 3.55-3.67 (m, CH_2N, 4H), 3.95 (t, CHO, 2H), 5.12 (s, CH_2Ph, 4H), 6.91 (s, CH=N, 2H), 7.09 (s, C=NH, 2H), 7.14-7.39 (m, Ar, 10H), 7.56 (s, NCHN, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.31 (CH_3), 43.44 (OCH_3), 48.05 (CH_2), 50.73 (CH_2), 69.57 (CHO), 99.24 (CHO), 119.25 (CH), 127.20 (Ar), 128.20 (Ar), 128.91 (Ar), 129.66 (Ar), 136.58 (CH), 137.36 (Ar).

FAB^{+} MS (m/z): 394.51 (M^{+}).

6.2.4. Synthesis of metal complexes from mono and di-NHC type salts

6.2.4.1. Synthesis of [RuCl(3a)(η^6-cymene)]OTf (11):



To a schlenk flask was added (2*R*,3*R*,4a*R*,9a*R*)-6,8-dibenzyl-2,3-dimethoxy-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) **(3a)** (20 mg, 0.035 mmol), AgOTf (12 mg, 0.046 mmol) and toluene (1 ml). The reaction was left stirring overnight at 50ºC in the dark. $[RuCl_2(\eta^6\text{-cymene})]_2$ (21.5 mg, 0.035 mmol) was added to the mixture and then stirred at 50ºC, for 2 h. The mixture was filtrated over *celite* and the solvent evaporated under reduced pressure. The crude solid was dissolved in CH_2Cl_2 and

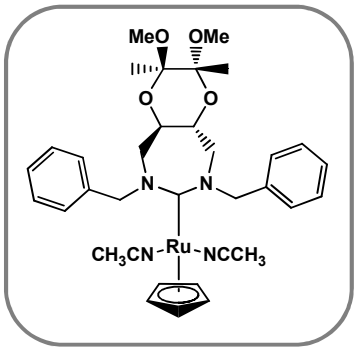
recrystallized with pentane. The desired complex [RuCl**(3a)**(η^6-cymene)]OTf **(11)** was obtained as an orange-red solid (42 mg, >90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.14 (s, CH_3, 6H), 1.26-1.34 (m, CH_3, 6H), 2.20 (s, CH_3, 3H), 2.70 (m, CH, 2H), 3.02 (s, OCH_3, 6H), 3.25-3.40 (m, CH_2N, 2H), 3.44 (m, CH_2N, 2H), 3.56-3.60 (m, CHO, 2H), 4.78-4.89 (q, CH_2, 4H), 5.47-5.51 (m, CH-Cy, 2H), 5.63-5.65 (m, CH-Cy, 2H), 7.35-7.40 (m, Ar, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.24 (CH_3), 18.99 (CH_3), 22.05 (CH_3), 22.17 (CH_3), 22.32 (CH_3), 31.04 (CH), 31.51 (CH), 48.22 (OCH_3), 51.58 (CH_2), 63.24 (CH_2), 67.44 (CHO), 78.26 (C), 78.96 (C), 99.27 (C-C), 128.85 (Ar), 129.42 (Ar), 132.96 (Ar), 159.89 (C=N).

ESI-TOF MS (m/z): 571.0 (M^+).

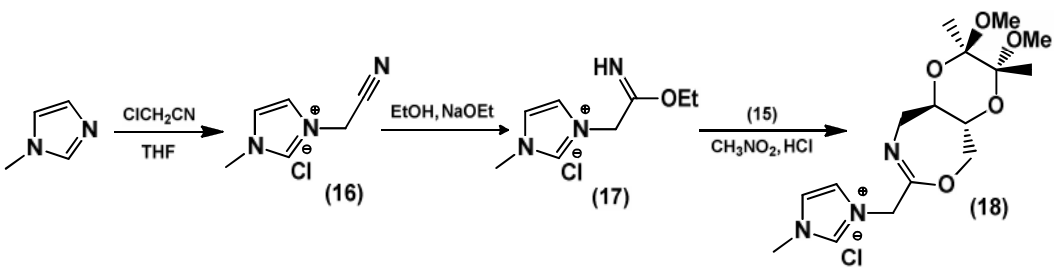
6.2.4.2. Synthesis of [RuCp(3a)($CH_3CN)_2$] (12):



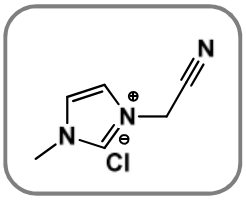
To a shlenk flask was added (2*R*,3*R*,4a*R*,9a*R*)-6,8-dibenzyl-2,3-dimethoxy-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate(V) **(3a)** (50 mg, 0.09 mmol), KO^{t}Bu (0.1 ml, 0.11 mol, 1M in THF) and THF (3 ml). The mixture was stirred at 50ºC during 2 h. [RuCp($CH_3CN)_3$]PF_6 (38 mg, 0.09 mmol) was added and the mixture was stirred at 50ºC, for 2h. The crude mixture was filtrated by cannula and the solvent evaporated under reduced pressure. The crude solid was dissolved in CH_2Cl_2 and recrystallized with hexane. The desired complex [RuCp**(3a)**($CH_3CN)_2$] **(12)** was obtained as a green oily solid (49 mg, 83%).

ESI-TOF MS (m/z): 670.5 (M^+).

6.2.5. Synthesis of NHC-oxazoline-type ligands and others



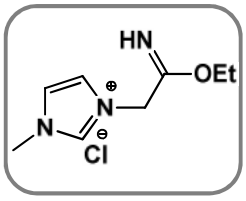
6.2.5.1. Synthesis of 1-(Cyanomethyl)-3-methylimidazolium Chloride (16):[5]



To a round-bottom flask fitted with a reflux condenser was added 1-methylimidazole (3.4 ml, 50 mmol) and THF (50 ml). Chloroacetonitrile (3.2 ml, 50 mmol) was added dropwise and the mixture was then refluxed overnight. The solvent was decanted and the solid washed with THF (2×20 ml). After evaporation of the residual solvents, the desired 1-(cyanomethyl)-3-methylimidazolium chloride **(16)** was obtained as a hygroscopic white solid (5.1 g, 65%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.88 (s, CH_3, 3H), 5.72 (s, NCH_2, 2H), 7.82 (s, NHC, 1H), 7.93 (s, NHC, 1H), 9.43 (s, NCH, 1H).

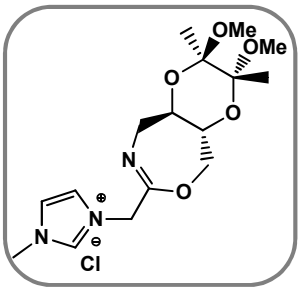
6.2.5.2. Synthesis of 3-((Ethoxycarbonimidoyl)methyl)-1-methylimidazolium chloride (17):[5]



To a round-bottom flask was added 1-(cyanomethyl)-3-methylimidazolium chloride **(16)** (1.5 g, 9.5 mmol), NaH (3.8 mg, 1 mol%) and EtOH (10 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to afford 3-((Ethoxycarbonimidoyl)methyl)-1-methylimidazolium chloride **(17)** as an orange solid (1.96 g, 96%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.04 (t, *J*= 7 Hz, CH_3, 3H), 3.89 (m, OCH_2, 2H), 4.97 (s, NCH_3, 3H), 5.32 (s, NCH_2, 2H), 7.45 (s, NCH, 1H), 7.68 (s, NCH, 1H), 9.47 (s, C=NH, 1H), 9.50 (s, NCHN, 1H).

6.2.5.3. Synthesis of 3-(((2*R*,3*R*,4a*R*,9a*R*)-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,9,9a-hexahydro-[1,4]dioxino[2,3-e][1,3]oxazepin-7-yl)methyl)-1-methyl-1H-imidazol-3-ium chloride (18):



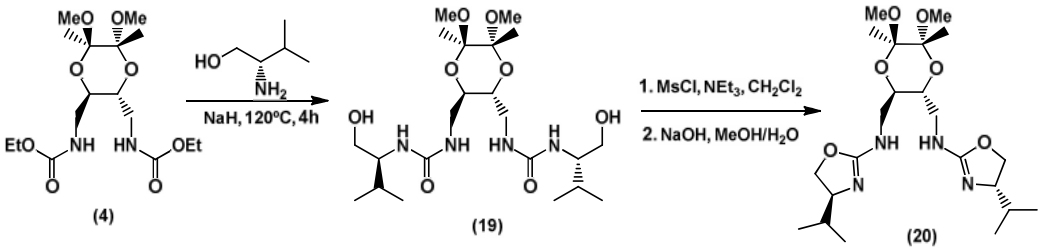
To a round-bottom flask fitted with a reflux condenser was added 3-((ethoxycarbonimidoyl)methyl)-1-methylimidazolium chloride **(17)** (0.15 g, 0.74

mmol), ((2*R*,3*R*,5*R*,6*R*)-3-(aminomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol **(15)** (0.17 g, 0.74 mmol), nitromethane (4 ml) and two drops of HCl 37%. The mixture was heated to 80ºC for 16 h. The solvents were evaporated under reduced pressure to afford 3-(((2*R*,3*R*,4a*R*,9a*R*)-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,9,9a-hexahydro-[1,4]dioxino[2,3-e][1,3]oxazepin-7-yl)methyl)-1-methyl-1H-imidazol-3-ium chloride **(18)** as a hygroscopic orange solid (0.26 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.22-1.44 (s, CH_3, 6H), 3.23 (s, OCH_3, 6H), 3.27-4.26 (m, CH_2N+CHO+CH_2O, 5H), 4.06 (s, CH_3, 3H), 5.24-5.87 (m, CH_2N+CHO, 3H), 7.30 (s, NCH, 1H), 7.62 (s, NCH, 1H), 9.64 (s, C=NH, 1H).

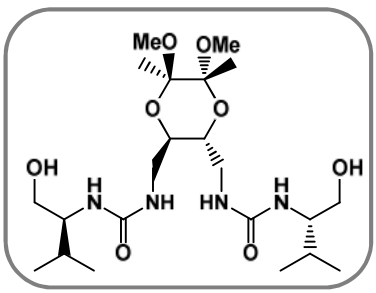
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.51 (CH_3), 29.63 (CH_3), 48.05 (OCH_3), 51.64 (CH_2O), 61.81 (=NCH), 68.11 (NCH_2), 70.97 (CHO), 98.85 (CO), 122.53 (CH), 123.44 (CH), 137.89 (CH), 165.03 (CNO).

Micro-TOF MS (m/z): 358.21 (M^+).



(4) (19) (20)

6.2.5.4. Synthesis of 1,1'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(3-((*S*)-1-hydroxy-3-methylbutan-2-yl)urea) (19):



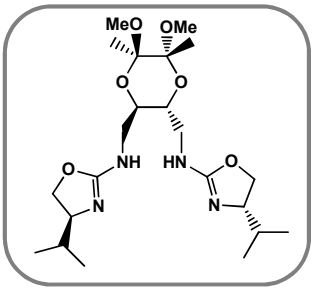
To a round-bottom flask was added diethyl (((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))dicarbamate **(4)** (0.6 g, 1.6 mmol), (*S*)-valinol (0.6 g, 5.8 mmol) and NaH (11.6 mg, 0.3 mmol). The mixture was stirred at 120ºC during 4 h. The EtOH formed was removed under reduced pressure and dissolved in CH_2Cl_2 (3 ml). The addition of pentane (50 ml) led to the precipitation of the product. After extensive drying under vacuum, the desired 1,1'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)) bis(3-((*S*)-1-hydroxy-3-methylbutan-2-yl)urea) **(19)** was obtained as a yellow oil (0.17 g, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (s, CH_3, 6H), 1.29 (m, CH_3, 6H), 1.69 (m, CH, 2H), 2.5 (s br, OH, 2H), 3.23 (s, OCH_3, 6H), 3.30 (t, CH_2OH, 4H), 3.65 (C*H*$_2$NH, 4H), 4.12 (m, C*H*NH, 2H), 4.45 (t, CHO, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 17.42 (CH_3), 18.03 (CH_3), 18.67 (CH_3), 18.73 (CH_3), 19.07 (CH_3), 19.66 (CH_3), 30.54 (CH), 48.13 (CH_2), 50.77 (CH_2), 58.21 (OCH_3), 58.60 (CH_2), 63.37 (CH), 68.52 (CH), 99.11 (CH), 160.05 (C=O).

ESI-TOF MS (m/z): 482.31 (M^+).

6.2.5.5. Synthesis of (4*S*,4'*S*)-*N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(4-isopropyl-4,5-dihydrooxazol-2-amine) (20):



To a round-bottom flask was added 1,1'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(3-((*S*)-1-hydroxy-3-methylbutan-2-yl)urea) **(19)** (0.14 g, 0.28 mmol), NEt_3 (0.2 ml, 1.4 mmol) and CH_2Cl_2 (5 ml).

The mixture was stirred at 0ºC and CH_3SO_2Cl (50 µl, 0.7 mmol) was added drop wise. The reaction was left stirring at room temperature for 4 h. It was quenched with NH_4Cl (aq. 5%) and extracted with CH_2Cl_2 (2×5 ml). After drying the organic phase with $MgSO_4$, the solvent was evaporated under reduced pressure. NaOH (44 mg, dissolved in 5 ml of MeOH/H_2O (1:1)) was added to the crude product and it was stirred at reflux temperature for 3 h. The MeOH was evaporated under reduced pressure and the aqueous mixture extracted with CH_2Cl_2 (4×5 ml). The organic phases were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude final product was purified by using deactivated silica gel chromatography (AcOEt) to afford (4*S*,4'*S*)-*N*,*N*'-(((2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(4-isopropyl-4,5-dihydrooxazol-2-amine) **(20)** as a yellow oil (24 mg, 20%).

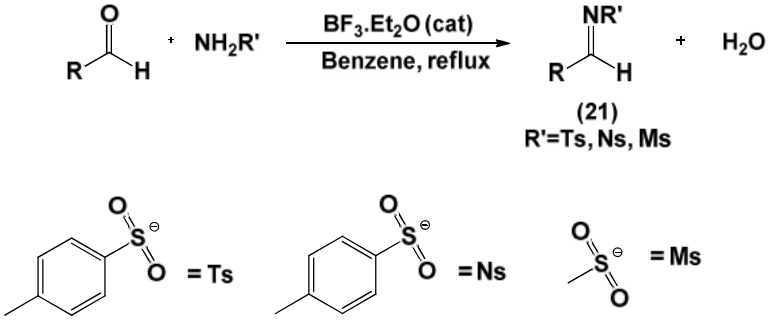
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91-0.99 (m, CH_3, 12H), 1.01 (s, CH_3, 6H), 1.88-1.92 (m, CH, 2H), 3.05 (s, OCH_3, 6H), 3.30 (m, CHN, 2H), 3.62-3.80 (m, CHO+CHO, 2H), 5.00 (m, CHO, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.09 (CH_3), 17.92 (CH_3), 29.68 (CH_3), 33.05 (CH), 47.93 (OCH_3), 56.59 (CH_2), 60.95 (CH_2), 68.86 (CH), 98.69 (CHO), 156.80 (C*q*), 162.97 (C=N).

ESI-TOF MS (m/z): 581.32.

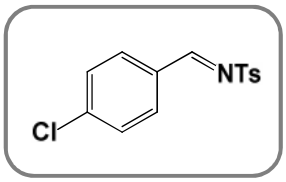
6.3. Enantioselective synthesis of chiral amines

6.3.1. Synthesis of aldimines – General procedure:[6]



By using a Dean-Stark trap to facilitate water removal and without an inert atmosphere, $BF_3.Et_2O$ (0.6 mmol) was added (through a syringe) to a refluxing solution of the aldehyde (36 mmol) and the amine (36 mmol) in benzene (135 ml). The mixture was refluxed until the theoretical amount of water (36 mmol) was collected. The solution was then cooled and washed with NaOH (2M aqueous solution) and water. The organic phase was separated and dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure to yield the desire imine product, which was recrystallized from CH_2Cl_2/petroleum ether (b.p. 60-80ºC) affording a clean solid.

6.3.1.1. Synthesis of *N*-(4-chlorobenzylidene)-4-methylbenzene sulfonamide (21a):[3,7,8]

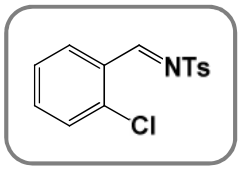


White solid (40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (s, CH_3, 3H), 7.35 (d, *J*= 8.1 Hz, Ar, 2H), 7.45-7.48 (m, Ar, 4H), 7.85-7.90 (m, Ar, 2H), 8.99 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (93:7), flow rate: 1.0 ml/min., wavelength detector at 230 nm, t_R= 7.4 min.

6.3.1.2. Synthesis of *N*-(2-chlorobenzylidene)-4-methylbenzene sulfonamide (21b):[3,7,8]

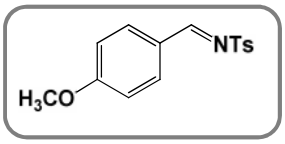


White solid (35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.45 (s, CH_3, 3H), 7.32-7.38 (m, Ar, 2H), 7.45-7.56 (m, Ar, 2H), 7.89-7.92 (d, *J*= 8.4 Hz, Ar, 2H), 8.14-8.17 (dd, *J*= 1.5 and 7.8 Hz, Ar, 2H), 9.50 (s, HC=N, 1H).

HPLC: Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate: 0.7 ml/min., wavelength detector at 230 nm, t_R= 26.1 min.

6.3.1.3. Synthesis of *N*-(4-methoxybenzylidene)-4-methylbenzene sulfonamide (21c):[3,7]

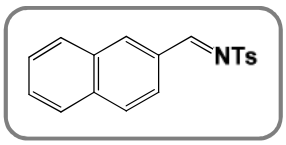


Yellow solid (38% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.43 (s, CH_3, 3H), 3.88 (s, OCH_3, 3H), 6.95-6.98 (d, *J*=8.7 Hz, Ar, 2H), 7.32-7.35 (d, *J*= 8.1 Hz, Ar, 2H), 7.86-7.90 (dd, *J*= 2.1, 2.4 and 8.6 Hz, Ar, 4H), 8.94 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 12.3 min.

6.3.1.4. Synthesis of 4-methyl-N-(naphthalen-2-ylmethylene)benzene sulfonamide (21d):[3,7]

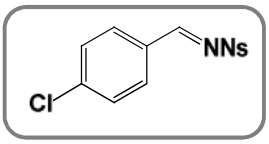


Pale yellow solid (64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (s, CH_3, 3H), 7.35-7.38 (m, Ar, 2H), 7.78-7.65 (m, Ar, 2H), 7.87-7.97 (m, Ar, 5H), 8.02-8.05 (m, Ar, 1H), 8.33 (s, Ar, 1H), 9.18 (s, HC=N, 1N).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 12.4 min.

6.3.1.5. Synthesis of (*E*)-*N*-(4-chlorobenzylidene)-4-nitrobenzene sulfonamide (21e):[9]

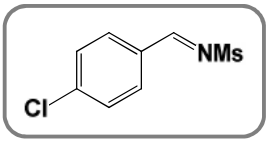


Pale yellow solid (44% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49-7.52 (d, Ar, 2H), 7.88-7.90 (d, Ar, 2H), 8.19-8.22 (d, Ar, 2H), 8.39-8.41 (d, Ar, 2H), 9.09 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 10.6min.

6.3.1.6. Synthesis of *N*-(4-chlorobenzylidene)methanesulfonamide (21f):[3]

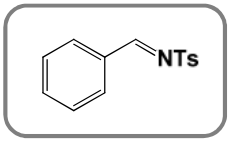


White solid (33% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.14 (s, CH_3, 3H), 7.51 (d, Ar, 2H), 7.89 (d, Ar, 2H), 8.99 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 10.5min.

6.3.1.7. Synthesis of *N*-benzylidene-4-methylbenzenesulfonamide (21g):[10]

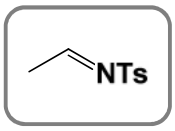


Pale yellow solid (36% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (s, CH_3, 3H), 7.34-7.36 (d, Ar, 3H), 7.46-7.51 (t, Ar, 2H), 7.59-7.64 (t, Ar, 2H), 7.88-7.94 (t, Ar, 2H), 9.03 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (93:7), flow rate: 1.0 ml/min., wavelength detector at 230 nm, t_R= 7.3 min.

6.3.1.8. Synthesis of *N*-ethylidene-4-methylbenzenesulfonamide (21h):

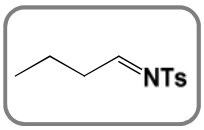


White solid (36% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.42 (s, CH_3, 3H), 3.81 (s, CH_3, 3H), 7.29-7.31 (d, Ar, 2H), 7.74-7.76 (d, Ar, 2H), 8.25-8.26 (d, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.3 ml/min., wavelength detector at 254 nm, t_R= 12 min.

6.3.1.9. Synthesis of *N*-butylidene-4-methylbenzenesulfonamide (21i):[3,7]

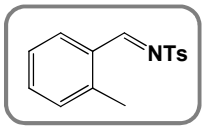


Colorless oil (10% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (m, CH_3, 3H), 1.51 (m, CH_2, 2H), 2.33 (m, CH_2, 2H), 2.42 (s, CH_3, 3H), 7.31 (d, Ar, 2H), 7.81 (d, Ar, 2H), 8.45 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.3 ml/min., wavelength detector at 230 nm, t_R= 18.8min.

6.3.1.10. Synthesis of 4-methyl-*N*-(2-methylbenzylidene)benzene sulfonamide (21j):[3,7]

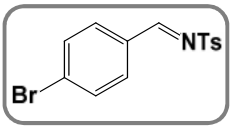


Yellow solid (73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (s, CH_3, 3H), 2.61 (s, CH_3, 3H), 7.25-7.36 (m, Ar, 4H), 7.45-7.50 (t, *J*= 7.5 Hz, Ar, 1H), 7.88-7.91 (d, *J*= 8.1 Hz, Ar, 2H), 7.99-8.02 (d, *J*= 7.8 Hz, Ar, 1H), 9.35 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 14 min.

6.3.1.11. Synthesis of *N*-(4-bromobenzylidene)-4-methylbenzene sulfonamide (21k):[3,7]

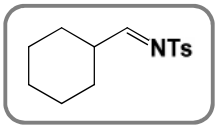


White solid (30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (s, CH3, 3H), 7.34-7.36 (m, Ar, 2H), 7.62-7.65 (d, Ar, 2H), 7.77-7.79 (d, Ar, 2H), 7.87-7.89 (d, Ar, 2H), 8.98 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.7 ml/min., wavelength detector at 230 nm, t_R= 10.7min.

6.3.1.12. Synthesis of *N*-(cyclohexylmethylene)-4-methylbenzene sulfonamide (21l):[3,7]

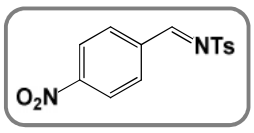


White solid (15% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.15-1.29 (m, CH_2, 6H), 1.76-1.81 (m, CH_2, 5H), 2.32 (s, CH_3, 3H), 7.19-7.21 (d, Ar, 2H), 7.69-7.73 (d, Ar, 2H), 8.37 (s, HC=N, 1H).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 11 min.

6.3.1.13. Synthesis of 4-methyl-N-(4-nitrobenzylidene)benzene sulfonamide (21m):[3,7]

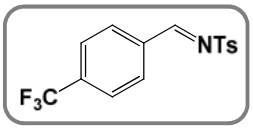


Pale yellow solid (22% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.46 (s, CH_3, 3H), 7.38 (d, Ar, 2H), 7.91 (d, Ar, 2H), 8.11 (d, Ar, 2H), 8.33 (d, Ar, 2H), 9.10 (s, HC=N, 1H).

HPLC: Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate: 0.7 ml/min., wavelength detector at 230 nm, t_R= 26.4min.

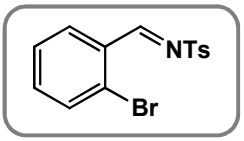
6.3.1.14. Synthesis of 4-methyl-*N*-(4-(trifluoromethyl)benzylidene) benzenesulfonamide (21n):[10]



White solid (75% yield).

^{1}H NMR (400 MHz, DMSO-d^6) δ (ppm): 2.37 (s, CH_3, 3H), 7.36 (d, J= 8 Hz, Ar, 2H), 7.71 (d, J= 8 Hz, Ar, 2H), 7.99 (d, J= 8 Hz, Ar, 2H), 8.12 (d, J= 8 Hz, Ar, 2H), 10.13 (s, HC=N, 1H).

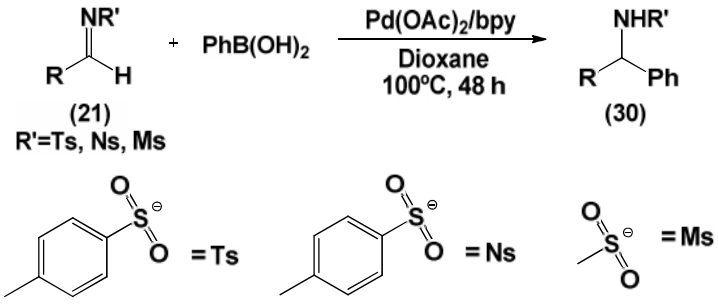
6.3.1.15. Synthesis of *N*-(2-bromobenzylidene)-4-methylbenzene sulfonamide (21o):[7]



White solid (68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.45 (s, CH_3, 3H), 7.35-7.37 (d, Ar, 2H), 7.39-7.45 (m, Ar, 2H), 7.64-7.67 (m, Ar, 1H), 7.89-7.91 (d, Ar, 2H), 8.13 (m, Ar, 1H), 9.43 (s, HC=N, 1H).

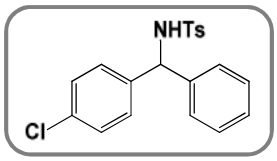
6.3.2. Synthesis of amines - General procedures:[3,8]



Catalytic asymmetric arylation of aldimines with organoboron reagents: Toluene (2 ml) was added to a round-bottom flask containing the metal pre-catalyst (Pd, Ru) (3 mol%), the chiral ligand (Phosphane or NHC) (3.3 mol%) and AgOTf (3 mol% in the case of NHC ligand was used), and the organoboron reagent (0.4 mmol). The mixture was stirred at 55ºC for 30 min. to form the active catalytic species. The aldimine **(21)** (0.2 mmol) and NEt_3 (0.4 mmol) were added sequentially to the flask, and the mixture was left stirring at 55ºC and monitored by TLC. HCl 0.2 M (5 ml) was added to quench the reaction. AcOEt (3×10 ml) was used to extract the product from the aqueous phase. The combined organic phases were washed with *brine* solution, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (Hex/AcOEt (5:1)) provided the final chiral arylamine product **(30)**.

The racemic chiral amines were prepared as followed: To a round-bottom flask was added the corresponding aldimine **(21)** (0.5 mmol), phenylboronic acid (1.0 mmol), $Pd(OAc)_2$ (5 mol%) and 2,2'-bipyridine (10 mol%) in 1,4-dioxane (2 ml), stirring at 100ºC during 48-72 hours. The reaction was monitored by TLC. This was followed by filtration using a sintered glass filter funnel with a silica gel layer giving the corresponding crude product, which was purified afterwards by chromatography with silica gel (Hex/AcOEt (5:1)) affording the desired racemic amine product **(30)**.

6.3.2.1. Synthesis of *N*-((4-chlorophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (30a):[3,7,8]



White solid.

m.p.: 132.0-133.5ºC (m.p. Lit.[7] 127.2-127.4ºC)

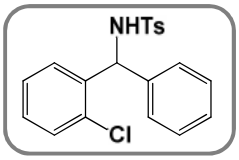
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.17 (s, CH_3, 3H), 5.04–5.05 (d, *J*= 4 Hz, CH, 1H), 5.52–5.54 (d, *J*= 8 Hz, NH, 1H), 7.03– 7.07 (m, Ar, 4H), 7.15–7.19 (m, Ar, 4H), 7.21–7.23 (m, Ar, 3H), 7.54–7.56 (d, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.64 (CH_3), 60.83 (CH), 126.62 (Ar), 127.34 (Ar) (Ar), 127.43 (Ar), 127.89 (Ar), 128.07 (Ar), 128.30 (Ar), 128.79 (Ar), 128.90 (Ar), 128.92 (Ar), 129.59 (Ar), 129.76 (Ar), 130.01 (Ar), 132.51 (Ar), 133.64 (Ar), 137.28 (Ar), 139.07 (Ar), 140.19 (Ar), 143.63 (Ar).

ESI-TOF MS (m/z): 394.07 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (93:7), flow rate: 1.0 mL/min., wavelength detector at 230 nm, t_R = 18.0 (*S*), 24.0 (*R*) min.

6.3.2.2. Synthesis of *N*-((2-chlorophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (30b):[3,7,8]



White solid.

m.p.: 177.4-179.0ºC (m.p. Lit.[7] 175.6-176.0ºC)

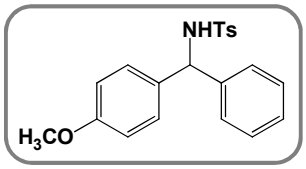
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.38 (s, CH_3, 3H), 5.31–5.33 (d, *J*= 8 Hz, CH, 1H), 5.90–5.92 (d, *J*= 8 Hz, NH, 1H), 7.05– 7.08 (m, Ar, 2H), 7.14–7.16 (m, Ar, 4H), 7.22–7.24 (m, Ar, 4H), 7.33–7.35 (m, Ar, 1H), 7.60–7.62 (d, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.64 (CH_3), 58.77 (CH), 127.07 (Ar), 127.35 (Ar), 127.39 (Ar), 127.98 (Ar), 128.78 (Ar), 128.79 (Ar), 128.79 (Ar), 128.97 (Ar), 129.48 (Ar), 129.55 (Ar), 129.56 (Ar), 129.57 (Ar), 130.03 (Ar), 132.93 (Ar), 137.05 (Ar), 137.61 (Ar), 139.40 (Ar), 143.52 (Ar).

ESI-TOF MS (m/z): 394.07 (M+1).

HPLC: Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate: 0.7 mL/min., wavelength detector at 230 nm, t_R = 27.9 (*S*), 31.8 (*R*) min.

6.3.2.3. Synthesis of *N*-((4-methoxyphenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (30c):[3,7]



Pale yellow solid.

m.p.: 119.7-121.0ºC (m.p. Lit.[7] 119.9-120.5ºC)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.38 (s, CH_3, 3H), 3.76 (s, OCH_3, 3H), 4.96-4.99 (d, *J*= 6.9 Hz, CH, 1H), 5.51-5.53 (d, *J*= 6.9 Hz, NH, 1H), 6.72-6.75 (d, *J*= 8.7 Hz, Ar, 2H), 6.98-7.01 (d, *J*= 8.7 Hz, Ar, 2H), 7.09-7.21 (m, Ar, 7H), 7.55-7.57 (d, *J*= 8.1 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.59 (CH_3), 54.83 (OCH_3), 55.60 (CH), 110.09 (Ar), 120.62 (Ar), 121.38 (Ar), 126.58 (Ar), 127.10 (Ar), 127.46 (Ar), 128.60 (Ar), 129.32 (Ar), 129.38 (Ar), 129.45 (Ar), 129.72 (Ar), 129.83 (Ar), 132.99 (Ar), 136.99 (Ar), 137.36 (Ar), 137.96 (Ar), 143.12 (Ar), 156.65 (Ar).

ESI-TOF MS (m/z): 389.65 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 20.5 min (*S*) and 31.7 min (*R*).

6.3.2.4. Synthesis of 4-methyl-*N*-(naphthalen-2-yl(phenyl)methyl)benzene sulfonamide (30d):[3,7]

Yellow solid.

m.p.: 165.0-165.9ºC (m.p. Lit.[7] 162.4-162.9ºC)

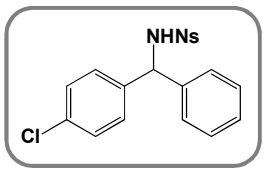
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.42 (s, CH_3, 3H), 5.41–5.43 (d, *J*= 8 Hz, CH, 1H), 5.72–5.74 (d, *J*= 8 Hz, NH, 1H), 7.02–7.04 (d, *J*= 8 Hz, Ar, 1H), 7.14–7.23 (m, Ar, 4H), 7.28–7.30 (d, *J*= 8 Hz, Ar, 2H), 7.43–7.45 (m, Ar, 2H), 7.50 (s, Ar, 1H), 7.53–7.55 (d, *J*= 8 Hz, Ar, 2H), 7.63–7.68 (m, Ar, 2H), 7.79–7.81 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.49 (CH_3), 61.59 (CH), 122.89 (Ar), 125.28 (Ar), 126.37 (Ar), 126.50 (Ar), 126.56 (Ar), 127.31 (Ar), 127.60 (Ar), 127.65 (Ar), 127.81 (Ar), 128.09 (Ar), 128.61 (Ar), 128.73 (Ar), 129.42 (Ar), 129.84 (Ar), 132.75 (Ar), 133.11 (Ar), 137.39 (Ar), 137.63 (Ar), 139.20 (Ar), 140.52 (Ar), 143.37 (Ar), 143.71 (Ar).

ESI-TOF MS (m/z): 410.12 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 mL/min., wavelength detector at 230 nm, t_R = 20.2 (*R*), 22.1 (*S*) min.

6.3.2.5. Synthesis of *N*-((4-chlorophenyl)(phenyl)methyl)-4-nitrobenzene sulfonamide (30e):[9]



Yellow solid.

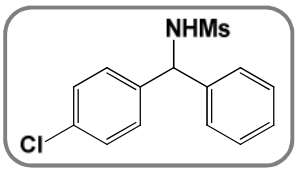
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.42 (m, CH, 1H), 5.68 (m, NH, 1H), 7.04-7.22 (m, Ar, 7H), 7.50-7.52 (m, Ar, 3H), 7.82-7.84 (m, Ar, 1H), 8.12-8.15 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 65.70 (CH), 121.09 (Ar), 122.99 (Ar), 127.06 (Ar), 127.08 (Ar), 128.15 (Ar), 128.77 (Ar), 128.87 (Ar), 129.14 (Ar), 129.56 (Ar), 133.19 (Ar), 138.45 (Ar), 141.45 (Ar), 143.60 (Ar), 149.57 (Ar).

ESI-TOF MS (m/z): 425.05 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 ml/min., wavelength detector at 230 nm, t_R= 32.3 min (*S*) and 58.8 min (*R*).

6.3.2.6. Synthesis of *N*-((4-chlorophenyl) (phenyl)methyl) methane sulfonamide (30f):[3]



White solid.

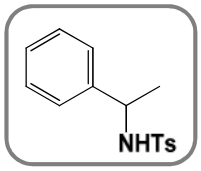
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.70 (s, CH_3, 3H), 5.17–5.18 (m, CH, 1H), 5.73–5.75 (m, NH, 1H), 7.28–7.40 (m, Ar, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 42.18 (CH_3), 60.79 (CH), 127.45 (Ar), 127.48 (Ar), 128.45 (Ar), 128.93 (Ar), 129.19 (Ar), 129.24 (Ar), 129.25 (Ar), 129.91 (Ar), 132.53 (Ar), 134.06 (Ar), 139.33 (Ar), 140.29 (Ar).

ESI-TOF MS (m/z): 318.04 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 mL/min., wavelength detector at 230 nm, t_R = 15.2 and 18.1 min.

6.3.2.7. Synthesis of 4-methyl-*N*-(1-phenylethyl)benzenesulfonamide (30g):



White solid.

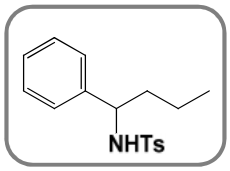
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.42 (s, CH_3, 3H), 3.71 (s, CH_3, 3H), 5.11 (s, CH, 1H), 5.19 (s br, NH, 1H), 7.38-7.39 (d, *J*= 4 Hz, Ar, 2H), 7.43-7.61 (m, Ar, 5H), 7.79-7.81 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 29.01 (CH), 55.38 (CH), 115.45 (Ar), 120.64 (Ar), 127.69 (Ar), 128.50 (Ar), 129.74 (Ar), 140.36 (Ar), 142.45 (Ar), 155.88 (Ar).

ESI-TOF MS (m/z): 297.56 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.3 ml/min., wavelength detector at 254 nm, t_R= 22.6 min (*R*) and 25.9 min (*S*).

6.3.2.8. Synthesis of 4-methyl-*N*-(1-phenylbutyl)benzenesulfonamide (30h):[3,7]



Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.84–0.98 (m, CH_3, 3H), 1.60–1.67 (m, CH_2, 2H), 2.28–2.32 (m, CH_2, 2H), 2.24 (s, CH_3, 3H), 4.07–4.11 (m, CH, 1H), 4.21–4.25 (m, NH, 1H), 7.31– 7.83 (m, Ar, 9H).

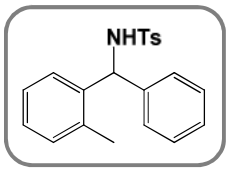
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.61 (CH_3), 19.89 (CH_2), 29.75 (CH_3), 44.89 (CH_2), 64.63 (CH), 126.15 (Ar), 126.64 (Ar), 127.20 (Ar), 127.45 (Ar), 127.49

(Ar), 127.90 (Ar), 128.34 (Ar), 128.56 (Ar), 129.01 (Ar), 129.80 (Ar), 129.85 (Ar), 130.13 (Ar).

ESI-TOF MS (m/z): 302.13 (M^+).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 mL/min., wavelength detector at 230 nm, t_R = 15.0 (*S*), 16.3 (*R*) min.

6.3.2.9. Synthesis of 4-methyl-*N*-(phenyl(o-tolyl)methyl)benzene sulfonamide (30i):[3,7]



Yellow solid.

m.p.: 117.0-118.9ºC (m.p. Lit.[7] 117.6-118.1ºC)

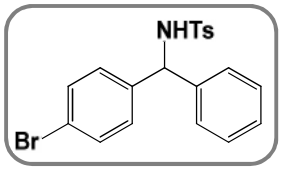
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.17 (s, CH_3, 3H), 2.43 (s, CH_3, 3H), 5.30 (s, CH, 1H), 6.02 (s, NH, 1H), 7.06–7.23 (m, Ar, 5H), 7.28–7.38 (m, Ar, 4H), 7.51–7.56 (m, Ar, 2H), 7.80–7.82 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.62 (CH_3), 22.84 (CH_3), 58.41 (CH), 125.80 (Ar), 126.28 (Ar), 126.30 (Ar), 126.39 (Ar), 126.63 (Ar), 127.20 (Ar), 127.26 (Ar), 127.69 (Ar), 127.74 (Ar), 127.77 (Ar), 128.64 (Ar), 128.70 (Ar), 128.85 (Ar), 129.47 (Ar), 129.89 (Ar), 130.70 (Ar), 139.16 (Ar), 143.81 (Ar).

ESI-TOF MS (m/z): 374.13 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 mL/min., wavelength detector at 230 nm, t_R = 12.3 (*R*), 15.3 (*S*) min.

6.3.2.10. Synthesis of *N*-((4-bromophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (30j):[3,7]



White solid.

m.p.: 122.8-123.7ºC (m.p. Lit.[7] 120.0-121.2ºC)

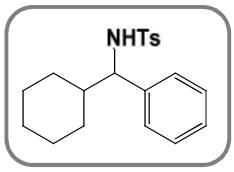
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.40 (s, CH_3, 3H), 4.96–4.98 (d, *J*= 8 Hz, CH, 1H), 5.51–5.52 (d, *J*= 4 Hz, NH, 1H), 6.99– 7.05 (m, Ar, 4H), 7.15–7.17 (d, *J*= 8 Hz, Ar, 2H), 7.21–7.23 (m, Ar, 3H), 7.31–7.35 (m, Ar, 2H), 7.54–7.56 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.74 (CH_3), 60.99 (CH), 121.79 (Ar), 126.64 (Ar), 127.35 (Ar), 127.43 (Ar), 128.11 (Ar), 128.92 (Ar), 129.27 (Ar), 129.60 (Ar), 129.89 (Ar), 131.74 (Ar), 136.84 (Ar), 137.09 (Ar), 137.38 (Ar), 138.24 (Ar), 139.56 (Ar), 140.10 (Ar), 143.52 (Ar), 143.86 (Ar).

ESI-TOF MS (m/z): 440.02 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.7 mL/min., wavelength detector at 230 nm, t_R = 11.6 (*S*), 14.2 (*R*) min.

6.3.2.11. Synthesis of *N*-(cyclohexyl(phenyl)methyl)-4-methylbenzene sulfonamide (30k):[3,7]



Pale yellow oil.

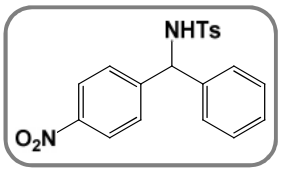
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.85–1.10 (m, CH_2, 2H), 1.22–1.28 (m, CH_2, 4H), 1.33–1.59 (m, CH_2, 4H), 2.41 (s, CH_3, 3H), 3.30–3.32 (d, *J*= 8 Hz, CH, 1H), 4.85–4.87 (d, *J*= 8 Hz, NH, 1H), 7.29–7.36 (m, Ar, 5H), 7.67–7.69 (d, *J*= 8 Hz, Ar, 2H), 7.79– 7.83 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.65 (CH_3), 22.37 (CH_2), 22.88 (CH_2), 25.81 (CH_2), 26.55 (CH_2), 28.89 (CH_2), 38.53 (CH), 66.33 (CH), 126.56 (Ar), 126.63 (Ar), 127.02 (Ar), 127.13 (Ar), 128.22 (Ar), 129.57 (Ar), 129.88 (Ar), 130.06 (Ar), 130.71 (Ar), 139.05 (Ar), 143.30 (Ar), 145.13 (Ar).

ESI-TOF MS (m/z): 266.13 $(M+1–Ph)^+$.

HPLC: Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate: 0.5 mL/min., wavelength detector at 230 nm, t_R = 10.9 (*S*), 14.0 (*R*) min.

6.3.2.12. Synthesis of 4-methyl-*N*-((4-nitrophenyl)(phenyl)methyl) benzenesulfonamide (30l):[3,7]



Light orange solid.

m.p.: 133.5-134.8ºC (m.p. Lit.[7] 135.8-136.2ºC)

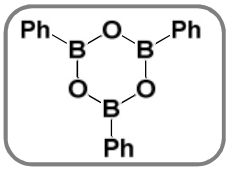
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.40 (s, CH_3, 3H), 5.25–5.27 (d, *J*= 8 Hz, CH, 1H), 5.61–5.62 (d, *J*= 4 Hz, NH, 1H), 6.98–7.00 (d, *J*= 8 Hz, Ar, 2H), 7.17–7.19 (d, *J*= 8 Hz, Ar, 2H), 7.35–7.39 (m, Ar, 4H), 7.57–7.59 (m, Ar, 3H), 8.07–8.09 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.70 (CH_3), 61.07 (CH), 123.80 (Ar), 124.45 (Ar), 126.85 (Ar), 127.20 (Ar), 127.34 (Ar), 127.44 (Ar), 128.38 (Ar), 128.56 (Ar), 128.60 (Ar), 129.26 (Ar), 129.74 (Ar), 130.64 (Ar), 136.96 (Ar), 139.40 (Ar), 142.85 (Ar), 144.04 (Ar), 147.35 (Ar), 147.80 (Ar).

ESI-TOF MS (m/z): 405.09 (M+1).

HPLC: Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate: 0.7 mL/min., wavelength detector at 230 nm, t_R = 19.9 (*S*), 25.5 (*R*) min.

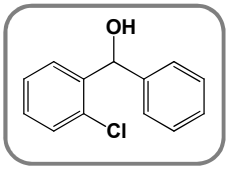
6.3.3. Synthesis of phenylboroxine:[11]



To a round-bottom flask, without an inert atmosphere, fitted with a Dean-Stark trap was added phenylboronic acid (1.7 g, 14 mmol) and benzene (80 ml). The mixture was refluxed for 2 hours, till the water (0.7 ml, 42 mmol) was removed azeotropically. The mixture was evaporated under reduced pressure to *ca.* 10 ml and then it was cooled to room temperature. The precipitate was collected by filtration, washed with hexane (5×10 ml), affording phenylboroxine (1g, 23% yield) as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50-7.54 (m, Ar, 6H), 7.59-7.63 (m, Ar, 3H), 8.25-8.27 (m, Ar, 6H).

6.3.4. Synthesis of (2-chlorophenyl)(phenyl)methanol (35):[12]



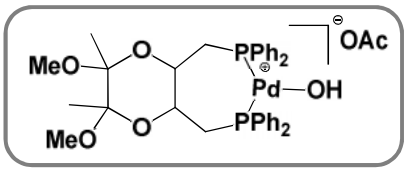
To a round-bottom flask was added $[Rh(COD)Cl]_2$ (2.6 mg, 1.5 mol%), PPh_3 (2.8 mg, 3 mol%), $PhB(OH)_2$ (86.8 mg, 0.7 mmol), *o*-chlorobenzaldehyde (50 mg, 0.35 mmol), KO^{t}Bu (40 mg, 0.35 mmol) and *t*-amyl alcohol (1 ml). The mixture was stirred at 60ºC and monitored by TLC. The solvent was evaporated under reduced pressure and the crude mixture purified by silica gel chromatography (Hex/AcOEt (9:1)), affording the title compound **(35)** as a yellow solid (70 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.40 (s br, OH, 1H), 6.26 (s, CH, 1H), 7.23-7.43 (m, Ar, 8H), 7.63-7.65 (d, *J*= 8 Hz, Ar, 1H).

HPLC: Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate: 0.7 ml/min., wavelength detector at 230 nm, t_R: 11.5 min (*R*) and 12.0 min (*S*).

6.3.5. Synthesis and isolation of metal complexes with phosphane ligands

6.3.5.1. Synthesis of Pd-DioxPhos complex (31):



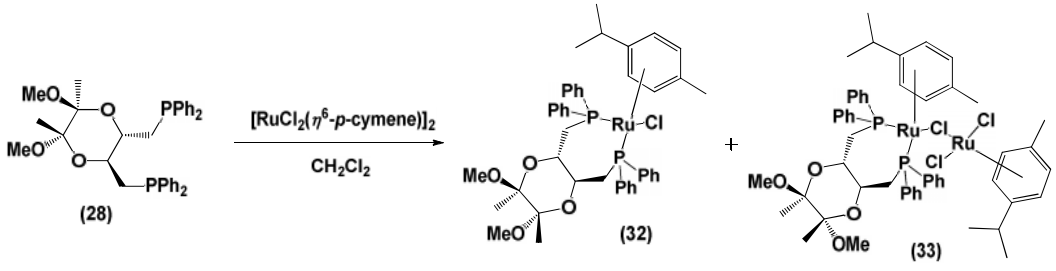
To a schlenk flask was added (*R*)-DioxPhos ligand **(28)** (20 mg, 0.035 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), $PhB(OH)_2$ (6.4 mg, 0.05 mmol) and CH_2Cl_2 (1 ml). The mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the crude solid re-crystalized with CH_2Cl_2/pentane. The Pd-DioxPhos complex **(31)** was synthesized as a red light solid (25 mg, 89.6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.12 (s, CH_3, 6H), 1.40 (s br, OH, 1H), 2.61 (m, CH_2P, 4H), 2.95 (s, OCH_3, 6H), 3.75 (m, CHO, 2H), 7.36-7.41 (m, Ar, 10H), 7.56-7.61 (m, Ar, 6H), 8.20 (m, Ar, 4H).

^{31}P NMR (160 MHz, $CDCl_3$) δ (ppm): 19.10.

ESI-TOF MS (m/z): 666.4 (M^+).

6.3.5.2. Synthesis of Ru-DioxPhos complexes (32) and (33):



To a schlenk flask were added $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (21.4 mg, 0.5 mol equiv.), (*S*)-DioxPhos ligand **(28)** (20 mg) and CH_2Cl_2 (2 ml). The mixture was stirred at room temperature overnight. The crude product was purified by silica gel chromatography (Hex/AcOEt (1:1)) and two fractions were collected. The solvents were evaporated under reduced pressure and both Ru-phosphine complexes **(32)** and **(33)** were isolated.

Ru-Phosphine dimer **(33):** orange solid (34.4 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.62 (s, CH_3, 3H), 0.77–0.78 (d, *J*= 4 Hz, CH_3, 3H), 1.02–1.04 (d, *J*= 8 Hz, CH_3, 3H), 1.24–1.27 (m, CH_3, 3H), 1.58 (s, CH_3, 3H), 1.78 (s, OCH_3, 3H), 2.38 (s, OCH_3, 3H), 2.48–2.58 (m, CH_2P, 4H), 2.72–2.74 (m, CH, 2H), 3.54–3.58 (m, CHO, 2H), 4.83–4.85 (d, *J*= 8 Hz, Ar-Cy, 1H), 5.21–5.23 (d, *J*= 8 Hz, Ar-Cy, 1H), 5.25–5.27 (d, *J*= 8 Hz, Ar-Cy, 1H), 5.36–5.37 (d, *J*= 4 Hz, Ar-Cy, 1H), 7.34 (m, Ar, 6H), 7.46–7.53 (m, Ar, 4H), 7.89–7.93 (m, Ar, 2H), 7.99–8.03 (m, Ar, 8H).

^{31}P NMR (160 MHz, $CDCl_3$) δ (ppm): 19.67.

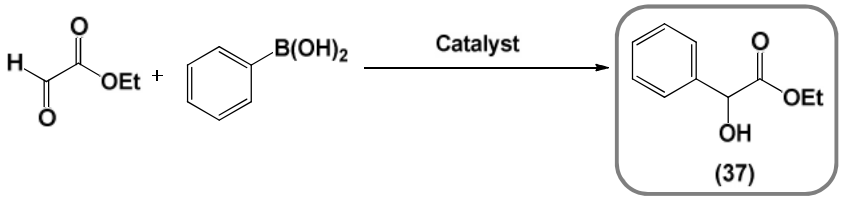
ESI-TOF MS (m/z): 1149 (M(^{35}Cl×3)), 1151 (M(^{35}Cl×2 + ^{37}Cl)).

Ru-Phosphine monomer **(32):** orange solid (10 mg, 10%).

ESI-TOF MS (m/z): 843 (M(^{35}Cl)), 845 (M(^{37}Cl)).

6.4. Catalytic arylation of activated C=O bonds; synthesis of α-hydroxyesters

6.4.1. Catalytic synthesis of ethyl mandelate – General procedures:[4]



[Ru] catalysts: To a round-bottom flask were added $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (4.5 mg, 1.5 mol%), PPh_3 (3.8 mg, 3 mol%) and toluene (3 ml). The mixture was stirred 30 minutes at room temperature to prepare the catalyst. Ethyl glyoxalate, 50% in toluene (100µl, 0.49 mmol), phenylboronic acid (119.2 mg, 0.98 mmol), base (0.98 mmol) and H_2O (0.3 ml) were then added and the mixture was left stirred at 80ºC for 12h, after which time the crude mixture was extracted using AcOEt, washed with saturated NH_4Cl and brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. Silica gel chromatography (Hex/AcOEt (5:1)) afforded the ethyl mandelate product **(37)** as colorless oil.

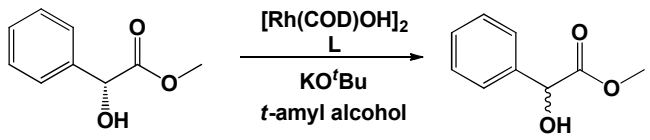
[Rh] catalysts: To a round-bottom flask were added sequentially $[Rh(I)]_2$ (1.5 mol%) or [Rh(I)] (3 mol%), ligand (3.3 mol%), boronic acid derivative (0.98 mmol), KO^tBu (54.2 mg, 0.49 mmol) and solvent (2 ml). Ethyl glyoxalate, 50% in toluene (100µl, 0.49 mmol) was added and the reaction was stirred at the desired temperature and monitored by TLC. The crude mixture was passed through a sintered glass filter and eluted with CH_2Cl_2. The solvents were concentrated under reduced pressure and the crude mixture purified by silica gel chromatography (Hex/AcOEt (5:1)), yielding the desired ethyl mandelate product **(37)** as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.21 (t, *J*= 4 Hz, CH_3, 3H), 3.56 (br s, OH, 1H), 4.17-4.26 (m, CH_2, 2H), 5.16 (s, CH, 1H), 7.34-7.42 (m, Ar, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.14 (CH_3), 62.33 (CH_2), 73.01 (CH), 126.63 (Ar), 128.49 (Ar), 128.66 (Ar), 138.53 (Ar), 173.76 (C=O).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 7.1 min (*S*) and 11.5 min (*R*).

6.4.2. Racemization studies with (*R*)-(-)-methyl mandelate:



(*R*)-(-)-Methyl Mandelate

General procedure A: To a round-bottom flask fitted with a reflux condenser was added (*R*)-(-)-methyl mandelate (50 mg, 0.3 mmol), $[Rh(COD)OH]_2$ (2.7 mg, 1.5 mol%), (*R*,*R*)-*i*-Pr-DuPhos **(25)** (2.7 mg, 3 mol%) and 1,4-dioxane (2 ml). The mixture was stirred at 100ºC and aliquots were taken hourly and analyzed by chiral stationary phase HPLC.

General procedure B: To a round-bottom flask was added (*R*)-(-)-methyl mandelate (50 mg, 0.3 mmol), $[Rh(COD)OH]_2$ (2.7 mg, 1.5 mol%), NHC **(3a)** (5.7 mg, 3.3 mol%), KO^{t}Bu (1,1 mg, 3.3 mol%) and *t*-amyl alcohol (1 ml). The mixture was stirred at room temperature and aliquots were taken hourly and analyzed by chiral stationary phase HPLC.

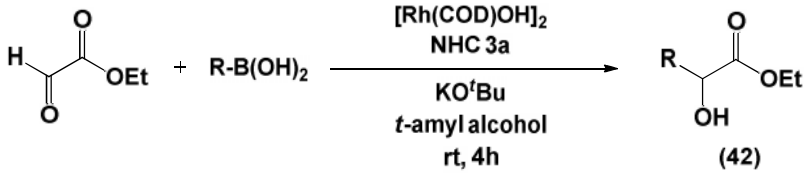
General procedure C: To a round-bottom flask was added (*R*)-(-)-methyl mandelate (50 mg, 0.3 mmol), $[Rh(COD)OH]_2$ (2.7 mg, 1.5 mol%), NHC **(3a)** (5.7 mg, 3.3 mol%), $PhB(OH)_2$ (73.4 mg, 0.6 mmol), KO^{t}Bu (1,1 mg, 3.3 mol%) and *t*-amyl alcohol (1 ml). The mixture was stirred at 60ºC and aliquots were taken hourly and analyzed by chiral stationary phase HPLC.

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 220 nm, t_R= 9.1 min (*S*) and 15.2 min (*R*).

6.4.3. Deuterium oxide studies

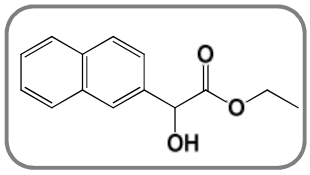
To a round-bottom flask was added $[Rh(COD)OH]_2$ (3.3 mg, 1.5 mol%), NHC precursor **(3a)** (8.3 mg, 3.3 mol%), $PhB(OH)_2$ (119.2 mg, 0.98 mmol), KO^{t}Bu (54.2 mg, 0.98 mmol), ethyl glyoxalate, 50% in toluene (100µl, 0.49 mmol), *t*-amyl alcohol (1.7 ml) and D_2O (0.3 ml). The mixture was stirred at room temperature for 4 hours. The crude mixture was passed through a sintered glass filter and eluted with CH_2Cl_2. The solvents were concentrated under reduced pressure and the crude mixture purified by silica gel chromatography (Hex/AcOEt (5:1)), yielding ethyl mandelate product **(37)** as colorless oil (see NMR analysis in 6.4.1.).

6.4.4. Synthesis of ethyl mandelate derivatives



For the general procedure see section 6.4.1.

6.4.4.1. Synthesis of ethyl 2-hydroxy-2-(naphthalen-2-yl)acetate (42a):[4]



White solid (36% yield).

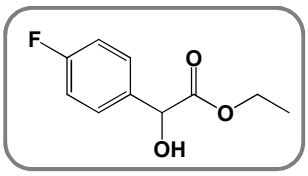
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.20 (m, CH_3, 3H), 3.71 (s br, OH, 1H), 4.15-4.21 (m, CH_2, 1H), 4.24-4.30 (m, CH_2, 1H), 5.33 (s, CH, 1H), 7.47-7.54 (m, Ar, 3H), 7.83-7.85 (m, Ar, 3H), 7.91 (s, Ar, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.45 (CH_3), 62.40 (CH_2), 73.08 (CH), 124.17 (Ar), 125.90 (Ar), 126.06 (Ar), 126.33 (Ar), 127.91 (Ar), 128.34 (Ar), 128.62 (Ar), 133.28 (Ar), 133.38 (Ar), 135.89 (Ar).

ESI-TOF MS (m/z): 213.10 (-OH), 231.10 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 10.9 min and 13.4 min.

6.4.4.2. Synthesis of ethyl 2-(4-fluorophenyl)-2-hydroxyacetate (42b):[4,13]



Colorless oil (>99% yield).

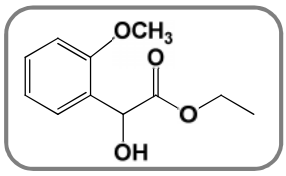
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.16 (m, CH_3, 3H), 3.88 (s br, OH, 1H), 4.12-4.18 (m, CH_2, 1H), 4.20-4.24 (m, CH_2, 1H), 5.11 (s, CH, 1H), 6.99-7.03 (m, Ar, 2H), 7.36-7.40 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.15 (CH_3), 62.36 (CH_2), 71.47 (CH), 115.49 (Ar), 115.61 (Ar), 128.24 (Ar), 134.37 (Ar), 161.42 (Ar), 164.06 (Ar), 173.67 (C=O).

ESI-TOF MS (m/z): 181.07 (-OH), 199.08 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 6.9 min (*S*) and 8.2 min (*R*).

6.4.4.3. Synthesis of ethyl 2-hydroxy-2-(2-methoxyphenyl)acetate (42d):[4]



Colorless oil (81% yield).

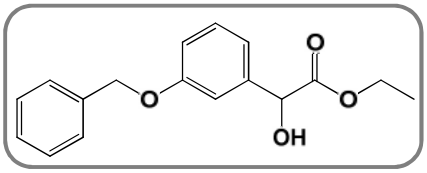
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.20 (t, *J*= 4 Hz, CH_3, 3H), 3.91 (s, OCH_3, 3H), 4.19-4.26 (m, CH_2, 2H), 5.28 (s, CH, 1H), 6.89-6.96 (m, Ar, 2H), 7.01-7.05 (m, Ar, 1H), 7.42-7.47 (m, Ar, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.31 (CH_3), 55.64 (OCH_3), 61.52 (CH_2), 71.45 (CH), 110.01 (Ar), 121.46 (Ar), 129.51 (Ar), 132.60 (Ar), 137.17 (Ar), 164.75 (Ar), 174.01 (C=O).

ESI-TOF MS (m/z): 193.10 (-OH), 211.10 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 11.6 min and 14.0 min.

6.4.4.4. Synthesis of ethyl 2-(3-(benzyloxy)phenyl)-2-hydroxyacetate (42e):[4]



Yellow oil (>99% yield).

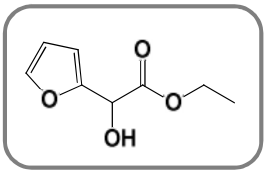
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (m, CH_3, 3H), 3.63 (br s, OH, 1H), 4.13-4.21 (m, CH_2, 1H), 4.23-4.31 (m, CH_2, 1H), 5.08 (s, CH_2, 2H), 5.15 (s, CH, 1H), 6.94-7.10 (m, Ar, 2H), 7.27-7.36 (m, Ar, 2H), 7.40-7.46 (m, Ar, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.94 (CH_3), 62.43 (CH_2), 70.41 (CH_2), 72.89 (CH), 113.03 (Ar), 114.92 (Ar), 119.20 (Ar), 127.50 (Ar), 127.58 (Ar), 128.01 (Ar), 128.65 (Ar), 129.56 (Ar), 129.69 (Ar), 136.91 (Ar), 140.15 (Ar), 159.08 (Ar), 173.65 (Ar).

ESI-TOF MS (m/z): 269.13 (-OH), 287.13 (M+1).

HPLC: not determined.

6.4.4.5. Synthesis of ethyl 2-(furan-2-yl)-2-hydroxyacetate (42f):[4]



Yellow oil (71% yield).

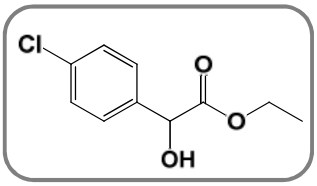
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.18 (m, CH_3, 3H), 3.78 (br s, OH, 1H), 4.20-4.28 (m, CH_2, 2H), 5.06 (s, CH, 1H), 6.33-6.36 (m, OCH, 1H), 7.31-7.42 (m, CH-CH, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.11 (CH_3), 61.86 (CH_2), 71.36 (CH), 108.81 (C_{fur}), 110.64 (C_{fur}), 126.62 (C_{fur}), 142.89 (C_{fur}), 170.59 (C=O).

ESI-TOF MS (m/z): 153.05 (-OH), 171.06 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 8.6 min and 10.4 min.

6.4.4.6. Synthesis of ethyl 2-(4-chlorophenyl)-2-hydroxyacetate (42g):[4,13]



Light yellow oil (34% yield).

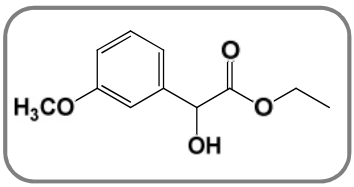
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.20 (m, CH_3, 3H), 3.61-3.69 (m, CH_2, 1H), 3.73-3.78 (br s, OH, 1H), 3.81-3.89 (m, CH_2, 1H), 4.93 (s, CH, 1H), 7.32-7.49 (m, Ar, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.12 (CH_3), 64.06 (CH_2), 71.82 (CH), 116.75 (Ar), 128.02 (Ar), 128.36 (Ar), 128.86 (Ar), 129.18 (Ar), 137.11 (Ar), 169.66 (C=O).

ESI-TOF MS (m/z): 213.11.

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 7.0 min (*S*) and 10.0 min (*R*).

6.4.4.7. Synthesis of ethyl 2-hydroxy-2-(3-methoxyphenyl)acetate (42h):[4]



Yellow oil (>99% yield).

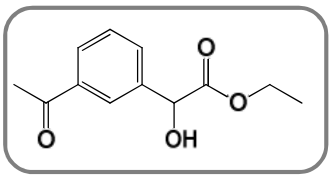
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.21 (t, *J*= 4 Hz, CH_3, 3H), 3.63 (br s, OH, 1H), 3.78 (S, OCH_3, 3H), 4.11-4.19 (m, CH_2, 1H), 4.20-4.28 (m, CH_2, 1H), 5.12 (s, CH, 1H), 6.83-6.85 (m, Ar, 1H), 6.96-6.98 (m, Ar, 2H), 7.23-7.27 (m, Ar, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.96 (CH_3), 55.29 (CH_2), 62.14 (OCH_3), 72.61 (CH), 111.85 (Ar), 114.32 (Ar), 118.92 (Ar), 129.46 (Ar), 140.23 (Ar), 159.73 (Ar), 173.97 (C=O).

ESI-TOF MS (m/z): 193.09 (-OH), 211.10 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 8.4 min and 9.4 min.

6.4.4.8. Synthesis of ethyl 2-(3-acetylphenyl)-2-hydroxyacetate (42i):[4]



Colorless oil (12% yield).

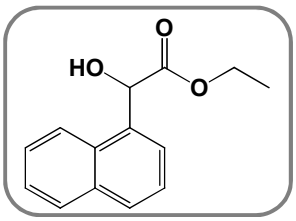
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (m, CH_3, 3H), 2.62 (s, CH_3 (Ac), 3H), 4.19-4.41 (m, CH_2, 2H), 5.35 (s, CH, 1H), 7.32-7.51 (m, Ar, 2H), 7.91-7.97 (m, Ar, 1H), 8.04 (s, Ar, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.03 (CH_3), 22.62 (CH_3), 62.83 (CH_2), 72.39 (CH), 128.41 (Ar), 128.66 (Ar), 129.01 (Ar), 131.30 (Ar), 137.55 (Ar), 139.17 (Ar), 173.06 (C=O), 198.14 (C=O).

ESI-TOF MS (m/z): 223.10 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 13.0 min and 14.8 min.

6.4.4.9. Synthesis of ethyl 2-hydroxy-2-(naphthalen-1-yl)acetate (42j):[4]



White solid (72% yield).

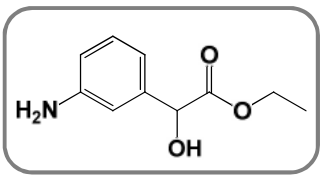
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26 (m, CH_3, 3H), 4.12-4.32 (m, CH_2, 2H), 5.81 (s, CH, 1H), 7.44-7.70 (m, Ar, 4H), 7.84-7.96 (m, Ar, 1H), 8.11-8.18 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.17 (CH_3), 62.06 (CH_2), 71.33 (CH), 123.46 (Ar), 123.70 (Ar), 125.13 (Ar), 125.68 (Ar), 125.78 (Ar), 126.48 (Ar), 127.84 (Ar), 128.80 (Ar), 129.36 (Ar), 134.07 (Ar), 174.48 (C=O).

ESI-TOF MS (m/z): 233.08 (M+2).

HPLC: Chiralcel OD-H column, hexane/2-propanol (90:10), flow rate: 1.0 ml/min., wavelength detector at 210 nm, t_R= 14.9 min and 15.6 min.

6.4.4.10. Synthesis of ethyl 2-(3-aminophenyl)-2-hydroxyacetate (42k):[4]

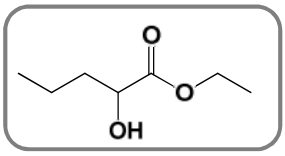


Colorless oil (vestigial quantities).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (m, CH_3, 3H), 2.17 (br s, OH, 1H), 3.92 (s, NH_2, 2H), 4.17-4.27 (m, CH_2, 2H), 5.67 (s, CH, 1H), 7.32-7.37 (m, Ar, 1H), 7.42-7.43 (d, Ar, 1H), 7.52-7.54 (m, Ar, 1H), 7.69-7.72 (m, Ar, 1H).

HPLC: not determined.

6.4.4.11. Synthesis of Ethyl 2-hydroxypentanoate (42l):[4]



Yellow oil (23% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87-0.93 (m, CH_3, 3H), 1.30-1.33 (m, CH_3, 3H), 1.32-1.35 (m, CH_2, 2H), 1.37-1.41 (m, CH_2, 2H), 2.07 (s, OH, 1H), 4.23-4.32 (m, CH_2, 2H), 5.32-5.34 (m, CH, 1H).

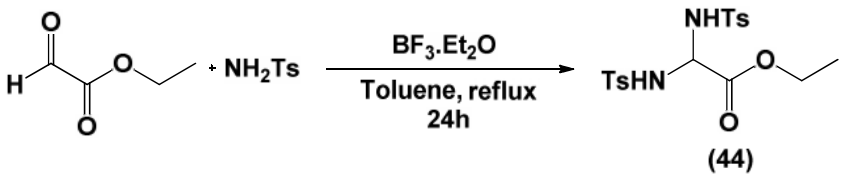
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.09 (CH_3), 14.27 (CH_3), 22.79 (CH_2), 36.42 (CH_2), 62.70 (CH_2), 73.11 (CH), 169.23 (C=O).

ESI-TOF MS (m/z): 146.07 (M^+).

HPLC: not determined.

6.5. Catalytic arylation on C=N bonds - Synthesis of unnatural α-amino acids

6.5.1. Synthesis of ethyl 2,2-bis(4-methylphenylsulfonamido)acetate (44):[6,14]



By using a Dean-Stark trap to facilitate water removal, $BF_3.Et_2O$ (0.2 ml, 1.6 mmol) was added through a syringe to a refluxing solution of ethyl glyoxalate (50% sol. in toluene, 19.8 ml, 0.1 mol) and *p*-toluenesulfonamide (17.1 g, 0.1 mol) in toluene (200 ml). The mixture was kept under reflux until the theoretical amount of water (1.8 ml, 0.1 mol) was collected. The solution was then cooled to room temperature and a white solid precipitated. The mixture was filtered and the white solid washed with toluene. After recrystallization with CH_2Cl_2, the desired ethyl 2,2-bis(4-methylphenylsulfonamido)acetate **(44)** (8.1 g, 19%) was obtained as a white solid.

m.p.: 178-189ºC (m.p. Lit.[15] 178-180ºC).

FTIR (cm^{-1}): 1200, 1344, 1597, 1728, 3257.

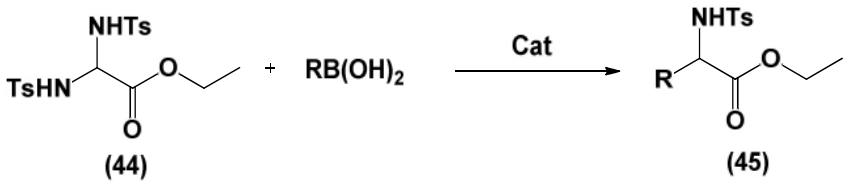
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 1.00 (t, *J*= 8 Hz, CH_3, 3H), 2.35 (s, CH_3Ts, 6H), 3.84-3.89 (q, *J*= 4 and 8 Hz, CH_2, 2H), 6.97-6.99 (d, *J*= 8 Hz, NH, 2H), 7.17-7.19 (d, *J*= 8 Hz, Ar, 2H), 7.62-7.64 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 13.64 (CH_3), 21.53 (CH_3), 62.51 (CH_2), 63.39 (CH), 127.08 (Ar), 129.41 (Ar), 137.92 (Ar), 143.35 (Ar), 167,43 (C=O).

ESI-TOF MS (m/z): 256.07 (M+1).

EA: calculated (%):C 50.69, H 5.20, N 6.57, S 15.04; found (%): C 50.77, H 5.29, N 6.56, S 14.94.

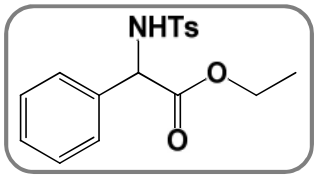
6.5.2. Catalytic synthesis of ethyl 2-(4-methylphenylsulfonamido)-2-phenylacetate (45) – General procedures:



[Pd] catalysts: To a round-bottom flask was added $Pd(OAc)_2$ (5 mol%), bpy ligand (10 mol%), the organoboron reagent (1.0 mmol), ethyl 2,2-bis(4-methylphenylsulfonamido)acetate **(44)** (0.3 mmol) and 1,4-dioxane (2.0 ml). The mixture was stirred at 100ºC for 2 days. The crude mixture was filtered over *celite* in a sintered glass filter and washed with CH_2Cl_2. The organic phase was washed with saturated NH_4Cl (aq), dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (Hex/AcOEt (5:1)) provided the desired α-amino ester product **(45)**.

[Rh] catalysts: To a round-bottom flask was added [Rh] (1.5 mol% or 3 mol%), chiral ligand (3.3 mol%), ethyl 2,2-bis(4-methylphenylsulfonamido)acetate **(44)** (0.12 mmol), organoboron reagent (0.4 mmol), additive (0.4 or 0.8 mmol) and solvent (2.0 ml). The mixture was stirred at specific temperature and monitored by TLC. The solvent was evaporated under reduced pressure and the crude mixture purified by silica gel chromatography (Hex/AcOEt (5:1)), providing the desired α-amine ester product **(45)**.

6.5.2.1. Synthesis of ethyl 2-(4-methylphenylsulfonamido)-2-phenylacetate (45a):[16]



White solid (93% yield).

m.p.: 88.6-90.4ºC (m.p. Lit.[20] 86-88ºC)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.09 (dd, *J*= 4 and 8 Hz, CH_3, 3H), 2.38 (s, CH_3Ts, 3H), 3.92-4.08 (m, CH_2, 2H), 5.02-5.04 (d, *J*= 4 Hz, CH, 1H), 5.69-5.71 (m, NH, 1H), 7.18-7.20 (d, *J*= 8 Hz, Ar, 2H), 7.22-7.26 (m, Ar, 5H), 7.62-7.64 (d, *J*= 8 Hz, Ar, 2H).

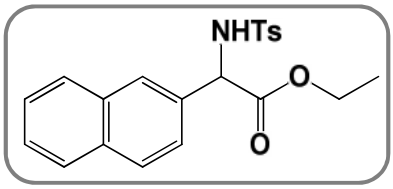
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.96 (CH_3), 21.61 (CH_3), 59.48 (CH_2), 62.35 (CH), 127.10 (Ar), 127.21 (Ar), 127.34 (Ar), 128.63 (Ar), 128.89 (Ar), 129.55

(Ar), 129.58 (Ar), 129.61 (Ar), 135.63 (Ar), 137.09 (Ar), 138.63 (Ar), 143.64 (Ar), 170.19 (C=O).

ESI-TOF MS (m/z): 334.12 (M+1).

HPLC: Chiralcel OD-H column, hexane/2-propanol (95:5), flow rate: 1.0 ml/min., wavelength detector at 230 nm, t_R= 20.1 min and 21.9 min.

6.5.2.2. Synthesis of ethyl 2-(4-methylphenylsulfonamido)-2-(naphthalen-2-yl)acetate (45b):[17]



Yellow solid (44% yield).

m.p.: 115.0-116.7ºC (m.p. Lit.[20] 111-113ºC)

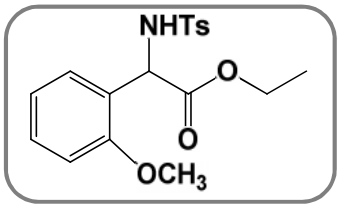
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.11 (dd, *J*= 4 and 8 Hz, CH_3, 3H), 2.26 (s, CH_3Ts, 3H), 4.16-4.31 (m, CH_2, 2H), 5.22-5.23 (m, CH, 1H), 5.86-5.88 (d, *J*= 8 Hz, NH, 1H), 7.14-7.15 (m, Ar, 2H), 7.29-7.34 (m, Ar, 2H), 7.40-7.44 (m, Ar, 1H), 7.48-7.49 (m, Ar, 1H), 7.73-7.77 (m, Ar, 3H), 7.84-7.86 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.08 (CH_3), 22.97 (CH_3), 59.64 (CH_2), 62.34 (CH), 109.60 (Ar), 117.93 (Ar), 123.67 (Ar), 124.26 (Ar), 126.04 (Ar), 126.46 (Ar), 126.60 (Ar), 127.88 (Ar), 128.57 (Ar), 129.02 (Ar), 129.49 (Ar), 129.92 (Ar), 133.43 (Ar), 134.73 (Ar), 135.85 (Ar), 153.60 (Ar), 173.79 (C=O).

ESI-TOF MS (m/z): 384.13 (M+1).

HPLC: not determined.

6.5.2.3. Synthesis of ethyl 2-(2-methoxyphenyl)-2-(4-methylphenylsulfonamido) acetate (45c):



White solid (50% yield).

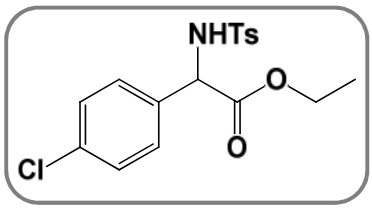
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.09 (dd, *J*= 8 Hz, CH_3, 3H), 2.36 (s, CH_3Ts, 3H), 3.92 (s, OCH_3, 3H), 4.02-4.24 (m, CH_2, 2H), 5.27-5.29 (d, *J*= 8 Hz, CH, 1H), 5.93-5.95 (d, *J*= 8 Hz, NH, 1H), 6.91-6.93 (d, *J*= 8 Hz, Ar, 2H), 7.02-7.06 (m, Ar, 2H), 7.44-7.47 (m, Ar, 2H), 7.85-7.87 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.06 (CH_3), 21.26 (CH_3), 55.62 (OCH_3), 61.72 (CH_2), 70.60 (CH), 110.10 (Ar), 111.23 (Ar), 120.97 (Ar), 121.39 (Ar), 127.20 (Ar), 127.49 (Ar), 129.41 (Ar), 130.01 (Ar), 130.27 (Ar), 132.70 (Ar), 133.11 (Ar), 136.98 (Ar), 164.64 (C=O).

ESI-TOF MS (m/z): 364.13 (M+1).

HPLC: not determined.

6.5.2.4. Synthesis of ethyl 2-(4-chlorophenyl)-2-(4-methylphenylsulfonamido)acetate (45d):[17]



Yellow oil (36% yield).

m.p.: 86.8-89.0ºC (m.p. Lit.[20] 87-88ºC)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.10 (m, CH_3, 3H), 2.39 (s, CH_3Ts, 3H), 3.97-4.10 (m, CH_2, 2H), 4.99-5.01 (d, *J*= 8 Hz, CH, 1H), 5.77-5.79 (d, *J*= 8 Hz, NH,

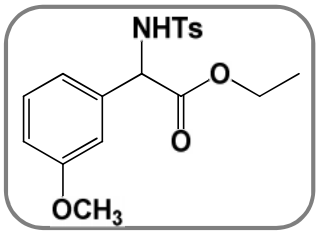
1H), 6.75-6.77 (d, *J*= 8 Hz, Ar, 2H), 7.14-7.22 (m, Ar, 2H), 7.32-7.38 (m, Ar, 2H), 7.59-7.61 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.07 (CH_3), 21.76 (CH_3), 58.73 (CH_2), 62.86 (CH), 116.80 (Ar), 127.20 (Ar), 127.92 (Ar), 128.53 (Ar), 128.98 (Ar), 129.50 (Ar), 129.59 (Ar), 133.94 (Ar), 134.64 (Ar), 136.86 (Ar), 143.92 (Ar), 154.42 (Ar), 169.75 (C=O).

ESI-TOF MS (m/z): 368.08 (M+1).

HPLC: not determined.

6.5.2.5. Synthesis of ethyl 2-(3-methoxyphenyl)-2-(4-methylphenylsulfonamido)acetate (45e):



Yellow oil (33% yield).

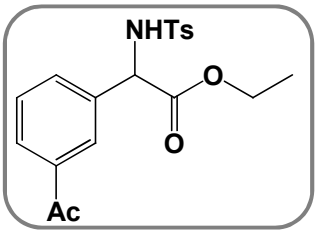
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.10 (dd, *J*= 4 and 8 Hz, CH_3, 3H), 2.38 (s, CH_3Ts, 3H), 3.72 (s, OCH_3, 3H), 3.93-4.11 (m, CH_2, 2H), 5.02 (d, *J*= 8 Hz, CH, 1H), 5.72-5.74 (d, *J*= 8 Hz, NH, 1H), 6.72 (m, Ar, 1H), 6.77-6.83 (m, Ar, 2H), 7.14-7.20 (m, Ar, 3H), 7.61-7.64 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.97 (CH_3), 21.60 (CH_3), 55.32 (OCH_3), 59.44 (CH_2), 62.38 (CH), 112.54 (Ar), 114.41 (Ar), 119.56 (Ar), 127.24 (Ar), 128.48 (Ar), 129.42 (Ar), 129.58 (Ar), 129.92 (Ar), 136.83 (Ar), 137.12 (Ar), 143.62 (Ar), 159.90 (Ar), 170.10 (C=O).

ESI-TOF MS (m/z): 364.14 (M+1).

HPLC: not determined.

6.5.2.6. Synthesis of ethyl 2-(3-acetylphenyl)-2-(4-methylphenylsulfonamido)acetate (45f):



White solid (36% yield).

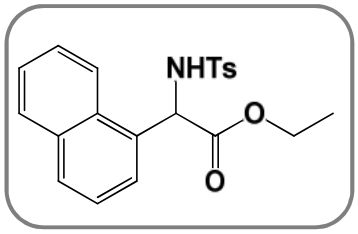
^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 0.97 (m, CH_3, 3H), 2.40 (s, CH_3, 3H), 2.49 (s, CH_3Ts, 3H), 3.81-3.86 (m, CH_2, 2H), 5.15-5.20 (m, CH, 1H), 5.90-6.05 (m, NH, 1H), 7.05-7.07 (d, *J*= 8 Hz, Ar, 2H), 7.19-7.22 (m, Ar, 2H), 7.33-7.38 (m, Ar, 1H), 7.44-7.45 (m, Ar, 2H), 7.71-7.73 (d, *J*= 8 Hz, Ar, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 13.64 (CH_3), 21.32 (CH_3), 29.59 (CH_3), 62.22 (CH_2), 63.36 (CH), 126.17 (Ar), 126.84 (Ar), 127.01 (Ar), 128.54 (Ar), 129.22 (Ar), 129.26 (Ar), 129.33 (Ar), 129.41 (Ar), 129.78 (Ar), 132.96 (Ar), 137.92 (Ar), 143.24 (Ar), 167.47 (C=O), 197.89 (C=O).

ESI-TOF MS (m/z): 376.12 (M+1).

HPLC: not determined.

6.5.2.7. Synthesis of ethyl 2-(4-methylphenylsulfonamido)-2-(naphthalen-1-yl)acetate (45g):



Yellow solid (98% yield).

^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 1.15 (m, CH_3, 3H), 2.31 (s, CH_3Ts, 3H), 3.98-4.25 (m, CH_2, 2H), 5.74 (s, CH, 1H), 5.81 (s, NH, 1H), 7.48-7.53

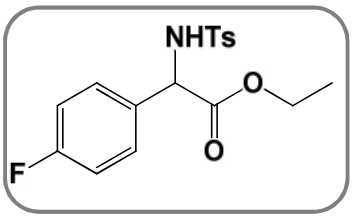
(m, Ar, 2H), 7.57-7.61 (m, Ar, 4H), 7.91-7.98 (m, Ar, 2H), 8.11-8.18 (m, Ar, 2H), 8.35-8.41 (m, Ar, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 14.13 (CH_3), 21.67 (CH_3), 57.25 (CH_2), 62.63 (CH), 125.16 (Ar), 125.30 (Ar), 125.95 (Ar), 126.60 (Ar), 127.01 (Ar), 127.28 (Ar), 128.05 (Ar), 128.96 (Ar), 129.85 (Ar), 130.96 (Ar), 132.55 (Ar), 133.55 (Ar), 137.76 (Ar), 139.20 (Ar), 143.75 (Ar), 149.27 (Ar), 157.94 (C=O).

ESI-TOF MS (m/z): 384.14 (M+1).

HPLC: not determined.

6.5.2.8. Synthesis of ethyl 2-(4-fluorophenyl)-2-(4-methylphenyl sulfonamido)acetate (45h):[17]



White solid (49% yield).

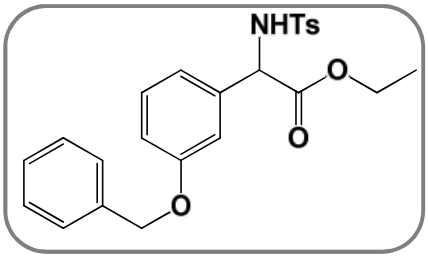
^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 0.92-0.97 (m, CH_3, 3H), 2.31 (s, CH_3Ts, 3H), 3.77-3.93 (m, CH_2, 2H), 5.12-5.17 (m, CH, 1H), 6.03 (s, NH, 1H), 7.13-7.19 (m, Ar, 4H), 7.39-7.53 (m, Ar, 1H), 7.57-7.59 (d, *J*= 8 Hz, Ar, 2H), 7.69-7.72 (m, Ar, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 13.60 (CH_3), 21.33 (CH_3), 63.00 (CH_2), 66.81 (CH), 115.26 (Ar), 115.42 (Ar), 125.71 (Ar), 126.92 (Ar), 128.20 (Ar), 128.72 (Ar), 129.09 (Ar), 137.08 (Ar), 137.86 (Ar), 138.08 (Ar), 140.34 (Ar), 142.94 (Ar), 167.23 (C=O).

ESI-TOF MS (m/z): 352.11 (M+1).

HPLC: not determined.

6.5.2.9. Synthesis of ethyl 2-(3-(benzyloxy)phenyl)-2-(4-methylpheny lsulfonamido)acetate (45i):



Colorless oil (20% yield).

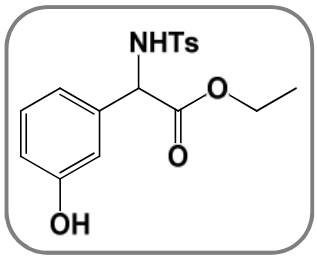
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.10 (dd, *J*= 8 Hz, CH_3, 3H), 2.36 (s, CH_3Ts, 3H), 3.94-4.07 (m, CH_2, 2H), 4.95-4.96 (d, *J*= 4 Hz, CH_2, 1H), 5.07 (s, CH_2, 1H), 5.12-5.14 (d, *J*= 8 Hz, CH, 1H), 5.74-5.76 (d, *J*= 8 Hz, NH, 1H), 6.83-6.88 (m, Ar, 2H), 7.18-7.20 (d, *J*= 8 Hz, Ar, 2H), 7.33-7.45 (m, Ar, 7H), 7.62-7.64 (d, *J*= 8 Hz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.06 (CH_3), 22.66 (CH_3), 59.33 (CH_2), 62.36 (CH_2), 69.43 (CH), 113.02 (Ar), 113.30 (Ar), 115.07 (Ar), 115.25 (Ar), 119.34 (Ar), 119.86 (Ar), 127.34 (Ar), 127.60 (Ar), 127.64 (Ar), 128.19 (Ar), 128.73 (Ar), 129.58 (Ar), 136.64 (Ar), 137.15 (Ar), 140.12 (Ar), 143.61 (Ar), 159.11 (Ar), 173.70 (C=O).

ESI-TOF MS (m/z): 440.17 (M+1).

HPLC: not determined.

6.5.2.10. Synthesis of ethyl 2-(3-hydroxyphenyl)-2-(4-methylphenyl sulfonamido) acetate (45j):



White solid (18% yield).

^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 0.97 (dd, *J*= 8 Hz, CH_3, 3H), 2.33 (s, CH_3Ts, 3H), 3.63 (s, OH, 1H), 3.81-3.93 (m, CH_2, 2H), 5.17-5.19 (d, *J*= 8 Hz, CH, 1H), 5.87 (s, NH, 1H), 6.77-6.79 (d, *J*= 8 Hz, Ar, 2H), 7.05-7.21 (m, Ar, 4H), 7.60-7.63 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 13.62 (CH_3), 21.07 (CH_3), 63.37 (CH_2), 66.55 (CH), 115.45 (Ar), 119.39 (Ar), 126.16 (Ar), 127.00 (Ar), 128.36 (Ar), 129.33 (Ar), 129.35 (Ar), 129.44 (Ar), 137.86 (Ar), 140.20 (Ar), 143.29 (Ar), 156.94 (Ar), 167.34 (C=O).

ESI-TOF MS (m/z): 350.11 (M+1).

HPLC: not determined.

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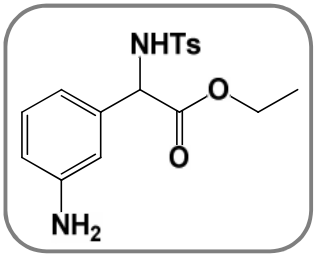
6.5.2.11. Synthesis of ethyl 2-(3-aminophenyl)-2-(4-methylphenyl sulfonamido)acetate (45k):[17]



Orange solid (22% yield).

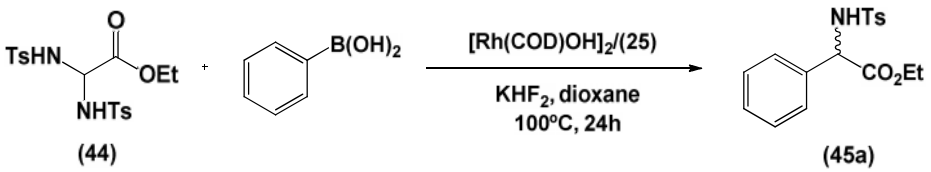
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (m, CH_3, 3H), 2.43 (s, CH_3Ts, 3H), 4.09-4.25 (m, CH_2+NH_2, 4H), 4.89-4.91 (d, *J*= 8 Hz, CH, 1H), 6.17 (s, Ar, 1H), 6.21-6.27 (m, NH, 1H), 6.96-7.01 (m, Ar, 2H), 7.29-7.36 (m, Ar, 2H), 7.79-7.83 (m, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.26 (CH_3), 21.65 (CH_3), 61.02 (CH_2), 62.03 (CH), 114.09 (Ar), 114.39 (Ar), 117.88 (Ar), 126.59 (Ar), 129.69 (Ar), 130.33 (Ar), 137.45 (Ar), 137.25 (Ar), 139.25 (Ar), 143.75 (Ar), 145.56 (Ar), 172.15 (C=O).

ESI-TOF MS (m/z): 287.15 (M+1).

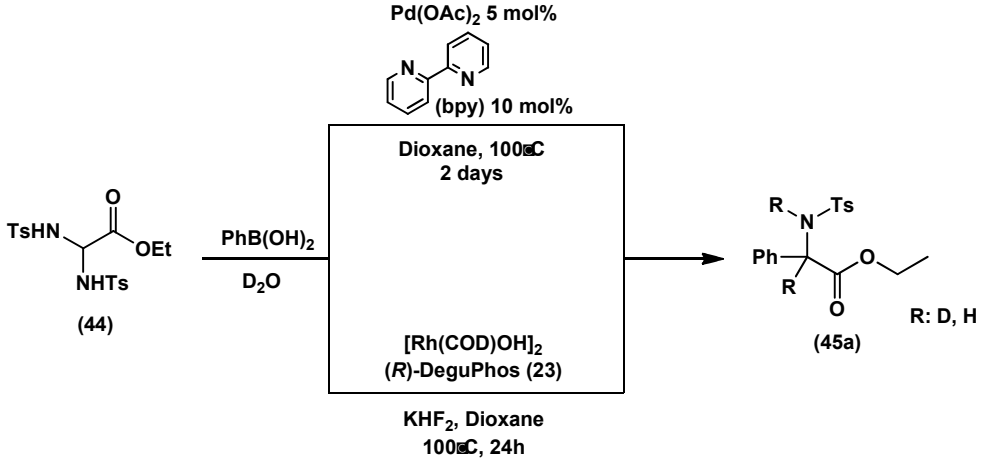
HPLC: not determined.

6.5.3. Racemization studies with ethyl 2,2-bis(4-methylphenyl sulfonamido)acetate (44):



To a round-bottom flask was added $[Rh(COD)OH]_2$ (2.7 mg, 1.5 mol%), (*R*,*R*)-*i*-Pr-DuPhos **(25)** (2.7 mg, 3.3 mol%), ethyl 2,2-bis(4-methylphenylsulfonamido)acetate **(44)** (50 mg, 0.12 mmol), $PhB(OH)_2$ (47.8 mg, 0.4 mmol), KHF_2 (61.2 mg, 0.8 mmol) and 1,4-dioxane (2.0 ml). The mixture was stirred at 100ºC and aliquots were taken hourly and analyzed by chiral stationary phase HPLC (see the conditions in section 6.5.2.1.)

6.5.4. Deuterium studies:



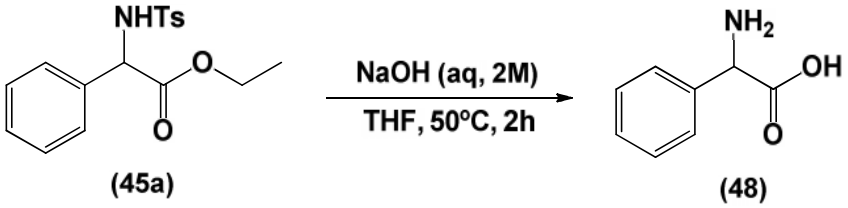
[Pd] catalyst: similar to the procedure described in Section 6.5.2., with the addition of D_2O (16 µ, 0.9 mmol). The product **(45a)** was analyzed by ^1H NMR (see Chapter 4, Figure 4.5).

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23 (m, CH_3, 3H), 2.38 (s, CH_3Ts, 3H), 4.13-4.31 (m, CH_2, 2H), 5.16 (m, CH, 1H), 7.32-7.44 (m, Ar, 9H).

[Rh] catalyst: similar to the procedure described in Section 6.5.2., with the addition of D_2O (6.5 µl, 0.36 mmol). The product **(45a)** was analyzed by ^1H NMR (see Chapter 4, Figure 4.5).

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (m, CH_3, 3H), 2.43 (s, CH_3Ts, 3H), 4.15-4.29 (m, CH_2, 2H), 4.70 (s, CH, 1H), 4.78 (s, ND, 1H), 7.31-8.26 (m, Ar, 9H).

6.5.5. Synthesis of α-phenylglycine (48):



(45a) (48)

To a round-bottom flask, without an inert atmosphere, was added, ethyl 2-(4-methylphenylsulfonamido)-2-phenylacetate **(45a)** (92.3 mg, 0.3 mmol), THF (5ml) and an aqueous solution of NaOH (2M) (1.0 ml, 1.5 mmol). The mixture was stirred at 50ºC and monitored by TLC. After two hours the THF was evaporated under reduced pressure and the mixture extracted with CH_2Cl_2 (5×10 ml). The aqueous phase was evaporated under reduced pressure and the desired α-phenylglycine **(48)**[18] was obtained as a white solid (>90% yield).

m.p.: (>300) (m.p. Lit.[18] >300ºC)

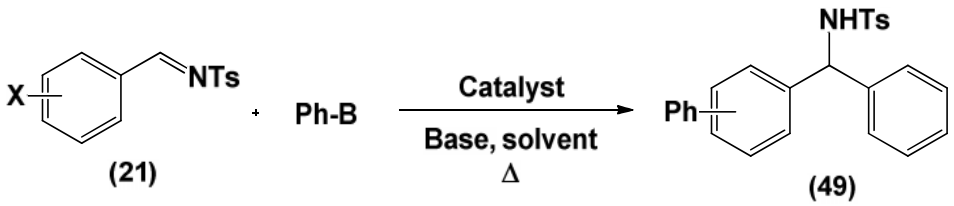
^1H NMR (400 MHz, D_2O) δ (ppm): 4.47 (s, CH, 1H), 7.18-7.19 (m, Ar, 5H).

^{13}C NMR (100 MHz, D_2O) δ (ppm): 65.63 (CH), 126.35 (Ar), 126.58 (Ar), 127.50 (Ar), 128.17 (Ar), 128.96 (Ar), 140.86 (Ar), 181. 51 (C=O).

ESI-TOF MS (m/z): 158.97 (M^+).

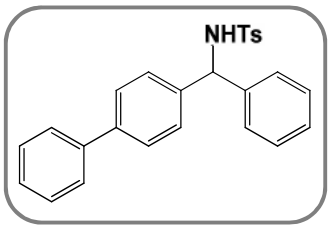
6.6. Sequential one-pot catalytic homogeneous and heterogeneous arylation: Synthesis of bi-aryl units

6.6.1. Homogeneous Catalysis – General procedure:



To a round-bottom flask was added the catalyst (3 mol% Pd plus 3.3 mol% ligand), the aldimine substrate **(21)** (60 mg, 0.15 mmol), the organoboron reagent (0.6 mmol, 4 mol equiv), the base (0.6 mmol, 4 mol equiv) and the solvent (2 ml). The mixture was stirred at 100ºC and monitored by TLC. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (Hex/AcOEt (5:1)) providing the desired biaryl product **(49)**.

6.6.1.1. Synthesis of *N*-([1,1'-biphenyl]-4-yl(phenyl)methyl)-4-methylbenzenesulfonamide (49):[7]



White solid (95% yield).

m.p.: 135.9-136.4ºC (m.p. Lit.[7] 149.9-151.0ºC).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (s, CH_3, 3H), 5.52 (d, *J*= 8 MHz, CH, 1H), 5.62 (d, *J*= 8 MHz, NH, 1H), 7.08 (d, *J*= 8 MHz, Ar, 2H), 7.13-7.18 (m, Ar, 7H), 7.40-7.44 (m, Ar, 5H), 7.50 (d, *J*= 8 MHz, Ar, 2H), 7.58 (d, *J*= 8 MHz, Ar, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.84 (CH_3), 61.45 (CH), 127.16 (Ar), 127.34 (Ar), 127.39 (Ar), 127.43 (Ar), 127.52 (Ar), 127.57 (Ar), 127.85 (Ar), 127.98 (Ar), 128.08 (Ar), 128.78 (Ar), 128.91 (Ar), 128.93 (Ar), 129.17 (Ar), 129.27 (Ar), 129.52 (Ar), 129.59 (Ar), 131.73 (Ar), 137.49 (Ar), 139.58 (Ar), 140.13 (Ar), 140.57 (Ar), 140.63 (Ar), 140.70 (Ar), 143.39 (Ar).

ESI-TOF MS (m/z): 436.13 (M^+).

HPLC: not determined.

6.6.2. Heterogeneous Catalysis

6.6.2.1. Representative protocol for SILPC preparation:[19]

PEPPSI-*i*Pr (198 mg, 0.29 mmol), [Bmim]PF_6 (100 mg, 0.35 mmol), silica nanopowder (1,02 g, spherical, porous, particle size = 5-15 nm (TEM), surface area = 590-690 m^2/g (TEM)) and THF (5 ml) were added in a round-bottom. The mixture was stirred overnight. After that the THF was evaporated under reduced pressure to give a pale yellow powder that was washed with diethyl ether until the diethyl ether layer became colorless. Finally, the yellowish powder (1.10 g) was dried under vacuum. The loading of the PEPPSI-*i*Pr catalyst was determined to be 0.41 mmol N/g, from 0.91 mmol N/g of [Bmim]PF_6-PEPPSI-*i*Pr as established by EA.

6.6.2.2. General procedure for the synthesis of *N*-([1,1'-biphenyl]-4-yl(phenyl)methyl)-4-methylbenzenesulfonamide (48), with SILPC:

To a suspension of the immobilized catalyst (500 mg, 0.04 mmol as PEPPSI-*i*Pr) in toluene (15 ml) was added the aldimine **(21k)** (451 mg, 1.3 mmol), $NaPh_4B$ (1.56 g, 5 mmol) and NEt_3 (0.63 ml, 5 mmol). The suspension was heated at 100ºC and monitored by TLC. After being cooled to room temperature, the suspension was passed through a plastic syringe attached to a kitasato flask, connected to a vacuum pump and washed with toluene. The toluene layer was

evaporated under reduced pressure and the crude product purified by silica gel liquid chromatography (Hex/AcOEt (5:1)) providing the desired *N*-([1,1'-biphenyl]-4-yl(phenyl)methyl)-4-methylbenzenesulfonamide **(49)**. The immobilized catalyst (SILPC) was dried under vacuum and reused for the next reaction without any pre-treatment.

6.7. References

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Catalytic Enantioselective Addition of Phenylboronic Acid and Phenylboroxine to *N*-Tosylimines: Pd^{II} and Rh^{I} Catalysis

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Keywords: *N*-Tosylarylimines / Phenylboronic acid / Addition / Chiral amines / Enantioselective catalysis

This is the first account of a successful, Pd^{II}-catalysed enantioselective addition of phenylboronic acid to electron-deficient *N*-tosylarylimines by using chiral diphosphane ligands. A number of commercial diphosphane ligands were screened. Despite moderate to good yields, *ee* values of 99% could be achieved with MeDuPhos. Novel Rh^{I} catalysts were also screened, and *ee* values as high as 74% could be obtained.

Introduction

The formation of carbon–carbon single bonds is one of the most fundamental, yet important reactions in organic synthesis. The addition of specific carbon nucleophiles to appropriate functionalities, like C=O, C=C and C=X is an attractive synthetic methodology for forming C–C bonds. In fact, the addition of arylboronic acids to arylimines in the presence of appropriate catalysts, like (phosphane)rhodium(I) complexes is a very attractive method for forming C–C bonds under very mild conditions, and at the same time, introducing the amino functional group in the product.[1] Due to the large variety of arylboronic acids, which are commercially available, a large array of α-arylamines can be quickly assessed by using this method. Many α-arylamines are known to be biologically active and are thus present in a number of natural products and drugs. For instance, (*S*)-ceterizine (Figure 1), an antihistaminic approved drug to treat allergic symptoms, can be obtained by using a diarylmethylamine precursor as a potential key intermediate.[2]

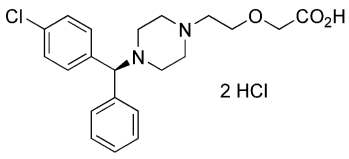

Figure 1. (*S*)-Ceterizine (Zyrtec®).

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Despite the attractiveness of this approach, catalytic asymmetric imine arylations with boronic acids still have yet to be fully exploited. In 2004, Tomioka and co-workers reported the arylation of *N*-tosylimines with both arylboronic acids and arylboroxines using Rh^{I} catalysts formed from a variety of novel *N*-Boc-L-valine amidomonophosphanes and (*S*)-BINAP.[3] The best result obtained was 92% *ee*. (*S*)-BINAP could only afford a maximum *ee* of 34%. In the same year, Hayashi's group reported the arylation of *N*-tosylimines with arylboroxines using chiral rhodium(I) catalysts that contain C_2-symmetric bicyclo[2.2.2]octadienes;[4] *ee* values as high as 99% were obtained. It was demonstrated that the *ee* values obtained with commercial chiral diphosphane ligands, like (*R*)-BINAP (31% *ee*), (*R*)-segphos (70% *ee*) and (*S*)-phosphoramidite (6% *ee*), were lower. The main disadvantages of this method are that the chiral diene must first be synthesised in order to prepare the chiral ligand, and toxic arylboroxines are used as reagents. Zhou and co-workers[5a] demonstrated the highly enantioselective addition of arylboronic acids to *N*-tosylarylimines catalysed by Rh complexes containing a spiro monophosphite ligand (*S*)-ShiP in aqueous media. The addition product was obtained in good yield (77%) and with high *ee* (93%). Gennari's group[5b] has reported the use of chiral binaphtholic phosphate and phosphoramidite ligands for the Rh^{I}-catalysed arylation of some *N*-tosylimines. The best *ee* values (76–99%) were obtained with the former ligands.

Afterwards, Xu and co-workers[6a] developed and tested a new type of C_2-symmetric chiral diene ligands, which proved to be a remarkably efficient ligand for asymmetric arylation of *N*-tosylarylimines using arylboronic acids. They obtained excellent enantioselectivities (98%). Trincado and Ellman[7] later made some changes to the procedure and tested several known chiral phosphanes, of which (*R*,*R*)-deguphos (**5**) (Figure 2) gave the best results. They concluded that pre-incubating the ligand, the precata-

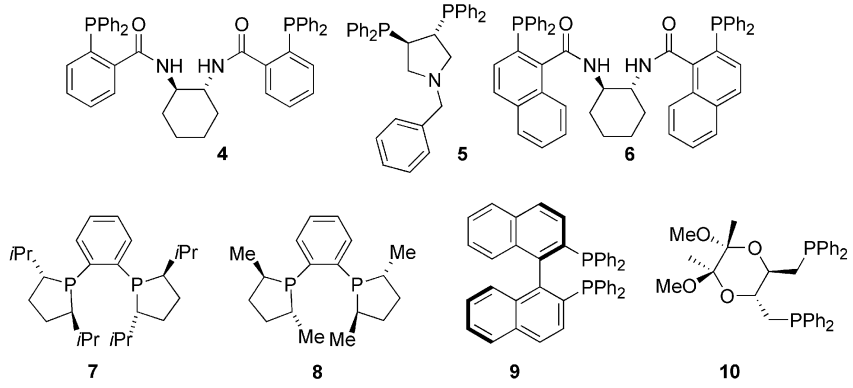


Figure 2. Chiral phosphane ligands screened.

lyst and the arylboronic acid for 90 min prior to the addition of the substrate improved the yield, but, in some cases decreased the enantioselectivity.

The application of palladium catalysts for catalytic asymmetric imine arylation is very poorly developed, and there are only a few reports in the literature as far as we are aware. Shi and co-workers[8a] reported on the application of C_2-symmetric cationic diaquo(NHC)Pd^{2+} complexes, where *ee* values of up to 94% have been achieved. Dai and Lu[8c] reported the first application of the diphosphane ligands SEGPHOS and BINAP in an attempt to phenylate *N*-tosyl-*p*-nitrophenylimine. However, the reaction failed. Besides offering such versatility for carbon–carbon bond formation,[9] Pd is a cheaper metal than rhodium and less toxic.

In this paper we wish to report our work with various chiral Pd and Rh catalysts for the catalytic asymmetric arylation of selected *N*-tosylimines.

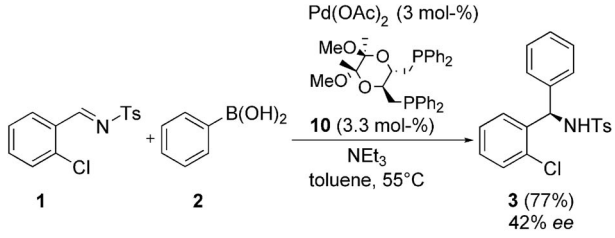
Results and Discussion

Initially, we looked at the effect and potential of palladium for this useful transformation. Lu and Dai have shown that *N*-tosylarylimines with strong electron-withdrawing groups are the best substrates for this reaction.[5c] For this reason we chose *N*-tosyl-*o*-chlorophenylimine as our substrate. $Pd(OAc)_2$ was used as the palladium source.

We investigated the reaction of the *N*-tosyl-*o*-chloroarylimine **1** with phenylboronic acid (**2**) in the presence of $Pd(OAc)_2$ (3 mol-%), Berens' DIOP analogue **10** and a base in toluene at 55 °C (Scheme 1). Berens' DIOP analogue **10** has been studied in a number of catalytic asymmetric reactions, like hydrogenation,[10a] asymmetric allylic alkylation,[10b] hydroboration[10c] and hydrosilylation.[10c] Gratifyingly as a first attempt, we could obtain the addition product **3** in 77% yield and with an *ee* of 42% (Scheme 1). The enantioselection favoured the (*R*) enantiomer.

We conducted a solvent screening study to determine if there were any solvent effects. The results are shown in Table 1.

This study showed that the reaction could be conducted in almost all the solvents described in Table 1, with the exception of CH_3CN and DMF. The yield decreased for all



Scheme 1. Asymmetric phenylation of *N*-tosylarylimine **1** with phenylboronic acid (**2**).

Table 1. Solvent screening reactions.

Entry	Solvent	Time [h]	η[a] [%]	*ee*[b] [%]
1	dioxane	20	24	10 (*R*)
2	$CHCl_3$	20	26	17 (*R*)
3	MeOH	20	13	45 (*R*)
4	DMF	20	<10	<5 (*R*)
5	THF	22	30	38 (*R*)
6	CH_2Cl_2	22	26	46 (*S*)
7	CH_3CN	22	<5	81 (*R*)

[a] Isolated yields. [b] Determined by HPLC using an AD column, *n*-hexane/2-propanol (90:10) at 0.7 mL/min, with wavelength detector at 230 nm.

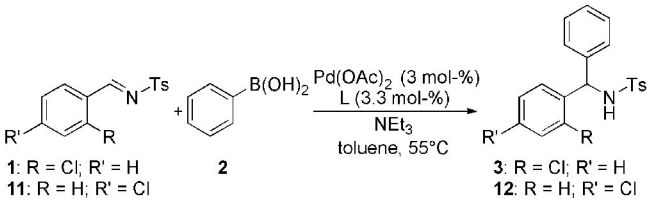
the solvents, despite the *ee* increasing slightly for some solvents, like MeOH, CH_2Cl_2 and CH_3CN (Table 1, Entries 3, 6 and 7, respectively). We believe that hydrolysis of the tosylimine was the main side reaction,[5c] which becomes kinetically more favourable in polar, coordinating solvents like MeOH, DMF and CH_3CN. Toluene is therefore the solvent of choice. The switch in the configuration of the major enantiomer to (*S*) on using CH_2Cl_2 (Table 1, Entry 6) was surprising and implied a structural change in the active catalyst and/or the mechanism in this case.

A diverse range of diphosphane ligands were then screened (Figure 2). These included Trost's ligands **4** and **6**, which have been very successful in the palladium-catalyzed asymmetric allylic alkylation reaction,[11] (*R*,*R*)-Me-DuPhos (**8**), which has also been very successful in the same reaction[12,13] and Berens' ligand **10**, which also has been quite good for Pd-catalysed reactions.[10b]

We screened the ligands with both *N*-tosyl-*o*-chloroarylimine **1** and *N*-tosyl-*p*-chloroarylimine **11** under the same conditions as described in Scheme 1.

By analysing the results obtained it could be seen that, generally speaking, the yields were moderate to good, with a highest of 77% (isolated) achieved (Table 2, Entry 12). The highest yields were achieved with **1**, which indicated that electronic effects were quite important. In fact, on using *para* substrate **11**, the yields were very poor, see for example Entry 3 (Table 2).

Table 2. Asymmetric phenylations of *N*-tosylimines **1** and **11** with phenylboronic acid and ligands **4**–**10**.

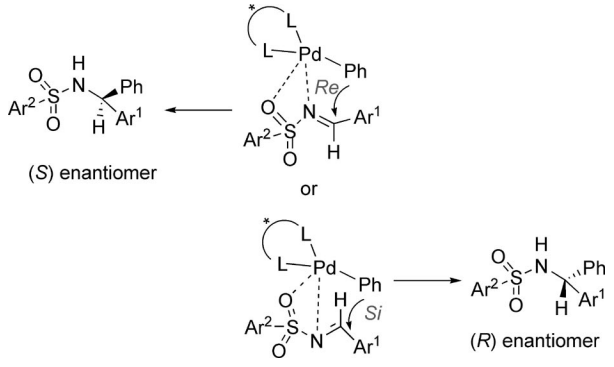


Entry	Substrate	Ligand	Time [h]	η[a] [%]	*ee*[b,c] [%]
1	**1**	**4**	70	27	82 (*R*)
2	**1**	**5**	41	57	72 (*R*)
3	**11**	**5**	40	<10	12 (*R*)
4	**1**	**6**	70	22	69 (*S*)
5	**11**	**6**	40	16	29 (*S*)
6	**1**	**7**	70	21	92 (*S*)
7	**11**	**7**	40	n.r.[d]	n.r.
8	**1**	**8**	70	41	>99 (*S*)
9	**11**	**8**	40	19	11 (*S*)
10	**1**	**9**	45	29	<5 (*S*)
11	**11**	**9**	45	10	<10 (*S*)
12	**1**	**10**	23	77	42 (*R*)
13	**11**	**10**	45	22	41 (*R*)

[a] Isolated yields. [b] Determined by HPLC by using an AD column, *n*-hexane/2-propanol (90:10) at 0.7 mL/min for substrate **1** and OD-H column, *n*-hexane/2propanol (93:7) at 0.7 mL/min for substrate **11**, both with wavelength detector at 230 nm. [c] The absolute configurations were determined by comparing the data with those already know in the literature. [d] No reaction.

Regarding the enantioselectivity of these reactions. Some very good to excellent *ee* values could be obtained. Overall it was substrate **1**, which gave the best *ee* values, and we attribute this to both electronic and sterochemical effects; for example, >99% *ee* with Me-DuPhos (**8**) (Table 2, Entry 8) using **1** as substrate and 92% *ee* using *i*Pr-DuPhos (**7**) as ligand with the same substrate (Table 2, Entry 6). The fact that less bulkier **8** gave higher *ee* values than **7** might imply the intervention of a more compact Pd catalyst in the former case. Surprisingly, although the phosphanes **7** and **8** have the opposite absolute configurations, the major amine enantiomer had the (*S*) configuration in each case. In fact, it was (*S*)-BINAP, which gave the lowest *ee* values, accompanied by low yields. However, this would be expected on the basis of Dai and Lu's[5c] results with *N*-tosyl-*p*-nitrophenylimine, and is in agreement with that of Zhou and coworkers, who achieved an *ee* of 10% with **11** as substrate, even though the pre-catalyst used was Rh(acac)$(CH_2$-$CH_2)_2$.[5a] Berens' ligand **10** gave moderate *ee* values of 42 and 41%, respectively (Table 2, Entries 12 and 13). Trost's ligands **4** and **6**, which are excellent for palladium-catalyzed allylic alkylations,[11] gave *ee* values of 82% and 69%, respectively (Table 2, Entries 1 and 4) with substrate **1**.

We have proposed the following working model to explain the resulting product configuration. This model was based partly on information furnished in Shi's paper.[8a] Due to the overall configuration of the key Pd^{I}–aryl species containing Trost's naphthyl ligand **6** or the DuPhos ligands **7/8** or the BINAP ligand **9** (which are expected to coordinate with the arylimine in the mode suggested in Scheme 2) the phenyl group will be delivered from the catalyst to the imine via *Re*-face attack with preferential formation of the (*S*)-amine enantiomer. Then delivery of the aryl group to the imine will occur by *Si*-face attack resulting in the preferential formation of the (*S*)-amine enantiomer (Scheme 2). In the case of Trost's phenyl ligand **4**, or the DeguPhos ligand **5**, or Berens' ligand **10** the aryl group is expected to be delivered by *Si*-face attack resulting in the preferential formation of the (*R*)-amine enantiomer (Scheme 2).



Scheme 2. Working model to explain the differential stereochemical outcomes by using different diphosphane ligands.

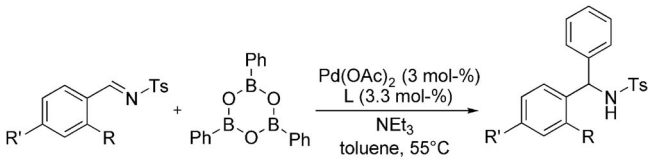
In an attempt to block imine hydrolysis,[15] the phenylboroxine **13** was investigated as the phenyl source. The results are highlighted in Table 3. Both **1** and **11** were used as substrates and **7** and **10** as ligands.

Concerning Berens' ligand **10**, the best result was achieved by using boroxine **13** and molecular sieves (Table 3, Entry 5). Compared with Entry 12 (Table 2) this method makes a significant difference, with both the yield and the *ee* remarkably improved. Like in the case of using phenylboronic acid (**2**) (Table 2, Entries 12 and 13) the aryl group is expected to be delivered by *Si*-face attack resulting in preferential formation of the (*R*)-amine (Scheme 2).

It was found that the yields increased on using phenylboroxine and molecular sieves as compared to using only phenylboroxine. With the bulkier *i*Pr-DuPhos ligand (**7**) the yield increased for all the reactions, although the enantioselectivities remained quite low.

Using the method of Zhou[5a] we have also screened some rhodium(I) catalysts with Berens' ligand **10**. Although the yields were quantitative, we could only achieve an *ee* as high as 16% using $[RhCl(COD)]_2$ with the *N*-tosyl-*o*-

Table 3. Asymmetric phenylations of *N*-tosylimines **1** and **11** with boroxine **13** and ligands **7** and **10**.



1: R = Cl; R' = H
11: R = H; R' = Cl

13

3: R = Cl; R' = H
12: R= H; R'= Cl

Entry	Substrate	Ligand	Mol. sieves (3 Å) [mg]	Time [h]	η[a] [%]	*ee*[b,c] [%]
1	**1**	**10**	none	44	< 10	36 (*R*)
2	**11**	**10**	none	44	27	40 (*R*)
3	**1**	**7**	none	44	27	38 (*S*)
4	**11**	**7**	none	44	< 10	<5 (*R*)
5	**1**	**10**	200	64	99	64 (*R*)
6	**11**	**10**	200	64	64	37 (*R*)
7	**1**	**7**	200	64	38	<5 (*S*)
8	**11**	**7**	200	64	29	<10 (*R*)

[a] Isolated yields. [b] Determined by HPLC using an AD column, *n*-hexane/2-propanol (90:10) at 0.7 mL/min for substrate **1** and OD-H column, *n*-hexane/2-propanol (93:7) at 0.7 mL/min for substrate **11**, both with wavelength detector at 230 nm. [c] The absolute configurations were determined by comparing the data with those already know in the literature.

chloroarylimine **1** and KF as base in toluene/water. However, when the reaction was conducted in the absence of water (with toluene as solvent) and triethylamine as base the *ee* dropped to 9% and the yield to 33%. This indicated that the presence of water was important somewhere in the catalytic cycle. On turning to $[Rh(COD)_2BF_4]_2$ with triethylamine as base in toluene, we could increase the *ee* up to 74%, despite obtaining a yield of only 14%. Analysis of the Rh pre-catalyst showed that it contained approx. 5.5% water, which was amassed during storage. When a fresh anhydrous sample of $[Rh(COD)_2BF_4]_2$ was used the *ee* was only 6%, but the yield had increased to 34%. This result is hard to explain, but implies that in the case of $[Rh(COD)_2BF_4]_2$ substoichiometric quantities of water promote higher enantioselection and at the same time, retard reaction efficiency. The actual mechanism is currently under investigation.

Conclusions

We have provided the first account of the successful application of a range of chiral diphosphane ligands in the palladium-catalysed arylation of electron-deficient *N*-tosylimines using both phenylboronic acid and phenylboroxine. An *ee* of >99% could be obtained with Me-DuPhos. The use of phenylboroxine in concert with molecular sieves increased the reaction yield.

Preliminary screening studies of some Rh^I catalysts were quite encouraging. They indicated the importance of water for catalyst activation.

Further studies are underway at screening other ligand types, like novel chiral NHCs, in this reaction.

Experimental Section

General Remarks: All reactions were performed under an inert gas, all the reagents were obtained from Aldrich, Fluka and Acros, and all the solvents were dried by using standard laboratory methods. The substrates **1** and **11** and phenylboroxine **13** were prepared by using literature procedures.[14,16] Berens' ligand **10** was provided by ChiraTecnics, Lda. Racemic products for chiral HPLC analysis were prepared from the corresponding *N*-tosylimines (0.5 mmol) with phenylboronic acid (1.0 mmol) in the presence of $Pd(OAc)_2$ (5 mol-%) and 2,2′-bypiridine (10 mol-%) in dioxane (1.5 mL) at 100 °C for 48–72 h.

General Procedure for the Catalytic Asymmetric Arylation of *N*-Tosylarylimines with Phenylboronic Acid or Phenylboroxine: Toluene (1.0 mL) was added to a round-bottom flask charged with phenylboronic acid or phenylboroxine (0.4 mmol), pre-catalyst (3 mol-%) and chiral ligand (3.3 mol-%) under nitrogen. The mixture was heated to 55 °C and stirred for 30 min. *N*-Tosylarylimine (0.2 mmol), toluene (1 mL) and NEt_3 (0.4 mmol) were added sequentially. After the mixture was stirred for 55 °C during 24–48 h, HCl (0.2 M, 5 mL) was added to quench the reaction. The mixture was extracted with EtOAc and washed with brine. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography to afford the desired diarylamine product.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data.

Acknowledgments

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Chiral Diphosphane- and NHC-Containing Ruthenium Catalysts for the Catalytic Asymmetric Arylation of Aldimines with Organoboron Reagents

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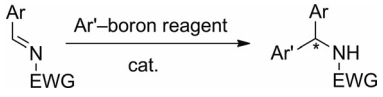
Keywords: Chirality / Amines / Ruthenium / Asymmetric catalysis / Arylboronic acids / N,P ligands

For the first time, we report the application of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ in the arylation of *N*-activated aldimines with boronic acids and its derivatives to afford chiral amines, which are important intermediates in the syntheses of key bioactive compounds. The behavior of the chiral ligands, the imine substrates, and the organoboron reagents were studied. Very good enantioselectivities were obtained.

Introduction

Many important drugs[1] used in the treatment of several chronic illnesses, like Parkinson's and Alzheimer's disease, have a chiral amine moiety. For this reason, it is important to develop new and more efficient methods for the creation of chiral amine units. The asymmetric addition of an aryl group to the C=N unit of an imine is one example. The arylation reaction of electron-withdrawing-group *N*-substituted arylimines with organoboron reagents is a suitable method for this (Scheme 1).



Scheme 1. Asymmetric synthesis of chiral amines. Addition of organoboron reagents to activated imines containing electron-withdrawing groups (EWGs).

In 2004, Tomioka[2] and co-workers used hemilabile chiral P,O-ligands and rhodium precatalysts along with arylboronic acids and arylboroxine compounds as the aryl transfer reagents to obtain enantioenriched arylamines in excellent yields. Hayashi[3] reported excellent results (98% yield and 99%*ee*) using chiral diene ligands coordinated to a rhodium center in the catalytic asymmetric arylation of *N*-tosylarylimines with arylboroxine reagents in aqueous media.

Employing analogous methods, Ellman's group[4–6] used chiral phosphane ligands with rhodium precatalysts, diphenylphosphinoylimine substrates, and arylboronic acids to give the corresponding chiral amines with excellent yields and enantioselectivities. Chiral palladium-containing catalysts have also been used. Ma's group[7] has reported the successful application of chiral Pd–NHC (N-heterocyclic carbene) catalysts, and Lu's group[8] has employed chiral palladium pyridine–oxazoline catalysts.

Not long ago, we employed chiral palladium catalysts in the arylation reaction of substituted *N*-tosylarylimines.[9] This reaction was reviewed in a very recent paper.[10] However, we were also interested in investigating new ruthenium catalysts for this reaction. This decision was made as a result of ruthenium being cheaper than rhodium and palladium and having an impressive application profile in organometallic chemistry.[11–15]

Results and Discussion

(i) Diphosphane–Ruthenium Complexes

Preliminary tests were conducted by using commercial $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ as a precatalyst and several commercial chiral phosphanes (Figure 1), which were already successfully used in the catalytic reaction with Rh and Pd.[9] By starting with the DioxPhos ligand (**3**, an analogue of the DIOP ligand, see Figure 1), *o*-chloro-*N*-tosylbenzaldimine as the substrate, and phenylboronic acid as the aryl source, the desired amine product was obtained in 63% yield and 57%*ee* (Table 1, Entry 1).

Motivated by this result, we applied this procedure to several imine substrates, which were synthesized according to literature procedures.[16] To compare the contribution of the electron-withdrawing and electron-donating effects on the outcome of the reaction, both electron-rich and electron-deficient imine substrates and arylboronic acid reagents were screened. Generally, the best yields were obtained when electron-poor imines were used (Table 1, Entries 1, 2, 11, and 15), as expected from the literature pre-

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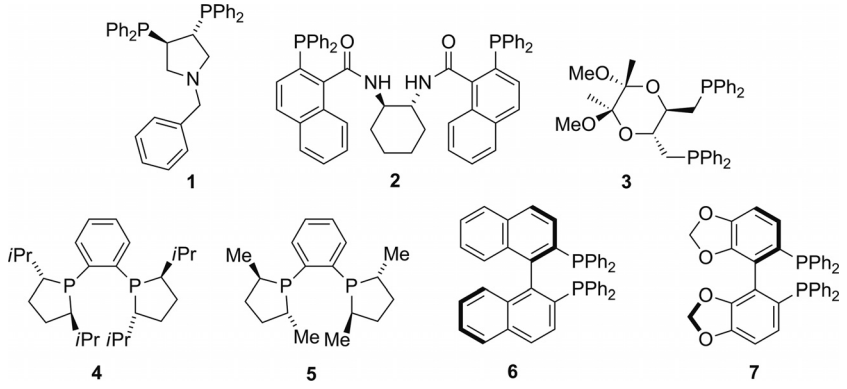
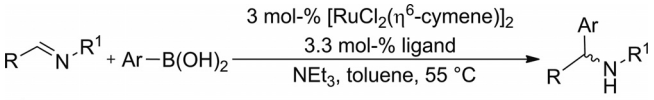


Figure 1. Library of chiral diphosphane ligands used in this work.

Table 1. Catalytic enantioselective arylation of *N*-protected aldimines with arylboronic acids.



R^1 = Ts, except for Entry 8 (Ms)

Entry[a]	R	L	Ar	*T* [h]	Yield [%][b]	*ee* [%][c]
1	*o*-ClC_6H_4	3	Ph	72	63	57 (*R*)
2	*p*-ClC_6H_4	3	Ph	48	14	90 (*R*)
3	2-naphthyl	3	Ph	48	12	44 (*R*)
4	*o*-$CH_3C_6H_5$	3	Ph	48	<10	14 (*S*)
5	cyclohexyl	3	Ph	48	17	17 (*S*)
6	*p*-BrC_6H_4	3	Ph	48	12	69 (*S*)
7	*p*-$NO_2C_6H_4$	3	Ph	48	<10	5 (*R*)
8	*p*-ClC_6H_4	3	Ph	48	10	75[d]
9	$CH_3CH_2CH_2$	3	Ph	48	13	8 (*R*)
10	*o*-ClC_6H_4	3	*p*-ClC_6H_4	48	12	88 (*S*)
11	*o*-ClC_6H_4	2	Ph	72	39	90 (*R*)
12	*o*-ClC_6H_4	6	Ph	72	<10	98 (*R*)
13	*o*-ClC_6H_4	1	Ph	72	16	16 (*R*)
14	*o*-ClC_6H_4	4	Ph	72	27	91 (*R*)
15	*o*-ClC_6H_4	5	Ph	72	38	94 (*R*)
16	*o*-ClC_6H_4	7	Ph	72	<10	12 (*S*)

[a] Reagents and conditions: imine (0.2 mmol), $ArB(OH)_2$ (2 equiv.), toluene (2 mL), NEt_3 (2 equiv.). [b] Isolated yields after chromatography. [c] Determined by chiral stationary-phase HPLC. [d] Preferred configuration not determined.

cedent.[17] A significant decrease in the yield was observed when electron-rich imine substrates were used (Table 1, Entry 4).

The best yields (38–63%) were obtained with *o*-chloro-*N*-tosylbenzaldimine, phenylboronic acid, and ligands **3**, **2**, and **5** (Table 1, Entries 1, 11, and 15). The best enantioselectivities were obtained with ligands **2**–**6** (88–98%*ee*). This was generally achieved with the *o*-chlorophenyl-substituted imine substrate, but in certain cases, the *p*-chlorophenyl-substituted substrates (Table 1, Entry 2) or the *p*-chlorophenyl-substituted arylboronic acid (Table 1, Entry 10) gave high enantioselectivities. The presence of an electron-donating group in either the substrate or the arylboronic acid reagent was of no advantage. In all of the reactions involving the *o*-chlorophenyl-substituted imine substrate and phenylboronic acid, the product configuration was (*R*), except when (*R*)-SegPhos (**7**) was used as ligand (Table 1, Entry 16). The change in the enantiofacial selectivity might be attributed to a subtle difference in the reaction mechanism. In addition, the imine activating group was investigated, and the mesyl (Ms) group was considered for this activation. Considering that the yield remained the same, the enantioselectivity dropped dramatically from 90%*ee* (with Ts, Table 1, Entry 2) to 75%*ee* (with Ms, Table 1, Entry 8), therefore, no improvements were gained. The lower enantioselectivity might be attributed to the reduced steric hindrance during the aryl addition step.[18] It was also possible to conduct the reaction with alkylimine substrates (see Table 1, Entries 5 and 9). However, this resulted in moderate enantioselectivities.

Secondary diaryl alcohols – the products of aldehyde arylation[19] – have been detected in this reaction, which was previously reported with chiral Ru catalysts.[20] The secondary alcohol product was always obtained in almost racemic form for all of the reactions using *o*-chloro-*N*-tosylbenzaldimine (<5%*ee*). The enantiopurities of all of the other secondary alcohol products were not determined.

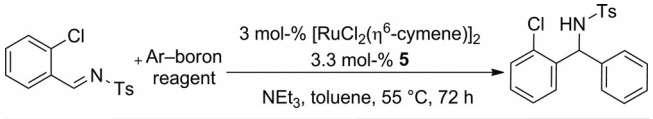
These imine substrates are very susceptible to hydrolysis, and under the reaction conditions (with arylboronic acids), there is sufficient water present to promote a ruthenium-catalyzed imine hydrolysis. This was confirmed by conducting an experiment with only the imine and the catalyst. Although we did not quantify the amount of the secondary alcohol produced in the reactions, as this came to our attention after the reactions were performed and analyzed, the analyses of the HPLC chromatograms showed that there were more than vestigial quantities present. In fact, an additional experiment was performed by using the conditions shown in Table 1, Entry 1, for a shorter time, which yielded the product amine (isolated yield of 8%, 57%*ee*) along with the corresponding secondary alcohol (35% yield) in racemic form. It seems that, at the outset, the formation of the alcohol might be more rapid than that of the amine, but the alcohol formation reaches a threshold, and then arylation of the imine proceeds.

To avoid this unwanted side reaction, we decided to implement some new countermeasures. One such measure was to add the *o*-chloro-*N*-tosylbenzaldimine substrate slowly to the reaction mixture containing phenylboronic acid and

(*R*)-Me-DuPhos (**5**). The addition was carried out over a 7 h period, and then the reaction was left for 2 d. The isolated yield was less than 10% with an enantioselectivity of 78%*ee*, in favor of the (*R*) enantiomer. Analysis of the crude product by HPLC showed that there was a vestigial quantity of the alcohol (racemic) present and small quantities of both the imine substrate and its aldehyde precursor. This strategy failed to improve the reaction yield. The lower observed enantioselectivity (78%*ee*), compared to that obtained in the original reaction (Table 1, Entry 15), might be an indication of subtle ligand dynamics forming hemilabile catalysts, perhaps during the course of the reaction.

Another approach to resolve this problem was to use more anhydrous arylboron reagents, like sodium tetraphenylborate (Ph_4BNa), potassium trifluoro(phenyl)borate ($PhBF_3K$), 1,3-propanediol boronic ester ($C_9H_{11}BO_2$), Ph_3B,[21] and phenylboroxine [$(PhBO)_3$]. This strategy worked to some extent, as the quantity of alcohol was reduced, but the isolated yield of the amine product did not improve. All of the results (except for those from using Ph_3B, which showed no improvements) are shown in Table 2. What was very surprising was the change in the configuration of the product from (*R*) to (*S*), even when phenylboronic acid was used (Table 2, Entry 6) in the presence of activated molecular sieves (MS). When the amount of water is reduced, there may be an alternative reaction mechanism taking place (see below for further discussion). The best aryl transfer reagents were phenylboroxine and 1,3-propanediol boronic ester (Table 2, Entries 1 and 4). It should be noted that this is the first report on the use of a boronic ester in this reaction. The only boron reagent that could compete successfully with phenylboronic acid in terms of enantioselectivity was Ph_4BNa, which gave an enantioselectivity of 93%*ee*.

Table 2. Catalytic enantioselective arylation of *o*-chloro-*N*-tosylbenzaldimine with several organoboron reagents.



Entry[a]	Ar–boron reagent	Yield [%][b]	*ee* [%][c]
1	$(PhBO)_3$	31	74 (*S*)
2	Ph_4BNa	<10	93 (*S*)
3	$PhBF_3K$	<10	68 (*S*)
4	$C_9H_{11}BO_2$	26	56 (*S*)
5[d]	$(PhBO)_3$	<10	78 (*S*)
6[d]	$PhB(OH)_2$	11	68 (*S*)

[a] Reagents and conditions: imine (0.2 mmol), Ar–boron reagent (2 equiv.), toluene (2 mL), NEt_3 (2 equiv.). [b] Isolated yields after chromatography. [c] Determined by chiral stationary-phase HPLC. [d] MS (3 Å; 200 mg) were added to the reaction vessel.

To better understand this phenomenon, we decided to carry out two key experiments using $(PhBO)_3$ and $PhB(OH)_2$ in the presence of activated molecular sieves (3 Å). Both the yields and the enantioselectivities dropped significantly (compare Table 1, Entry 15 with Table 2, Entry 6 and compare Table 2, Entry 1 with Entry 5). Water may play an important role as a coligand on the active catalyst.

We also tried to get a handle on the type of active catalyst involved in this reaction. For this purpose, the enantiopode (*S*)-**3** [as we had no (*R*)-**3** available] was stirred with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.5 equiv.) in dry CH_2Cl_2 at room temperature overnight. After purification by silica gel column chromatography, two principle fractions were obtained, which yielded orange solids. These compounds were identified by mass spectrometry to be the monomer **8** (10% yield, Figure 2) with observed molecular peaks at *m*/*z* = 843 [M(^{35}Cl)] and 845 [M(^{37}Cl)] and the dimer **9** (82% yield, Figure 2) with observed molecular peaks at *m*/*z* = 1149 [M(^{35}Cl × 3)] and 1151 [M(^{35}Cl × 2 + ^{37}Cl)]. These isolated complexes were then screened in the appropriate arylation reaction of *o*-chloro-*N*-tosylbenzaldimine with phenylboronic acid by using the conditions shown in Table 1. It was found that each complex was capable of arylating this substrate. In the case of **8** (at a loading of 5 mol-%), the product was obtained with a yield of 41% and an enantioselectivity of 34%*ee* in favor of the (*R*) enantiomer. In the case of complex **9** (at 20 mol-% loading), the product was obtained with a yield of 27% and an enantioselectivity of 54% in favor again of the (*R*) enantiomer. Vestigial quantities of both the alcohol (racemic) and the aldehyde were observed. The fact that the major amine product had the (*R*) configuration came as a surprise, as the (*S*) enantiomer was expected. This result mirrors those seen earlier when water was kept at a minimum in the reaction with (*R*)-Me-DuPhos (**5**, see discussion above and Table 2), and together they seem to imply that water may form an alternative competing active catalyst to those putative catalysts shown in Figure 2, perhaps with water substituting for the chloride ions.

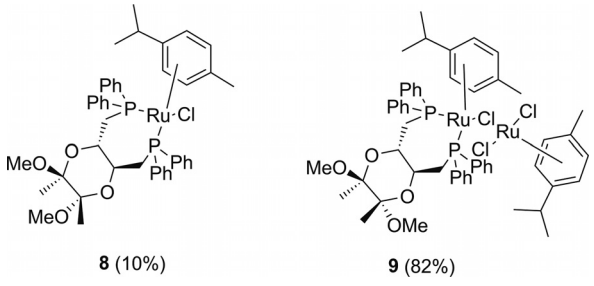


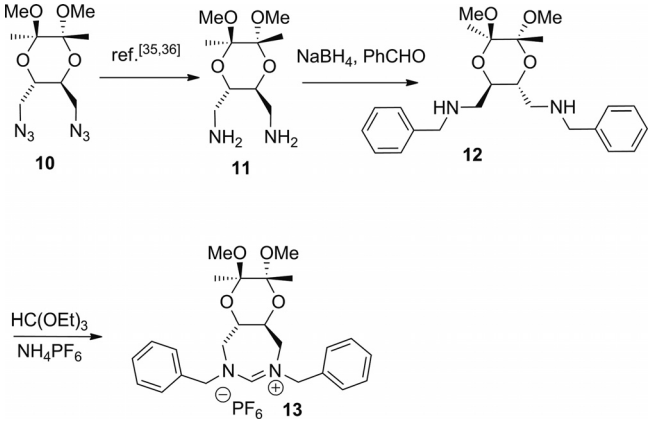
Figure 2. The monomeric (**8**) and dimeric (**9**) ruthenium complexes exhibiting catalytic activity.

(ii) NHC–Ruthenium Complexes – New Catalysts

Although the preliminary results with these chiral diphosphane ligands were very encouraging, we were also interested in investigating other ligand types, notably, N-heterocyclic carbenes (NHCs), which show strong σ-electron-donating properties[22–24] and strong NHC–metal bonding.[25] The possibility of tuning the electronic and stereochemical characteristics of NHC ligands, almost at will, represents another strong advantage of this class of li-

gands.[26] Making structural changes to the catalyst can lead to better results.[27]

Previous work in our laboratory[28–31] and from other groups[32–38] has shown the applicability of the conformationally locked cyclic diacetal backbone in asymmetric synthesis and particularly in asymmetric catalysis. Chiral diamine **11**[35,36] (Scheme 2) was obtained from the commercially available diazide **10** through a simple metal-catalyzed hydrogenation.[35] Diamine **11** underwent a reductive amination to give the dibenzylated amine **12** (which had previously been obtained by an alternative route[36]), which was then converted by standard methods to the dihydroimidazolinium salt **13** in 57% yield.

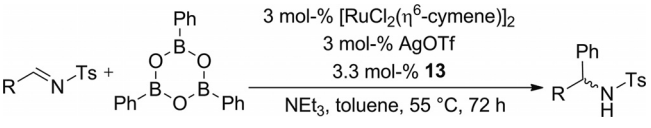


Scheme 2. Synthetic pathway to the mono(dihydroimidazolinium) salt **13**.

To use this dihydroimidazolinium salt **13** (Scheme 2) as a chiral NHC ligand, deprotonation of the imidazolium halide was required. Silver salts are often employed for the in situ generation of cationic transition-metal catalysts.[39–41] They behave as halide scavenger agents, forming a weak Ag–NHC bond, and easily undergo a transmetalation step with the required metal atom.[42–44] We decided to carry out a screening study with some ruthenium precatalysts, the NHC ligand precursor **13** (Scheme 2), and silver salts to form the active carbene species. In the first reaction, silver triflate (AgOTf) was added to **13**, followed by the addition of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (in situ) with *N*-tosylnaphthaldimine as the substrate and $PhB(OH)_2$ as the phenyl transfer agent. The desired amine product was obtained in 15% yield and 89%*ee* [the major enantiomer had the (*S*) configuration]. The low yield was probably due to the hydrolysis of the imine substrate, as 2-naphthaldehyde was detected in the HPLC chromatogram. Consequently, we decided to use $(PhBO)_3$ as the phenyl transfer reagent,[43] with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$, AgOTf, and the NHC precursor **13**. The results obtained are shown in Table 3.

To investigate the reaction scope with $(PhBO)_3$ as the phenyl transfer reagent, a number of reactions were performed. In some cases, small quantities of molecular sieves (3 Å; 200 mg)[6–8] were added to determine the influence of water on the reaction yield and enantioselectivity (Table 3, Entries 5–7). In the case of *N*-tosyl-2-naphthaldimine (Table 3, Entry 7), the yield increased significantly.

Table 3. Catalytic enantioselective arylation of *N*-tosylarylaldimines with $(PhBO)_3$ and NHC precursor **13**.



Entry[a]	R	Yield [%][b]	*ee* [%][c]
1	*o*-ClC_6H_4	29	20 (*S*)
2	*p*-ClC_6H_4	32	31 (*R*)
3	2-naphthyl	22	72 (*R*)
4	*p*-$CH_3OC_6H_4$	53	80 (*S*)
5[d]	*o*-ClC_6H_4	27	*rac*
6[d]	*p*-ClC_6H_4	19	23 (*S*)
7[d]	2-naphthyl	77	<10 (*S*)

[a] Reagents and conditions: imine (0.2 mmol), $(PhBO)_3$ (2 equiv.), toluene (2 mL), NEt_3 (2 equiv.). [b] Isolated yields after chromatography. [c] Determined by chiral stationary-phase HPLC. [d] MS (3 Å; 200 mg) were added to the reaction vessel. *rac* = racemic product.

When molecular sieves were used, the enantioselectivities dropped significantly (Table 3, compare Entries 1 and 5, and compare Entries 3 and 7). This result seems to support the postulate that water coordinates with the metal atom, making the catalyst more bulky and leading to greater enantiofacial discrimination at the imine reaction site. High enantioselectivities (72 and 80%*ee*) were obtained when electron-rich substrates were used (Table 3, Entries 3 and 4, respectively). Vestigial quantities of the corresponding secondary alcohols were observed by HPLC analysis.

It is known from the literature that NHC–Ag^I complexes can be used in catalysis.[45,46] To determine if the silver complex was, in fact, catalyzing the reaction, an experiment was performed by using the same protocol, but in the absence of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$. Only the substrate and the organoboron reagent were recovered, showing that the silver–NHC complex derived from **13** (Scheme 2) was not the active catalyst in this particular transformation.

Conclusions

We report the first application of ruthenium catalysts in the arylation of both electron-rich and electron-deficient *N*-protected aldimine substrates, using boronic acids and its derivatives as the aryl transfer reagents. Commercial chiral diphosphane ligands and a new NHC-type chiral ligand were used for the first time in this catalytic transformation. Some very good enantioselectivities were obtained. We are currently conducting thorough mechanistic and structural studies to understand the nature of the active catalysts involved in this reaction.

Experimental Section

General Remarks: All of the reagents were obtained from Aldrich, Fluka, and Acros. The commercial phosphane ligands were obtained either from Strem Chemicals or from Aldrich, with the ex-

ception of ligand **1**, (*R*)- and (*S*)-DioxPhos ligand **3** and diazide **10**, which were obtained from ChiraTecnics, Lda (Portugal). Toluene as well as NEt_3[47] were distilled from CaH_2 under an inert gas. Phenylboronic acid and derivatives were used as received. Phenylboroxine and the *N*-protected imine substrates were synthesized according to literature procedures.[16,41] Column chromatography was carried out on silica gel (sds, 70–200 μm). Thin layer chromatography (TLC) was carried out on aluminium-backed Kieselgel 60 F254 plates (Merck). The plates were visualized either by UV light or with phosphomolybdic acid in ethanol. NMR spectroscopic data were recorded with a Bruker Avance instrument (400 MHz) by using $CDCl_3$ as the solvent and by using the signal from the residual $CHCl_3$ as an internal standard. High performance liquid chromatographic (HPLC) analyses were performed with an Agilent 1100 series instrument. The conditions used were p_{max} = 50 bar, $flux_{max}$ = 1 mL/min, detector = wavelength light (λ = 230 nm), eluent = hexane/2-propanol, column = Chiralcel OD-H (0.46 cm × 25 cm) and AD-H (0.46 cm × 25 cm), both fitted with a guard column composed of the same stationary phase. Mass spectra were recorded either with a Waters-Micromass MaldiTOF or with a MicroTOF Focus (Bruker Daltonics) by using the TOF (time-of-flight) technique.

General Procedure for the Synthesis of the Imine Substrates:[16] By using a Dean–Stark apparatus to facilitate water removal, $BF_3{\cdot}Et_2O$ (0.6 mmol) was added (through a syringe) to a refluxing solution of the aldehyde (0.036 mol) and the amine with an EWG group (0.036 mol) in benzene (135 mL). The mixture was heated at reflux until the theoretical amount of water (0.036 mol) was collected. The solution was then cooled and washed with NaOH (2 M solution) and water. The organic phase was separated and dried with $MgSO_4$, and the solvent was evaporated under vacuum to yield a solid, which was crystallized from dichloromethane/petroleum ether (b.p. 60–80 °C) to give the desired product.

***N*-(2-Chlorobenzylidene)-4-methylbenzenesulfonamide:**[7,17,48] White solid (35% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 7.32–7.38 (m, 2 H, Ar), 7.45–7.56 (m, 2 H, Ar), 7.89–7.92 (d, J = 8.4 Hz, 2 H, Ar), 8.14–8.17 (dd, J = 1.5, 7.8 Hz, 2 H, Ar), 9.5 (s, 1 H, HC=N) ppm. HPLC [Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate = 0.7 mL/min, wavelength detector at 230 nm]: t_R = 26.1 min.

***N*-(4-Chlorobenzylidene)-4-methylbenzenesulfonamide:**[7,17,48] White solid (40% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 7.35 (d, J = 8.1 Hz, 2 H, Ar), 7.45–7.48 (m, 4 H, Ar), 7.85–7.90 (m, 2 H, Ar), 8.99 (s, 1 H, HC=N) ppm. HPLC [Chiralcel OD-H column, hexane/2-propanol (93:7), flow rate = 1.0 mL/min, wavelength detector at 230 nm]: t_R = 7.4 min.

4-Methyl-*N*-(naphthalen-2-ylmethylene)benzenesulfonamide:[7,17,48] Pale yellow solid (64% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 7.35–7.38 (m, 2 H, Ar), 7.78–7.65 (m, 2 H, Ar), 7.87–7.97 (m, 5 H, Ar), 8.02–8.05 (m, 1 H, Ar), 8.33 (s, 1 H, Ar), 9.18 (s, 1 H, HC=N) ppm. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 12.4 min.

***N*-(4-Chlorobenzylidene)methanesulfonamide:** White solid (33% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.14 (s, 3 H, CH_3), 7.50–7.52 (d, 2 H, Ar), 7.89–7.91 (d, 2 H, Ar), 8.99 (s, 1 H, HC=N) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.39 (CH_3), 129.85, 130.62, 132.50, 141.85, 170.41 (HC=N) ppm. MS: m/z = 218.01 [M + 1]$^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 10.5 min.

***N*-Butylidene-4-methylbenzenesulfonamide:**[7,17,48] Colorless oil (10% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (m, 3 H, CH_3), 1.51 (m, 2 H, CH_2), 2.33 (m, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 7.31 (d, 2 H, Ar), 7.81 (d, 2 H, Ar), 8.45 (s, 1 H, HC=N) ppm. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.3 mL/min, wavelength detector at 230 nm]: t_R = 18.8 min.

4-Methyl-*N*-(2-methylbenzylidene)benzenesulfonamide:[7,17,48] Yellow solid (73% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 7.25–7.36 (m, 4 H, Ar), 7.45–7.50 (t, J = 7.5 Hz, 1 H, Ar), 7.88–7.91 (d, J = 8.1 Hz, 2 H, Ar), 7.99–8.02 (d, J = 7.8 Hz, 1 H, Ar), 9.35 (s, 1 H, HN=C) ppm. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 14 min.

***N*-(4-Bromobenzylidene)-4-methylbenzenesulfonamide:**[7,17,48] White solid (30% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 7.34–7.36 (m, 1 H, Ar), 7.62–7.65 (d, 1 H, Ar), 7.77–7.79 (d, 1 H, Ar), 7.87–7.89 (d, 1 H, Ar), 8.98 (s, 1 H, HN=C) ppm. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.7 mL/min, wavelength detector at 230 nm]: t_R = 10.7 min.

***N*-(Cyclohexylmethylene)-4-methylbenzenesulfonamide:**[7,17,48] White solid (15% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.29 (m, 6 H, CH_2), 1.76–1.81 (m, 5 H, CH_2), 2.32 (s, 3 H, CH_3), 7.19–7.21 (d, 2 H, Ar), 7.69–7.73 (d, 2 H, Ar), 8.37 (s, 1 H, HN=C) ppm. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 11 min.

4-Methyl-*N*-(4-nitrobenzylidene)benzenesulfonamide:[7,17,48] Pale yellow solid (22% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 7.38 (d, 2 H, Ar), 7.91 (d, 2 H, Ar), 8.11 (d, 2 H, Ar), 8.33 (d, 2 H, Ar), 9.10 (s, 1 H, HN=C) ppm. HPLC [Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate = 0.7 mL/min, wavelength detector at 230 nm]: t_R = 26.4 min.

Preparation of Phenylboroxine:[41] A solution of phenylboronic acid (1.7 g, 14 mmol) in benzene (80 mL) was heated at reflux for 2 h, during which H_2O (0.7 mL, 42 mmol) was removed azeotropically (with a Dean–Stark apparatus). The mixture was concentrated under reduced pressure to ca. 10 mL, and then it was cooled to room temperature. The precipitate was collected by filtration, washed with hexane (5×) to give the boroxine (1 g, 23% yield) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.54 (m, 6 H, Ar), 7.59–7.63 (m, 3 H, Ar), 8.25–8.27 (m, 6 H, Ar) ppm.

General Procedure for the Catalytic Asymmetric Arylation of *N*-Protected Aldimines with Organoboron Reagents: Toluene (2 mL) was added to a round-bottomed flask containing $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (3 mol-%), the chiral ligand (3.3 mol-%) and AgOTf (3 mol-%, in the case of NHC precursor **13**), and the organoboron reagent (0.4 mmol) under nitrogen. The mixture was stirred at 55 °C for 30 min to form the active catalytic species. The *N*-protected aldimine substrate (0.2 mmol) and NEt_3 (0.4 mmol) were added to the flask, and the mixture was stirred at 55 °C for 2–3 d. HCl (0.2 M solution, 5 mL) was added to quench the reaction. AcOEt (3 × 10 mL) was used to extract the product from the aqueous phase. The combined organic phases were washed with NaCl (aqueous, saturated), dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography (SiO_2 gel, hexane/AcOEt, 5:1) provided the final chiral diarylamine product. Note: Racemic products for chiral HPLC analysis were prepared by using the appropriate *N*-protected aldimines (0.5 mmol) with phenylboronic acid (1.0 mmol) in the presence of $Pd(OAc)_2$ (5 mol-%) and 2,2′-bypiridyl (10 mol-%) in dioxane (1.5 mL) at 100 °C for 48–72 h.

***N*-[(4-Chlorophenyl)(phenyl)methyl]-4-methylbenzenesulfonamide:**[7,17,48] White solid (14% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s,

3 H, CH_3), 5.04–5.05 (d, 1 H, CH), 5.52–5.54 (d, 1 H, NH), 7.03–7.07 (m, 4 H, Ar), 7.15–7.19 (m, 4 H, Ar), 7.21–7.23 (m, 3 H, Ar), 7.54–7.56 (d, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.64 (CH_3), 60.83 (CH), 126.62, 127.34, 127.43, 127.89, 128.07, 128.30, 128.79, 128.90, 128.92, 129.59, 129.76, 130.01, 132.51, 133.64, 137.28, 139.07, 140.19, 143.63 ppm. MS (ESI-TOF): *m*/*z* = 394.07 $[M + 1]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (93:7), flow rate = 1.0 mL/min, wavelength detector at 230 nm]: t_R = 18.0 (*S*), 24.0 (*R*) min.

***N*-[(2-Chlorophenyl)(phenyl)methyl]-4-methylbenzenesulfonamide:**[7,17,48] White solid (63% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 5.31–5.33 (d, 1 H, CH), 5.90–5.92 (d, 1 H, NH), 7.05–7.08 (m, 2 H, Ar), 7.14–7.16 (m, 4 H, Ar), 7.22–7.24 (m, 4 H, Ar), 7.33–7.35 (m, 1 H, Ar), 7.60–7.62 (d, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.64 (CH_3), 58.77 (CH), 127.07, 127.35, 127.39, 127.98, 128.78, 128.79, 128.79, 128.97, 129.48, 129.55, 129.56, 129.57, 130.03, 132.93, 137.05, 137.61, 139.40, 143.52 ppm. MS (ESI-TOF): *m*/*z* = 394.07 $[M + 1]^+$. HPLC [Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate = 0.7 mL/min, wavelength detector at 230 nm]: t_R = 27.9 (*S*), 31.8 (*R*) min.

4-Methyl-*N*-[naphthalen-2-yl(phenyl)methyl]benzenesulfonamide:[7,17,48] Yellow solid (12% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 5.41–5.43 (d, 1 H, CH), 5.72–5.74 (d, 1 H, NH), 7.02–7.04 (d, 1 H, Ar), 7.14–7.23 (m, 4 H, Ar), 7.28–7.30 (d, 2 H, Ar), 7.43–7.45 (m, 2 H, Ar), 7.50 (s, 1 H, Ar), 7.53–7.55 (d, 2 H, Ar), 7.63–7.68 (m, 2 H, Ar), 7.79–7.81 (d, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.49 (CH_3), 61.59 (CH), 122.89, 125.28, 126.37, 126.50, 126.56, 127.31, 127.60, 127.65, 127.81, 128.09, 128.61, 128.73, 129.42, 129.84, 132.75, 133.11, 137.39, 137.63, 139.20, 140.52, 143.37, 143.71 ppm. MS (ESI-TOF): *m*/*z* = 410.12 $[M + 1]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 20.2 (*R*), 22.1 (*S*) min.

***N*-[(4-Chlorophenyl)(phenyl)methyl]methanesulfonamide:** White solid (10% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.70 (s, 3 H, CH_3), 5.17–5.18 (m, 1 H, CH), 5.73–5.75 (m, 1 H, NH), 7.28–7.40 (m, 9 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.18 (CH_3), 60.79 (CH), 127.45, 127.48, 128.45, 128.93, 129.19, 129.24, 129.25, 129.91, 132.53, 134.06, 139.33, 140.29 ppm. MS (ESI-TOF): *m*/*z* = 318.04 $[M + 1]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 15.2, 18.1 min.

4-Methyl-*N*-(1-phenylbutyl)benzenesulfonamide:[7,17,48] Colorless oil (13% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.98 (m, 3 H, CH_3), 1.60–1.67 (m, 2 H, CH_2), 2.28–2.32 (m, 2 H, CH_2), 2.24 (s, 3 H, CH_3), 4.07–4.11 (d, 1 H, CH), 4.21–4.25 (d, 1 H, NH), 7.31–7.83 (m, 9 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.61 (CH_3), 19.89 (CH_2), 29.75 (CH_3), 44.89 (CH_2), 64.63 (CH), 126.15, 126.64, 127.20, 127.45, 127.49, 127.90, 128.34, 128.56, 129.01, 129.80, 129.85, 130.13 ppm. MS (ESI-TOF): *m*/*z* = 302.13 $[M]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 15.0 (*S*), 16.3 (*R*) min.

4-Methyl-*N*-[phenyl(*o*-tolyl)methyl]benzenesulfonamide:[7,17,48] Yellow solid (<10% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 5.30 (s, 1 H, CH), 6.02 (s, 1 H, NH), 7.06–7.23 (m, 5 H, Ar), 7.28–7.38 (m, 4 H, Ar), 7.51–7.56 (m, 2 H, Ar), 7.80–7.82 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.62 (CH_3), 22.84 (CH_3), 58.41 (CH), 125.80, 126.28, 126.30, 126.39, 126.63, 127.20, 127.26, 127.69, 127.74, 127.77, 128.64, 128.70, 128.85, 129.47, 129.89, 130.70, 139.16, 143.81 ppm. MS (ESI-TOF): *m*/*z* = 374.13 $[M + 1]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 12.3 (*R*), 15.3 (*S*) min.

***N*-[(4-Bromophenyl)(phenyl)methyl]-4-methylbenzenesulfonamide:**[7,17,48] White solid (12% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 4.96–4.98 (d, 1 H, CH), 5.51–5.52 (d, 1 H, NH), 6.99–7.05 (m, 4 H, Ar), 7.15–7.17 (d, 2 H, Ar), 7.21–7.23 (m, 3 H, Ar), 7.31–7.35 (m, 2 H, Ar), 7.54–7.56 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.74 (CH_3), 60.99 (CH), 121.79, 126.64, 127.35, 127.43, 128.11, 128.92, 129.27, 129.60, 129.89, 131.74, 136.84, 137.09, 137.38, 138.24, 139.56, 140.10, 143.52, 143.86 ppm. MS (ESI-TOF): *m*/*z* = 440.02 $[M + 1]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.7 mL/min, wavelength detector at 230 nm]: t_R = 11.6 (*S*), 14.2 (*R*) min.

***N*-[Cyclohexyl(phenyl)methyl]-4-methylbenzenesulfonamide:**[7,17,48] Light yellow oil (17% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85–1.10 (m, 3 H, CH_2), 1.22–1.28 (m, 4 H, CH_2), 1.33–1.59 (m, 4 H, CH_2), 2.41 (s, 3 H, CH_3), 3.30–3.32 (d, 1 H, CH), 4.85–4.87 (d, 1 H, NH), 7.29–7.36 (m, 5 H, Ar), 7.67–7.69 (d, 2 H, Ar), 7.79–7.83 (d, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.65 (CH_3), 22.37 (CH_2), 22.88 (CH_2), 25.81 (CH_2), 26.55 (CH_2), 28.89 (CH_2), 38.53 (CH), 66.33 (CH), 126.56, 126.63, 127.02, 127.13, 128.22, 129.57, 129.88, 130.06, 130.71, 139.05, 143.30, 145.13 ppm. MS (ESI-TOF): *m*/*z* = 266.13 $[M + 1 - Ph]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (80:20), flow rate = 0.5 mL/min, wavelength detector at 230 nm]: t_R = 10.9 (*S*), 14.0 (*R*) min.

***N*-[(2-Chlorophenyl)(4-chlorophenyl)methyl]-4-methylbenzenesulfonamide:**[7,17,48] White solid (12% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 5.41–5.42 (d, 1 H, CH), 5.87–5.89 (d, 1 H, NH), 7.01–7.04 (d, 2 H, Ar), 7.14–7.25 (m, 8 H, Ar), 7.58–7.60 (d, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.70 (CH_3), 58.23 (CH), 127.30, 128.78, 128.89, 129.24, 129.39, 129.59, 129.85, 130.02, 130.18, 130.34, 130.62, 132.86, 133.85, 135.77, 136.96, 137.16, 137.95, 143.65 ppm. MS (ESI-TOF): *m*/*z* = 428.03 $[M + 1]^+$. HPLC [Chiralcel OD-H column, hexane/2-propanol (70:30), flow rate = 0.7 mL/min, wavelength detector at 230 nm]: t_R = 8.2 (*S*), 11.7 (*R*) min.

4-Methyl-*N*-[(4-nitrophenyl)(phenyl)methyl]benzenesulfonamide:[7,17,48] Light orange solid (<10% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 5.25–5.27 (d, 1 H, CH), 5.61–5.62 (d, 1 H, NH), 6.98–7.00 (d, 2 H, Ar), 7.17–7.19 (d, 2 H, Ar), 7.35–7.39 (m, 4 H, Ar), 7.57–7.59 (m, 3 H, Ar), 8.07–8.09 (d, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.70 (CH_3), 61.07 (CH), 123.80, 124.45, 126.85, 127.20, 127.34, 127.44, 128.38, 128.56, 128.60, 129.26, 129.74, 130.64, 136.96, 139.40, 142.85, 144.04, 147.35, 147.80 ppm. MS (ESI-TOF): *m*/*z* = 405.09 $[M + 1]^+$. HPLC [Chiralcel AD-H column, hexane/2-propanol (90:10), flow rate = 0.7 mL/min, wavelength detector at 230 nm]: t_R = 19.9 (*S*), 25.5 (*R*) min.

Synthesis of the Chiral NHC Precursor 13

[(2*S*,3*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl]dimethanamine (11):[35,36] To a round-bottomed flask containing diazide **10** (5 mmol), dry EtOH (50 mL), and Pd/C (10 mol-%) was attached a rubber balloon filled with H_2, and the mixture was stirred 24 h. The mixture was then filtered through a sintered glass filter, and the filtrate was concentrated under vacuum. The diamine product (81% yield) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 6 H, CH_3), 1.83 (br. s, 4 H, NH_2), 2.76 (d, 4 H, CH_2), 3.28 (s, 3 H, OCH_3), 3.59 (m, 2 H, CHO) ppm.

***N*,*N*′-[(2*R*,3*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl]bis(methylene)bis(1-phenylmethanamine) (12):**[36] Diamine **11**

(0.4 mmol) was added to a round-bottomed flask containing dry MeOH (35 mL) and benzaldehyde (10 mmol). The mixture was heated at reflux and stirred under nitrogen overnight. After cooling the reaction mixture to room temperature, dry toluene (50 mL) and $NaBH_4$ (21 mmol, added in small portions over a 20 min period) were added. The mixture was stirred for 2 h, and then the solvents were removed under vacuum. H_2O (50 mL) and AcOEt (50 mL) were added to the crude mixture to extract the product, and the layers were separated. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and filtered. The solvent was evaporated under vacuum. The crude product was purified by column chromatography (SiO_2 gel, hexane/AcOEt, 1:1) to give the desired diamine product **12** (35% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 6 H, CH_3), 2.46 (s, 2 H, CH_2NH), 2.63 (s, 2 H, CH_2NH), 3.22 (s, 3 H, OCH_3), 3.68–3.81 (m, 6 H, CHO and CH_2Ar), 5.25 (s, 2 H, NH), 7.22 (m, 10 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.30 (CH_3), 47.81 (CH_2N), 49.30 (OCH_3), 53.54 (CH_2Ar), 68.93 (CHO), 98.17 (CO), 126.66 (Ar), 127.87 (Ar), 139.49 (Ar) ppm. MS (ESI-TOF): *m*/*z* = 415.27 [M + 1]$^+$.

(2*S*,3*S*,4a*R*,9a*R*)-6,8-Dibenzyl-2,3-dimethoxy-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2*H*-[1,4]dioxino[2,3-*e*][1,3]diazepin-6-ium Hexafluorophosphate (13): Secondary diamine **12** (0.26 mmol), NH_4PF_6 (0.26 mmol), and triethyl orthoformate (0.26 mmol) were added to a round-bottomed flask under an inert gas. The reaction mixture was stirred at 120 °C for 3 h. The EtOH byproduct was evaporated under vacuum, and the crude product was recrystallized from EtOH to give the desired NHC precursor **13** (57% yield) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 6 H, CH_3), 3.02 (s, 6 H, OCH_3), 3.20–3.28 (m, 2 H, CH_2N), 3.37–3.42 (m, 2 H, CH_2N), 3.55–3.56 (m, 2 H, CHO), 4.67–4.79 (q, *J* = 12 Hz, 4 H, CH_2Ar), 7.33–7.38 (m, 10 H, Ar), 8.37 (s, 1 H, NH=N) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.10 (CH_3), 48.04 (OMe), 51.21 (CH_2Ar), 63.12 (NCH_2C), 67.20 (CHO), 99.08 (C–C), 128.78 (Ar), 129.18 (Ar), 129.28 (Ar), 132.63 (Ar–C), 159.06 (C=N) ppm. MS (MicroTOF): *m*/*z* = 425.25 [M]$^+$, 426.26 [M + 1]$^+$, 427.26 [M + 2]$^+$.

Preparation of a Ruthenium–Phosphane Complex: Into a round-bottomed flask under an inert gas were added $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (21.4 mg, 0.5 equiv.), (*S*)-DioxPhos ligand (**3**, 20 mg), and dry CH_2Cl_2 (2 mL). The mixture was stirred at room temperature overnight. The crude product was purified by silica gel liquid chromatography (hexane/AcOEt, 1:1). Two fractions were obtained, and the solvents were evaporated to dryness. Data for fraction 1: Dimer complex **9** (82% yield) was obtained as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.62 (s, 3 H, CH_3), 0.77–0.78 (d, 3 H, CH_3), 1.02–1.04 (d, 3 H, CH_3), 1.24–1.27 (m, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.78 (s, 3 H, OCH_3), 2.38 (s, 3 H, OCH_3), 2.48–2.58 (m, 4 H, CH_2P), 2.72–2.74 (m, 2 H, CH), 3.54–3.58 (m, 2 H, CHO), 4.83–4.85 (d, 2 H, cymene), 5.21–5.23 (d, 2 H, cymene), 5.25–5.27 (d, 2 H, cymene), 5.36–5.37 (d, 2 H, cymene), 7.34 (m, Ar), 7.46–7.53 (m, Ar), 7.89–7.93 (m, Ar), 7.99–8.03 (m, Ar) ppm. ^{31}P NMR (400 MHz, $CDCl_3$): δ = 19.67 ppm. MS (ESI): *m*/*z* = 1149 [M(^{35}Cl × 3)], 1151 [M(^{35}Cl × 2 + ^{37}Cl)]. Data for fraction 2: Monomer complex **8** (10% yield) was obtained as an orange solid. MS (ESI): *m*/*z* = 843 [M(^{35}Cl)], 845 [M(^{37}Cl)].

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra and mass spectra.

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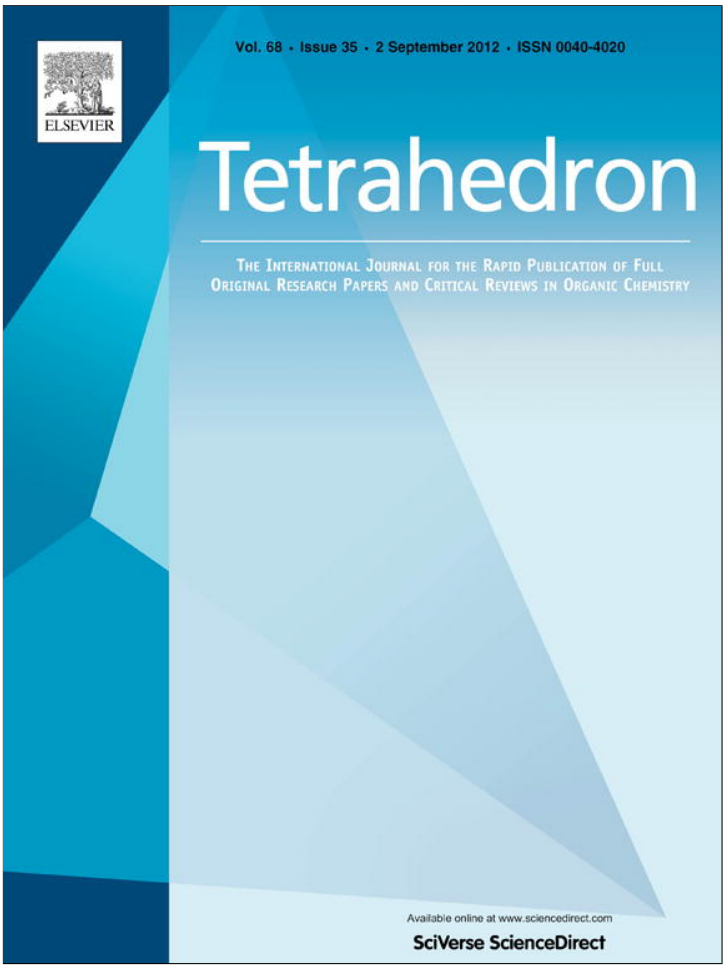

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Expeditious and novel synthesis of α-hydroxyesters via rhodium–NHC catalyzed arylation of ethyl glyoxalate

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ABSTRACT

The rhodium–NHC catalyzed arylation reaction of ethyl glyoxalate with aryl and alkyl boronic acids provides an efficient method for the synthesis of α-hydroxyesters. A wide range of α-hydroxyesters (up to 12) were prepared in good to excellent yields. KO^{t}Bu was the base of choice, along with *tert*-amyl alcohol as the solvent. As far as we are aware, this is the first report of this catalytic arylation, using rhodium–NHC catalysts with this specific substrate type.

1. Introduction

The efficient synthesis of α-hydroxyesters is of considerable interest given that this structural moiety is found in a plethora of complex natural products and therapeutic molecules[1] (Fig. 1), as well as being important in the synthesis of α-aminoesters.[2] A number of synthetic methods exist in the literature, with the reduction of aliphatic α-ketoesters as the most common method.[3]

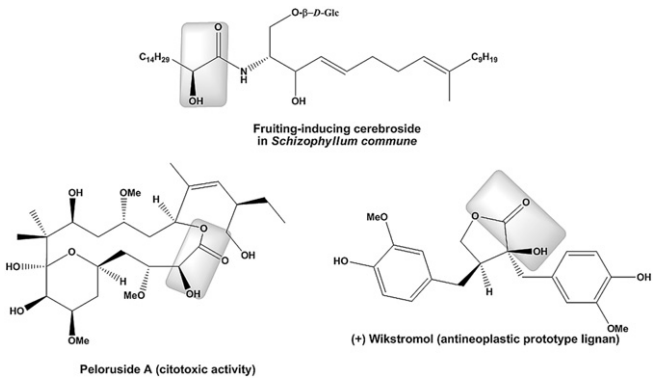

Fig. 1. Selection of biologically active molecules prepared from optically active α-oxy functionalized carbonyl building blocks.

Over the last six years our group has had an interest in the development of new efficient methods for the stereoselective synthesis of chiral α-hydroxyesters.[1,4] As an extension of our work on the development of the catalytic arylation of activated imine substrates with boronic acids and derivatives[5,6] we decided to investigate the arylation of glyoxalate esters as a route to such products. As far as we are aware, there is only one example of a catalytic reaction with this substrate type, one that employs a Suzuki–Miyaura coupling reaction with Pd and phosphine ligands.[7]

2. Results and discussion

Taking into account our experience in working with conformationally locked cyclic diacetal backbone molecules,[8–11] we decided to synthesize a new family of *N*-heterocyclic carbene (NHC) type ligands, based on this structural motif, using known methods from the literature[12,13] (Scheme 1). Starting with the known chiral diamine (**2**) we obtained the dibenzylated amine molecules (**3a**–**c**) by reductive amination. These products were then converted into the mono-imidazolium type salts (**4a**–**c**).

We synthesized the di-imidazolium type salt (**6**) in 78% yield (Scheme 1) from the dichloride molecule (**5**) (obtained from (+)-diol (**1**)), using a literature method.[13] The synthesis and application of (**4a**) in the ruthenium catalyzed arylation of activated imines has already been achieved by us.[6]

The method of choice was the preparation of the NHCs in situ by deprotonation of the corresponding imidazolium salts.[6,14] Their

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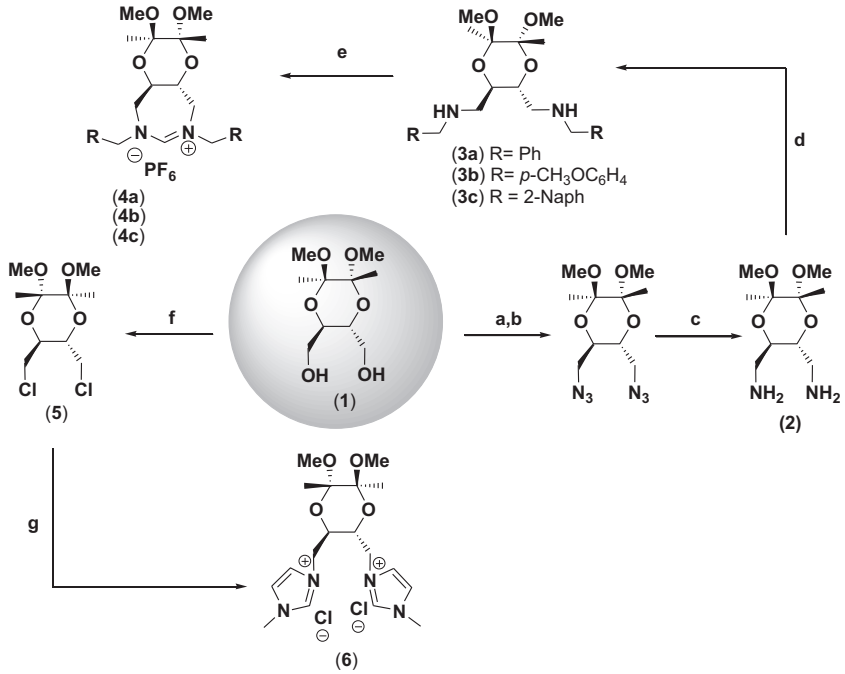


Scheme 1. Synthetic pathways to mono-NHC salts (**4a**–**c**) and di-NHC salt (**6**) from (+)-diol (**1**). Reagents and conditions: (a) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0 °C, 3 h; (b) NaN_3, DMF, 60 °C, overnight; (c) Pd/C, H_2, EtOH, rt, 24 h; (d) benzaldehyde, MeOH, reflux, 3 h, $NaBH_4$, toluene, rt, 2 h; (e) $HC(OEt)_3$, NH_4PF_6, 120 °C, 3 h; (f) PPh_3, CCl_4, pyridine, CH_2Cl_2, rt, 24 h; (g) 1-methylimidazole, CH_3CN, 140 °C, 2 days.

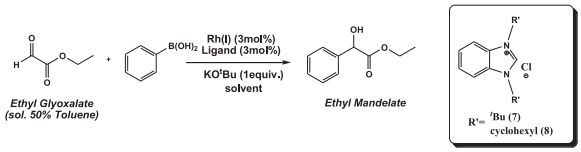
neutrality and capacity for two-electron-donating (σ-donating) with negligible π back-bonding make them notable molecules for catalysis.[15–20]

Inspired by the pioneering work of Gois and co-workers,[21] which concerned the arylation of aldehydes with Rh(II)–NHC complexes and boronic acids, we decided to extend this methodology for the synthesis of α-hydroxyesters with Rh(I) metal catalysts and our NHC type ligands (Scheme 1). Ethyl glyoxalate (50% solution in toluene) was the substrate chosen for the catalytic arylation reactions. For comparative purposes, two commercial aquiral benzimidazolium salts (**7**) and (**8**) were tested as well. The preliminary results can be seen in Table 1.

Our study commenced by screening the rhodium pre-catalysts with ligand precursor (**4a**) in *tert*-amyl alcohol at 60 °C, with KO^{t}Bu to evaluate the best rhodium catalyst for this reaction (Table 1, entries 1–4). The best results were obtained with $[Rh(OH)COD]_2$ and $Rh(COD)_2BF_4$ (Table 1, entries 2 and 4, respectively), giving the desired product in 97 and >99% yield, respectively. Encouraged by these results, we decided to screen our NHC-type ligands (Scheme 1). In general, the results with $Rh(COD)_2BF_4$ were quite impressive (Table 1, entries 8–10), with excellent yields obtained with all the NHC-type ligands tested (up to 95% yield). It seems that the bulkiness of the ligand has a detrimental effect on the reaction yield (Table 1, see entries 5 and 6). This observation would be expected from partial blockage of part of the coordination sphere of the active catalyst formed in situ. With regards to the $[Rh(OH)COD]_2$ pre-catalyst, the best results were obtained with ligand precursors (**4a**) (97%) (Table 1, entry 2) and (**6**) (>99%) (Table 1, entry 7). Ligand (**4a**) (less bulky) was screened using both the rhodium pre-catalysts described above. The best pre-catalyst proved to be $[Rh(OH)COD]_2$, providing the desired α-hydroxyester in >99% yield (Table 1, entry 11) in less than an hour. In fact, we showed that the reaction occurs at low temperature (Table 1, entry 13) with almost total conversion of the substrate within 4 h. Preliminary studies using phosphine ligands[6] have shown that these NHC ligands provide superior ligand acceleration.

To compare the efficiency of the ligands synthesized above (Scheme 1) we conducted four test reactions using the commercial imidazoliums (**7**) and (**8**) as NHC precursors (Table 1, entries 18–21). These ligands had already been applied with success in arylation of aldehydes with boronic acids by Gois and co-workers.[21]

Table 1
Rh(I)–NHC catalytic arylation of ethyl glyoxalate with phenylboronic acid



Entry[a]	Rh(I)	Ligand	Solvent	*T*/°C	*t*/h	Yield[b]/%
1	$[Rh(COD)Cl]_2$	**4a**	*tert*-Amyl alcohol	60	7	68
2	$[Rh(OH)COD]_2$	**4a**	*tert*-Amyl alcohol	60	4	97
3	$Rh(acac)(C_2H_4)$	**4a**	*tert*-Amyl alcohol	60	4	43
4	$Rh(COD)BF_4$	**4a**	*tert*-Amyl alcohol	60	4	>99
5	$[Rh(OH)COD]_2$	**4b**	*tert*-Amyl alcohol	60	4	73
6	$[Rh(OH)COD]_2$	**4c**	*tert*-Amyl alcohol	60	4	58
7	$[Rh(OH)COD]_2$	**6**	*tert*-Amyl alcohol	60	4	>99
8	$Rh(COD)BF_4$	**4b**	*tert*-Amyl alcohol	60	4	95
9	$Rh(COD)BF_4$	**4c**	*tert*-Amyl alcohol	60	4	>99
10	$Rh(COD)BF_4$	**6**	*tert*-Amyl alcohol	60	4	>99
11	$[Rh(OH)COD]_2$	**4a**	*tert*-Amyl alcohol	rt	0,5	>99
12	$Rh(COD)BF_4$	**4a**	*tert*-Amyl alcohol	rt	4	66
13	$[Rh(OH)COD]_2$	**4a**	*tert*-Amyl alcohol	0	4	>99
14	$[Rh(OH)COD]_2$	**4a**	MeOH	60	4	47
15	$[Rh(OH)COD]_2$	**4a**	Dioxane	60	4	90
16	$[Rh(OH)COD]_2$	**4a**	DME/H_2O (5/1)	60	4	21
17	$[Rh(OH)COD]_2$	**4a**	DME	60	4	>99
18	$[Rh(OH)COD]_2$	**7**	*tert*-Amyl alcohol	rt	4	46
19	$[Rh(OH)COD]_2$	**7**	*tert*-Amyl alcohol	60	4	59
20	$[Rh(OH)COD]_2$	**8**	*tert*-Amyl alcohol	rt	4	12
21	$[Rh(OH)COD]_2$	**8**	*tert*-Amyl alcohol	60	4	14
22	$[Rh(OH)COD]_2$	—	*tert*-Amyl alcohol	60	4	5

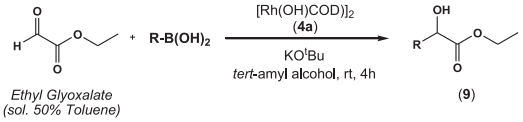
[a] Reaction conditions: $[Rh(I)]_2$ (1.5 mol %) or [Rh(I)] (3 mol %), ligand precursor (3.3 mol %), KO^{t}Bu (1 equiv), $PhB(OH)_2$ (2 equiv), *tert*-amyl alcohol (1 ml).
[b] Isolated yields.

The yields were lower than those obtained with NHC precursor (**4a**) (Table 1, compare entry 11 with entries 18 and 20). Upon increasing the temperature to 60° there was a slight increase in the yield (Table 1, entries 19 and 21), showing that the NHCs resulting from (**7**) and (**8**) were less efficient in this particular transformation. It was the less bulky NHC ligand derived from (**7**), which gave better results compared to the NHC derived from (**8**) (Table 1, compare entries 18 and 19 with entries 20 and 21, respectively). We think that specific stereochemical factors in the formation of the catalytic active species might be the reason.

To test for possible solvent effects, we decided to use the optimal conditions found previously with a variety of different solvents, ranging from polar protic ones, like MeOH and H_2O (Table 1, entries 14 and 16), and aprotic polar ones, like DME (Table 1, entry 16) to non-polar ones, like 1,4-dioxane (Table 1, entry 15). In fact, the best results were obtained using *tert*-amyl alcohol with $[Rh(OH)COD]_2$ and ligand precursor (**4a**), allowing the formation of the ethyl mandelate product in high yield under mild conditions, without any water present (see Table 1, entry 11). Finally, to prove the efficiency of the NHC type ligands used in this transformation, a test reaction in the absence of ligand was made (Table 1, entry 22). A vestigial quantity of ethyl mandelate was only obtained.

To investigate the scope and limitations of this reaction, we screened various arylboronic acids bearing electron-donating and electron-withdrawing substituents in the *ortho*, *meta* and *para* positions of the phenyl ring, as well as aliphatic boronic acids using the optimized catalytic system discovered above. The results can be seen in Table 2.

Table 2
Catalytic arylation of ethyl glyoxalate, applying a number of aryl and alkyl substituted boronic acids



Entry[a]	R	Product (**9**)	Yield[b]/%
1	2-Naph	**a**	36
2	4-FC_6H_4	**b**	>99
3	3-HOC_6H_4	**c**	nr
4	2-$CH_3OC_6H_4$	**d**	81
5	3-$CH_3OC_6H_4$	**e**	>99
6	2-Fur	**f**	71
7	4-ClC_6H_4	**g**	34
8	3-$CH_3OC_6H_4$	**h**	>99
9	3-AcC_6H_4	**i**	12
10	1-Naph	**j**	72
11	3-$NH_2C_6H_4$	**k**	Trace
12	CH_3CH_2	**l**	23

[a] Reaction conditions: $[Rh(OH)COD]_2$ (1.5 mol %), (**4a**) (3.3 mol %), KO^{t}Bu (1 equiv), $RB(OH)_2$ (2 equiv), *tert*-amyl alcohol (1 ml).
[b] Isolated yields; nr=no reaction.

In most cases the reaction proceeded with remarkable efficiency (up to 99% yield of isolated product (entries 2, 5 and 8, Table 2), and between 71 and 81% yield of isolated product (entries 4, 6 and 10, Table 2)), under mild conditions. The lower yields were observed when certain electron-donating groups were present in the organoboron reagent (Table 2, entries 1, 11 and 12). No reaction was observed when 3-$HOC_6H_4B(OH)_2$ was used (Table 1, entry 3) and only a vestigial quantity of product (**9k**) was obtained, with 3-$NH_2C_6H_4B(OH)_2$ (Table 2, entry 11). Moreover, electron-withdrawing substituents in the *ortho* position (Table 2, entry 4) seem to have no significant influence on the yield, which indicates that the reaction does not suffer from steric hindrance around the reacting center. The aliphatic product (**9l**) obtained upon using ethylboronic acid was formed in poor yield (23%, Table 2, entry 12).

Unfortunately all the α-hydroxyester products that were formed were racemic, despite the use of chiral Rh–NHC catalysts—one of which has already proved to give high levels of enantiofacial selectivity for the arylation of activated imines using Ru catalysts (to be precise, $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$).[6] This was first considered to be a racemization processes, which has already been observed for such compounds in the presence of Rh(II) catalysts.[21c,22] Key experiments were performed with (*R*)-(−)-methyl mandelate. In one flask, 50 mg of this compound was stirred at room temperature with 1.5 mol % of $[Rh(OH)COD]_2$, 3.3 mol % of ligand precursor (**4a**) and KO^{t}Bu (1 equiv relative to the ligand), in 1 ml of dry *tert*-amyl alcohol, during 24 h. Simultaneously, in another flask, 50 mg of (*R*)-(−)-methyl mandelate was stirred at 60 °C with 1.5 mol % of $[Rh(OH)COD]_2$, 3.3 mol % of ligand precursor (**4a**), 2 equiv of $PhB(OH)_2$ and 1 equiv of KO^{t}Bu (relative to the mandelate), in 1 ml of dry *tert*-amyl alcohol, for 4 h.

No racemization was observed, thus suggesting that there may be competing transition states in this reaction. However, in the absence of concrete experimental evidence, the principle mechanism (as pointed out by one of the referees) could be analogous to that proposed by Nolan[23] (which is based on that originally suggested by Hayashi[24]) and perhaps the lack of any observable enantioselectivity could be due to substitution of the NHC unit (present in a very likely square planar complex) by the glyoxylate substrate during the catalytic cycle (also suggested by the same referee). If this proves to be the case, and given the fact that the reaction yield in the absence of NHC ligand was very poor (Table 1, entry 22—proving that there is pronounced ligand acceleration in this reaction), then it might be safe to assume that the formation of an NHC–Rh-aryl intermediate (isolated by Nolan[23] in their particular case), is the key rate determining step.

We are currently investigating this mechanism and obviously wish to develop a system that provides high enantioselectivities.

3. Conclusion

In summary, we have developed novel Rh(I) complexes in situ from $[Rh(OH)COD]_2$ and NHC-type ligands and used them in the efficient, high yielding synthesis of a diverse range of substituted α-hydroxyesters. As far as we are aware, only one example on the use of NHC–Rh(I) complexes in arylation processes has been reported todate.[23] Our chiral NHC based catalytic systems have proved more efficacious than those derived from some commercial achiral NHC precursors. Further investigations on an asymmetric version are in progress, including studies directed at exploring the full mechanism of this reaction.

4. Experimental section

4.1. General remarks

All the reagents were purchase from Aldrich, Fluka, Acros and Alfa Aeser. The chiral diazide (precursor to diamine (**2**)) (**2**) was obtained from ChiraTecnics Lda. The solvents used were dry under current laboratory techniques: *tert*-amyl alcohol was distilled from CaH_2, as well as MeOH, toluene, CH_2Cl_2, CH_3CN and DME (1,2-dimethoxyethane). 1,4-Dioxane was distilled from Na and benzophenone. Pyridine was distilled from KOH. CCl_4 was kept under 4 Å molecular sieves and then distilled. The phenylboronic acid and derivatives were used as received, as well as ethyl glyoxalate (50% solution in toluene).

Column chromatography was carried out on silica gel (SDS, 70–200 μm). Thin layer chromatography (TLC) was carried out on

aluminium backed Kieselgel 60 F_{254} plates (Merck). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. The NMR analysis were recorded on a Bruker Avance instrument (400 MHz) using $CDCl_3$ as solvent and the signal from the residual $CHCl_3$ as an internal standard. Mass spectra were recorded on a Waters-Micromass (MaldiTOF, MicroTOF, ESI) or FAB Focus (Bruker Daltonics) using the TOF technique. Melting points were measured in a Barnstead/Electrothermal 9100 instrument. Specific rotation measurements were measured on a Perkin–Elmer 241 polarimeter.

4.2. NHC-type salts synthesis

*4.2.1. Synthesis of N,N′-((2R,3R,5S,6S)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)bis(1-phenylmethanamine)(**3a**).*[13a] Diamine (**2**) (0.4 mmol) was added to a round bottom flask containing dry MeOH (35 ml) and benzaldehyde (10 mmol). The mixture was stirred under nitrogen and reflux overnight. Dry toluene (50 ml) and $NaBH_4$ (21 mmol, added in small portions over a 20 min period) were added to the cooled solution (cooled to rt). The mixture was stirred for 2 h and then the solvents were removed under vacuum. H_2O (50 ml) and AcOEt (50 ml) were added to the crude mixture and extracted. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and the solvent was again evaporated under vacuum. The crude product was purified using column chromatography (SiO_2 gel, Hexane/AcOEt (1/1)), giving the desired diamine product (**3a**) (colourless oil) in 35% yield. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.25 (s, 6H, CH_3), 2.46 (s, 2H, CH_2NH), 2.63 (s, 2H, CH_2NH), 3.22 (s, 3H, OCH_3), 3.68–3.81 (m, 6H, CHO+CH_2Ar), 5.25 (s, 2H, NH), 7.22 (m, 10H, Ar). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.30 (CH_3), 47.81 (CH_2N), 49.30 (OCH_3), 53.54 (CH_2Ar), 68.93 (CHO), 98.17 (C–O), 126.66 (Ar), 127.87 (Ar), 139.49 (Ar). ESI-TOF MS (m/z): 415.27 (M^{+1}).

*4.2.2. Synthesis of N,N′-((2R,3R,5S,6S)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)bis(1-(4-methoxyphenyl)methanamine) (**3b**).* The same procedure was applied, using *p*-anisaldehyde (2.13 mmol) to 0.85 mmol of diamine (**2**). The crude product was purified using column chromatography (SiO_2 gel, Hexane/AcOEt (1/1)), giving the desired diamine product (**3b**) (yellow oil) in 48% yield. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.28 (s, 6H, CH_3), 2.04 (s, 2H, CH_2NH), 2.65–2.67 (m, 4H, CH_2NH), 3.26 (s, 3H, OCH_3), 3.69–3.77 (m, 4H, CH_2Ar), 3.79 (s, 6H, OCH_3), 4.08–4.16 (m, 2H, CHO), 6.83–6.86 (d, 4H, Ar), 7.20–7.23 (d, 4H, Ar). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.10 (CH_3), 48.29 (CH_2), 49.58 (OCH_3), 53.08 (CH_2), 55.42 (OCH_3), 69.41 (CHO), 98.80 (CHO), 113.95 (Ar), 129.84 (Ar), 134.18 (Ar), 158.99 (Ar). ESI-TOF MS (m/z): 475.30 (M^{+1}).

*4.2.3. Synthesis of N,N′-((2R,3R,5S,6S)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)bis(1-(naphthalen-2-yl)methanamine) (**3c**).* The same procedure was applied, using 2-naphthaldehyde (2.13 mmol) to 0.85 mmol of diamine (**2**). The crude product was purified using column chromatography (SiO_2 gel, Hexane/AcOEt (1/1)), giving the desired diamine product (**3c**) (colourless oil) in 41% yield. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.29 (s, 6H, CH_3), 1.92 (s, 2H, CH_2NH), 2.69–2.70 (m, 4H, CH_2NH), 3.28 (s, 3H, OCH_3), 3.91–3.93 (m, 6H, CH_2Ar+CHO), 7.42–7.48 (m, 2H, Ar), 7.72–7.74 (m, 2H, Ar), 7.77–7.82 (m, 3H, Ar). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.78 (CH_3), 48.26 (CH_2), 49.63 (OCH_3), 54.06 (CH_2), 69.55 (CHO), 98.83 (CHO), 125.80 (Ar), 126.22 (Ar), 126.82 (Ar), 126.90 (Ar), 127.74 (Ar), 127.85 (Ar), 127.94 (Ar), 128.28 (Ar), 128.64 (Ar), 132.82 (Ar), 133.52 (Ar), 138.73 (Ar). ESI-TOF MS (m/z): 515.30 (M^{+1}).

*4.2.4. Synthesis of (2S,3S,4aR,9aR)-6,8-dibenzyl-2,3-dimethoxy-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate (**4a**).*[12] The secondary diamine product (**3a**) (0.26 mmol), NH_4PF_6 (0.26 mmol) and triethylorthoformate (0.26 mmol) were added to a round bottom flask under an inert atmosphere. The reaction mixture was stirred at 120 °C for 3 h. The EtOH formed by-product was evaporated under vacuum and the crude product was recrystallized from EtOH to give the desired NHC precursor product (**4a**) (white crystals) in 57% yield. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.14 (s, 6H, CH_3), 3.02 (s, 6H, OCH_3), 3.20–3.28 (m, 2H, CH_2N), 3.37–3.42 (m, 2H, CH_2N), 3.55–3.56 (m, 2H, CHO), 4.67–4.79 (q, J=12 Hz, 4H, CH_2Ar), 7.33–7.38 (m, 10H, Ar), 8.37 (s, 1H, NH=N). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.10 (CH_3), 48.04 (OCH_3), 51.21 (CH_2Ar), 63.12 (NCH_2C), 67.20 (CHO), 99.08 (C–C), 128.78 (Ar), 129.18 (Ar), 129.28 (Ar), 132.63 (Ar–C), 159.06 (C=N). MicroTOF MS m/z: 425.25 (M^+), 426.26 (M^{+1}), 427.26 (M^{+2}). $[\alpha]_D^{25}$ −67.8 (c 0.96, $CHCl_3$).

*4.2.5. Synthesis of (2R,3R,4aR,9aR)-2,3-dimethoxy-6,8-bis(4-methoxybenzyl)-2,3-dimethyl-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate (V) (**4b**).* The same procedure was applied using 0.38 mmol of the diamine (**3b**). The crude product was recrystallized from EtOH to give the desire NHC precursor product (**4b**) (yellowish crystals) in 59% yield. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (s, 6H, CH_3), 3.07 (s, 6H, OCH_3), 3.18–3.26 (m, 2H, CH_2N), 3.37–3.42 (m, 2H, CH_2N), 3.50–3.60 (m, 2H, CHO), 3.80 (s, 6H, OCH_3), 4.66 (m, 4H, CH_2Ar), 6.86 (d, 4H, Ar), 7.22–7.26 (d, 4H, Ar), 8.23 (s, 1H, NH=N). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.26 (CH_3), 48.24 (OCH_3), 51.22 (CH_2), 55.43 (OCH_3), 62.91 (CH_2), 67.32 (CHO), 99.17 (CHO), 114.76 (Ar), 124.58 (Ar), 130.50 (Ar), 158.21 (Ar), 160.38 (C=N). (ESI) MS m/z: 485.26 (M^+), 486.27 (M^{+1}), 487.27 (M^{+2}).

*4.2.6. Synthesis of (2R,3R,4aR,9aR)-2,3-dimethoxy-2,3-dimethyl-6,8-bis(naphthalen-2-ylmethyl)-3,4a,5,8,9,9a-hexahydro-2H-[1,4]dioxino[2,3-e][1,3]diazepin-6-ium hexafluorophosphate (V) (**4c**).* The same procedure was applied using 0.37 mmol of the diamine (**3c**). The crude product was recrystallized from EtOH to give the desired NHC precursor product (**4c**) (yellow crystals) in 78% yield. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.06 (s, 6H, CH_3), 2.94 (s, 6H, OCH_3), 3.27–3.35 (m, 2H, CH_2N), 3.45–3.49 (m, 2H, CH_2N), 3.63–3.64 (m, 2H, CHO), 4.86–4.97 (m, 4H, CH_2Ar), 7.36–7.39 (m, 4H, Ar), 7.46–7.49 (m, 4H, Ar), 7.72–7.79 (m, 6H, Ar), 8.47 (s, 1H, NH=N). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.15 (CH_3), 48.13 (OCH_3), 51.42 (CH_2), 63.56 (CH_2), 67.37 (CHO), 99.20 (CHO), 125.37 (Ar), 126.75 (Ar), 126.88 (Ar), 127.79 (Ar), 128.23 (Ar), 128.68 (Ar), 129.53 (Ar), 130.03 (Ar), 133.28 (Ar), 133.49 (Ar), 159.14 (C=N). (ESI) MS m/z: 525.27 (M^+), 526.28 (M^{+1}), 527.28 (M^{+2}).

*4.2.7. Synthesis of (2S,3S,5S,6S)-5,6-bis(chloromethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**5**).*[13] In a round bottom flash under an inert atmosphere was added commercial ((2*R*,3*R*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanol (**1**) (1.38 mmol), PPh_3 (5.54 mmol), dry pyridine (5.54 mmol), dry CCl_4 (5.54 mmol) and dry CH_2Cl_2 (10 ml). The mixture was left stirring 24 h at room temperature in the dark. The solvents was evaporated under vacuum and the crude product was purified by liquid chromatography (SiO_2 gel, Hexane/AcOEt (1/1)), giving the desired product (**5**) (as a white solid) in 99% yield (mp=67.4–68.6 °C). ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.33 (s, 6H, CH_3), 3.29 (s, 6H, OCH_3), 3.55–3.67 (m, 4H, CH_2–Cl), 3.94–3.96 (m, 2H, CHO). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.35 (CH_3), 43.48 (CH_2–Cl), 48.08 (OCH_3), 69.68 (CHO), 99.31 (CO). MicroTOF MS m/z: 295.05 (M^{+1}). $[\alpha]_D^{20}$ −196.7 (c 1.33, $CHCl_3$).

4.2.8. Synthesis of 3,3′-((2R,3R,5S,6S)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)bis(1-methyl-1H-imidazol-

*3-ium) chloride (**6**).*[13] In a round bottom flask fitted with a reflux condenser and under an inert atmosphere, was added the dichloride compound (**5**) (7.32 mmol), 1-methylimidazole (37 mmol) and dry CH_3CN (50 ml). The mixture was stirred 2 days at 90 °C. The solvent was evaporated under vacuum and the crude brown oil was washed several times with pentane. The pentane fractions were evaporated under vacuum, giving the desired product (**6**) in 47% yield (colourless crystals). ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm): 1.28 (s, 6H, CH_3), 3.24 (s, 6H, OCH_3), 3.55–3.63 (m, 4H, CH_2N), 3.65 (s, 6H, CH_3), 3.90–3.91 (m, 2H, CHO), 6.84 (s, 2H, NHC), 7.01 (s, 2H, NHC), 7.39 (s, 2H, NCHN). ^{13}C NMR analysis ($CDCl_3$, 100 MHz) δ (ppm): 17.31 (CH_3), 33.20 (CH_3), 43.47 (CH_2), 48.01 (OCH_3), 69.56 (CHO), 99.24 (CHO), 120.02 (NC), 129.44 (NC), 137.77 (NCN). (FAB$^+$) MS *m*/*z*: 365.0 (M^+).

4.3. Catalytic reactions

4.3.1. General procedure. $[Rh(I)]_2$ (1.5 mol %, 7.34×10^{-3} mmol) or [Rh(I)] (3 mol %, 0.015 mmol) was added to a round bottom flask, under an inert atmosphere. NHC precursor (3.3 mol %, 0.015 mmol), arylboronic acid or derivative (2 equiv, 0.98 mmol), KO^{t}Bu (1 equiv, 0.49 mmol) and solvent (2 ml) were added sequentially. Finally, ethyl glyoxalate (50% in toluene, 0.49 mmol, 100 μl) was added and the reaction was stirred at the desired temperature, and monitored by TLC. The crude mixture was passed through a porous ceramic glass filter and eluted with CH_2Cl_2. The solvents were concentrated under reduced pressure and the residue purified by liquid chromatography (SiO_2 gel, Hexane/AcOEt (5/1)), yielding the desire α-hydroxyester product.

4.3.2. Ethyl mandelate.[7] Obtained in >99% isolated yield, at room temperature in 30 min. Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (t, 3H, CH_3), 3.56 (br s, 1H, OH), 4.17–4.26 (m, 2H, CH_2), 5.16 (s, 1H, CH), 7.34–7.42 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.14, 62.33, 73.01, 126.63, 128.49, 128.66, 138.53, 173.76.

*4.3.3. Ethyl 2-hydroxy-2-(naphthalen-2-yl)acetate (**9a**).* Isolated yield (36%). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (t, 3H, CH_3), 3.71 (br s, 1H, OH), 4.15–4.21 (m, 1H, CH_2), 4.24–4.30 (m, 1H, CH_2), 5.33 (s, 1H, CH), 7.47–7.54 (m, 3H, Ar), 7.83–7.85 (m, 3H, Ar), 7.91 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.45, 62.40, 73.08, 124.17, 125.90, 126.06, 126.33, 127.91, 128.34, 128.62, 133.28, 133.38, 135.89. ESI-TOF MS (*m*/*z*): 213.10 (−OH), 231.10 (M^{+1}).

*4.3.4. Ethyl 2-(4-fluorophenyl)-2-hydroxyacetate (**9b**).*[7] Isolated yield (>99%). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (t, 3H, CH_3), 3.88 (br s, 1H, OH), 4.12–4.18 (m, 1H, CH_2), 4.20–4.24 (m, 1H, CH_2), 5.11 (s, 1H, CH), 6.99–7.03 (m, 2H, Ar), 7.36–7.40 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.15, 62.36, 71.47, 115.49, 115.61, 128.24, 134.37, 161.42, 164.06, 173.67. ESI-TOF MS (*m*/*z*): 181.07 (−OH), 199.08 (M^{+1}).

*4.3.5. Ethyl 2-hydroxy-2-(2-methoxyphenyl)acetate (**9d**).*[7] Isolated yield (81%). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (t, 3H, CH_3), 3.91 (s, 3H, OCH_3), 4.19–4.26 (m, 2H, CH_2), 5.28 (s, 1H, CH), 6.89–6.96 (m, 2H, Ar), 7.01–7.05 (m, 1H, Ar), 7.42–7.47 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.31, 55.64, 61.52, 71.45, 110.01, 121.46, 129.51, 132.60, 137.17, 164.75, 174.01. ESI-TOF MS (*m*/*z*): 193.10 (−OH), 211.10 (M^{+1}).

*4.3.6. Ethyl 2-(3-(benzyloxy)phenyl)-2-hydroxyacetate (**9e**).* Isolated yield (>99%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (t, 3H, CH_3), 3.63 (br s, 1H, OH), 4.13–4.21 (m, 1H, CH_2), 4.23–4.31 (m, 1H, CH_2), 5.08 (s, 2H, CH_2), 5.15 (s, 1H, CH), 6.94–7.10 (m, 2H, Ar), 7.27–7.36 (m, 2H, Ar), 7.40–7.46 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.94, 62.43, 70.41, 72.89, 113.03, 114.92, 119.20, 127.50, 127.58, 128.01, 128.65, 129.56, 129.69, 136.91, 140.15, 159.08, 173.65. ESI-TOF MS (*m*/*z*): 269.13 (−OH), 287.13 (M^{+1}).

*4.3.7. Ethyl 2-(furan-2-yl)-2-hydroxyacetate (**9f**).* Isolated yield (71%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, 3H, CH_3), 3.78 (br s, 1H, OH), 4.20–4.28 (m, 2H, CH_2), 5.06 (s, 1H, CH), 6.33–6.36 (m, 1H, OCH), 7.31–7.42 (m, 2H, CH–CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.11, 61.86, 71.36, 108.81, 110.64, 126.62, 142.89, 170.59. ESI-TOF MS (*m*/*z*): 153.05 (−OH), 171.06 (M^{+1}).

*4.3.8. Ethyl 2-(4-chlorophenyl)-2-hydroxyacetate (**9g**).*[7] Isolated yield (34%). Light yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (t, 3H, CH_3), 3.61–3.69 (m, 1H, CH_2), 3.73–3.78 (br s, 1H, OH), 3.81–3.89 (m, 1H, CH_2), 4.93 (s, 1H, CH), 7.32–7.49 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.12, 64.06, 71.82, 116.75, 128.02, 128.36, 128.86, 129.18, 137.11, 169.66. ESI-TOF MS (*m*/*z*): 213.11.

*4.3.9. Ethyl 2-hydroxy-2-(3-methoxyphenyl)acetate (**9h**).* Isolated yield (>99%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (t, 3H, CH_3), 3.63 (br s, 1H, OH), 3.78 (S, 3H, OCH_3), 4.11–4.19 (m, 1H, CH_2), 4.20–4.28 (m, 1H, CH_2), 5.12 (s, 1H, CH), 6.83–6.85 (m, 1H, Ar), 6.96–6.98 (m, 2H, Ar), 7.23–7.27 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.96, 55.29, 62.14, 72.61, 111.85, 114.32, 118.92, 129.46, 140.23, 159.73, 173.97. ESI-TOF MS (*m*/*z*): 193.09 (−OH), 211.10 (M^{+1}).

*4.3.10. Ethyl 2-(3-acetylphenyl)-2-hydroxyacetate (**9i**).* Isolated yield (12%). Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (t, 3H, CH_3), 2.62 (s, 3H, CH_3 (Ac)), 4.19–4.41 (m, 2H, CH_2), 5.35 (s, 1H, CH), 7.32–7.51 (m, 2H, Ar), 7.91–7.97 (m, 1H, Ar), 8.04 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.03, 22.62, 62.83, 72.39, 128.41, 128.66, 129.01, 131.30, 137.55, 139.17, 173.06, 198.14. ESI-TOF MS (*m*/*z*): 223.10 (M^{+1}).

*4.3.11. Ethyl 2-hydroxy-2-(naphthalen-1-yl)acetate (**9j**).* Isolated yield (72%). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, 3H, CH_3), 4.12–4.32 (m, 2H, CH_2), 5.81 (s, 1H, CH), 7.44–7.70 (m, 4H, Ar), 7.84–7.96 (m, 1H, Ar), 8.11–8.18 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.17, 62.06, 71.33, 123.46, 123.70, 125.13, 125.68, 125.78, 126.48, 127.84, 128.80, 129.36, 134.07, 174.48. ESI-TOF MS (*m*/*z*): 233.08 (M^{+2}).

*4.3.12. Ethyl 2-(3-aminophenyl)-2-hydroxyacetate (**9k**).* Obtained in vestigial quantities. Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (t, 3H, CH_3), 2.17 (br s, 1H, OH), 3.92 (s, 2H, NH_2), 4.17–4.27 (m, 2H, CH_2), 5.67 (s, 1H, CH), 7.32–7.37 (m, 1H, Ar), 7.42–7.43 (d, 1H, Ar), 7.52–7.54 (m, 1H, Ar), 7.69–7.72 (m, 1H, Ar).

*4.3.13. Ethyl 2-hydroxypentanoate (**9l**).* Isolated yield (23%). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87–0.93 (m, 3H, CH_3), 1.30–1.33 (m, 3H, CH_3), 1.32–1.35 (m, 2H, CH_2), 1.37–1.41 (m, 2H, CH_2), 2.07 (s, 1H, OH), 4.23–4.32 (m, 2H, CH_2), 5.32–5.34 (m, 1H, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.09, 14.27, 22.79, 36.42, 62.70, 73.11, 169.23. ESI-TOF MS (*m*/*z*): 146.07 (M^+).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.05.129.

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Advances in the Catalytic Asymmetric Arylation of Imines using Organoboron Reagents: An Approach to Chiral Arylamines

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The production of chiral amines by means of catalytic asymmetric synthesis is a current challenge in the field of drug discovery and is discussed in this review. The use of cheap, easily handled, and low toxic organoboron reagents, such as boronic acids and derivatives, and easily prepared imine substrates, such as diphenylphosphinoyl, *N*-Boc, *N*-tosylaryl, *N*-nosylaryl, or dimethylsulfamoyl imines, together with rhodium and palladium catalysts give the corresponding chiral amine products in excellent yields and enantioselectivities. A diverse range of chiral ligands, such as phosphines, phosphites, phosphoramidites, *P,O*-ligands, olefins, NHCs, and *N,N*-ligands can be used with this method, showing, therefore, its versatility. The application of aliphatic imine substrates and with the use of different palladium complexes show, on the other hand, the versatility of the method described.

Introduction

The constant quest for useful pharmaceutical compounds continues to interest practitioners from both academic and industrial quarters. Molecules with an arylmethylamine group have great potential as pharmaceutically active ingredients (or their intermediates) (Figure 1), many of which exhibit antihistaminic, antiarrhythmic, diuretic, antidepression, and laxative properties, etc. For example, included in this category is the high profile drug Cetirizine,[1a] which is an antihistaminic approved drug to treat allergic symptoms, Sertraline, the anti-depression drug,[1b] and a host of other biologically active compounds (Figure 1). Several synthetic procedures exist for the synthesis of chiral arylmethylamines, ranging from stereospecific nucleophilic displacement at the benzylic position of appropriately substituted benzylic compounds,[2] to asymmetric reduction of imine C=N bonds with appropriate organometallic reagents.[3] There have already been some recent reviews on this subject, which have focused mainly on 1,4-additions,[4] including one recent monograph.[2]

In this review we focus our attention on catalytic asymmetric imine arylation with organoboron reagents and Rh and Pd catalysts, the only two metals that have been used successfully to date in this reaction (Scheme 1).

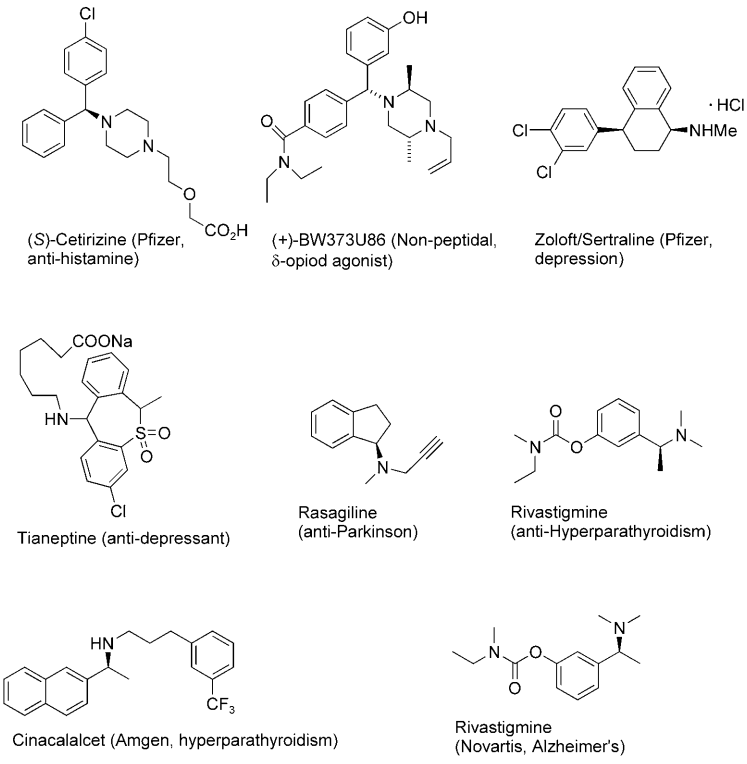
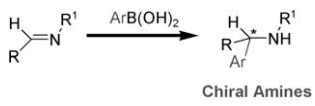


Figure 1. Important chiral arylamine pharmaceutical drugs.



Scheme 1. Chiral amine synthesis: Addition of organoboronic acids and other organoboranes (not shown) to activated imines.

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Over the past 20 years, the stereoselective introduction of carbon–carbon single bonds has been a challenge for chemists working in the field of asymmetric synthesis. In fact, the enantioselective introduction of aryl groups into the C=N function leading to chiral non-racemic amine products has been one major synthetic breakthrough. This approach is highly desirable from the atom economical viewpoint, as it is an addition process and thus represents a sustainable approach to the synthesis of these compounds. Arylating reagents containing zinc,[5] tin,[6] and titanium[7] have been previously successfully applied in this reaction. However, owing to the cost of the metals, their difficulty to work with, and their toxicity, arylboron reagents are a very welcome alternative. Arylboronic acid reagents, which have many applications in other synthetic processes, such as the Suzuki–Miyaura reaction,[8] have proven to be very efficient reagents for the arylation of imine substrates and have made their mark as one of the choice reagents for this purpose. Moreover, a large number of arylboronic acids are already available commercially. Some of their advantageous characteristics include, stability to air/moisture, easy preparation, low toxicity, and wide functional group diversity.

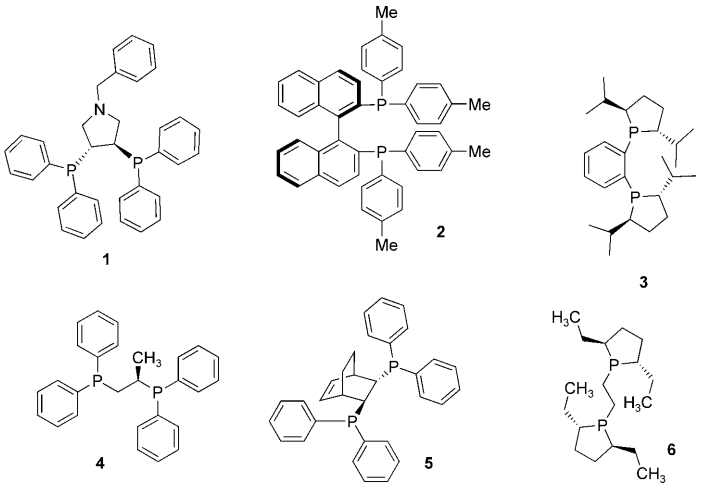


Figure 2. Chiral diphosphine ligands screened by Ellman's group,[9a] (*R,R*)-DeguPHOS (**1**), (*R*)-*tol*-BINAP (**2**), (*R,R*)-*i*-Pr-DUPHOS (**3**), (*R*)-PROPHOS (**4**), (*S,S*)-NORPHOS (**5**), and (*R,R*)-Et-BPE (**6**).

Rhodium Catalysts

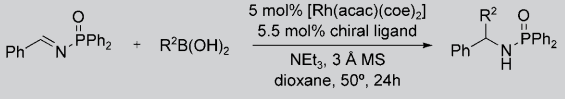
Chiral phosphines

Ellman's group[9a] reported the highly enantioselective addition of arylboronic acids to diphenylphosphinoyl imines, using [Rh(acac)(coe)$_2$] (acac = acetylacetonate; coe = cyclooctene) and several commercial chiral diphosphine ligands (Table 1 and Figure 2). The diphenylphosphinoyl group is a very desirable imine activating group because it is easily cleaved from the amine product. They found that by using powdered MS 3 Å and one equivalent of NEt_3 it produced yields that were quite good. On screening a wide variety of chiral diphosphines (Figure 2), it was revealed that diphosphines with a rigid backbone give higher conversions (Table 1, entries 1, 3, 7–10).

The disphosphine (*R,R*)-DeguPHOS (**1**, Figure 2) provided the best results in terms of yield and enantioselectivity (Table 1, entry 7). On applying both electron rich and electron poor arylboronic acids, good yields and enantioselectivities of chiral amines were produced (Table 1, entries 8–10).

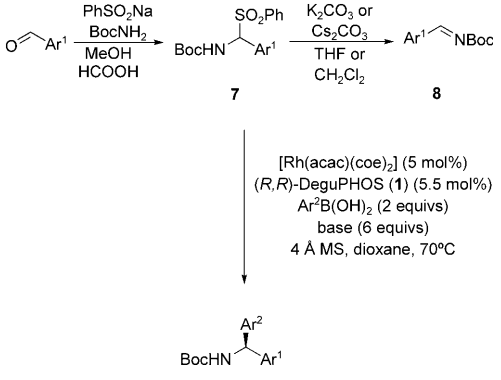
To improve the efficacy of this method, and particularly to facilitate the isolation of the final amine product, Ellman's group[9b] focused their attention on the identification of alternative imine activating groups. They studied *N*-Boc imines (**8**) (Scheme 2), by using arylboronic acids. To our knowledge this is the first example of the use of this kind of substrate for this reaction. Using a previously known procedure from the literature,[9b] they synthesized a library of *N*-Boc imines under mild conditions and in good yields via α-carbamoyl sulfone intermediates (**7**) (Scheme 2). The first step was to study the reaction conditions and screen several organic and inorganic

Table 1. Catalytic enantioselective arylation reaction of diphenylphosphinoyl imines with arylboronic acids.[9a]



Entry	R^2	Chiral Ligand	Yield[a] [%]	*ee* [%]
1[b]	4-ClC_6H_4	**2**	89	32 (*R*)
2	4-ClC_6H_4	**4**	35	65 (*R*)
3[b]	4-ClC_6H_4	**3**	86	60 (*R*)
4	4-ClC_6H_4	**5**	37	75 (*S*)
5	4-ClC_6H_4	**6**	45	90 (*S*)
6	4-ClC_6H_4	**1**	46	96 (*R*)
7[b]	4-ClC_6H_4	**1**	97	94 (*R*)
8[b,c]	3-AcC_6H_4	**1**	93	88 (*R*)
9[b,c]	4-$CF_3C_6H_4$	**1**	87	88 (*R*)
10[b,c]	4-MeOC_6H_4	**1**	93	93 (*R*)

[a] Isolated yields after chromatography. [b] Reaction run at 70 °C. [c] Reaction run with 3 equiv of boronic acid reagent added over 20 h.



Scheme 2. In situ generation of *N*-Boc imines (**7**) substrates for enantioselective arylboronic acid arylation, using (*R,R*)-DeguPHOS (**1**) as the chiral ligand.[9b]

bases. By using (*R,R*)-DeguPHOS (**1**) (Figure 2), which has already been used in this catalytic reaction with success,[9a] with K_2CO_3 or NEt_3 as additives, a best yield of 76% and a highest enantioselectivity of 98% *ee* were produced (Table 2, entry 1). The reaction was not complete; this was attributed to competitive substrate hydrolysis and/or catalyst decomposition.

Table 2. Enantioselective addition of arylboronic acids to *N*-Boc imines generated in situ (Scheme 2).[9b]

Entry[a]	Ar^1	Ar^2	Yield[b] [%]	*ee*[c] [%]
1	Ph	4-ClC_6H_4	76	98
2	Ph	4-MeC_6H_4	70	96
3	Ph	4-$MeOC_6H_4$	76	93
4	Ph	4-$CF_3C_6H_4$	51	95
5	Ph	3-ClC_6H_4	55	99
6	Ph	3-MeC_6H_4	66	95
7	Ph	3-AcC_6H_4	52	94
8	Ph	2-MeC_6H_4	62	93
9	4-MeC_6H_4	Ph	71	90
10	3-MeC_6H_4	Ph	70	95
11	2-MeC_6H_4	Ph	63	97
12	4-BrC_6H_4	Ph	59	90
13	2-Thienyl	Ph	71	96
14	4-$MeOC_6H_4$	Ph	76	96
15	4-$CF_3C_6H_4$	Ph	69	79

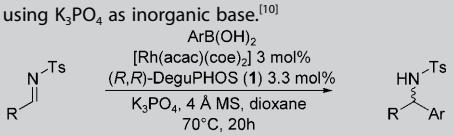
[a] Reaction conditions: 5 mol% [Rh(acac)(coe)$_2$]; 5.5 mol% (*R,R*)-DeguPHOS (**1**); 2 equivs $Ar_2B(OH)_2$; 6 equivs K_2CO_3; 1.5 equivs NEt_3; 4 Å MS, dioxane, 70 °C. [b] Isolated yields after chromatography. [c] Determined by chiral stationary phase HPLC.

Electron-rich arylboronic acids provided the desired product in good yields and excellent enantioselectivities (Table 2, entries 2, 3), however, electron-poor substituents in the aromatic ring also gave excellent enantioselectivities, but their yields were lower (Table 2, entries 4, 7). Significant steric hindrance is also tolerated (Table 2, entries 8, 11) including the presence of heterocyclic aromatic groups (Table 2, entry 13).

Trincado and Ellman have recently used similar conditions with aliphatic imines (Table 3).[10] These optimized conditions included the use of dioxane as solvent, NEt_3 as base and molecular sieves. [Rh(acac)(coe)$_2$] was used as precatalyst and (*R,R*)-DeguPHOS (**1**) as the chiral ligand. Prior studies with a 1.4:1 ligand/Rh ratio proved to give the best enantioselectivities (90%) and it was found that, pre-incubating the ligand, the precatalyst and the boronic acid for about 90 min prior to initiating the reaction showed improved results. On the basis of a report by Sakuma and Miyaura using inorganic bases as accelerators in the addition of arylboronic acids to α,β-unsaturated amides,[11] Trincado and Ellman studied K_3PO_4 as the base and found that 20 mol% of K_3PO_4 had a pronounced effect on increasing the yield, while the enantioselectivities remained high.[10] The results obtained with several aliphatic *N*-tosylimines are shown in Table 3.

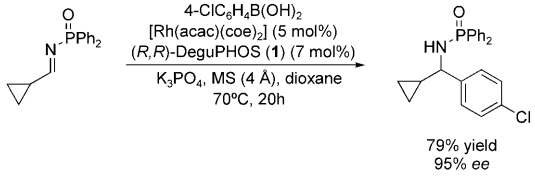
There was no significant difference in the enantioselectivities for the branched (Table 3, entries 5–9) or the non-branched *N*-tosylimines (Table 3, entry 3). The good results obtained in the reaction using acetyloxy-substituted arylboronic acids (Table 3, entries 10, 12) is proof of the excellent functional group compatibility of this process. β-Branched imines (Table 3, entry 3) and α-branched imines (Table 3, entries 5–11) showed good yields and high enantioselectivities. It was also possible to produce good yields and enantioselectivities by applying the same conditions using aliphatic *N*-diphenylphosphoryl (*N*-dpp) substituted imines (Scheme 3).

Table 3. Asymmetric arylation of activated aliphatic imines with arylboronic acids using K_3PO_4 as inorganic base.[10]



Entry	R	Ar	Yield[a] [%]	*ee*[b] [%]
1	$PhCH_2CH_2$	4-ClC_6H_4	94	95
2	$CH_3CH_2CH_2$	4-ClC_6H_4	89	93
3	$(CH_3)_2CHCH_2$	4-ClC_6H_4	96	91
4	$CH_2=CHCH_2CH_2$	4-ClC_6H_4	87	98
5	cyclohexyl	4-ClC_6H_4	80	96
6	cyclohehyl	4-MeC_6H_4	71	96
7	cyclohexyl	4-$MeOC_6H_4$	74	90
8	cyclohexyl	4-$CF_3C_6H_4$	89	91
9	cyclohexyl	3-ClC_6H_4	75	90
10	cyclohexyl	3-AcC_6H_4	81	89
11	cyclohexyl	3-ClC_6H_4	74	93
12	$PhCH_2CH_2$	3-AcC_6H_4	80	90

[a] Yield of isolated product. [b] Determined by chiral stationary phase HPLC.



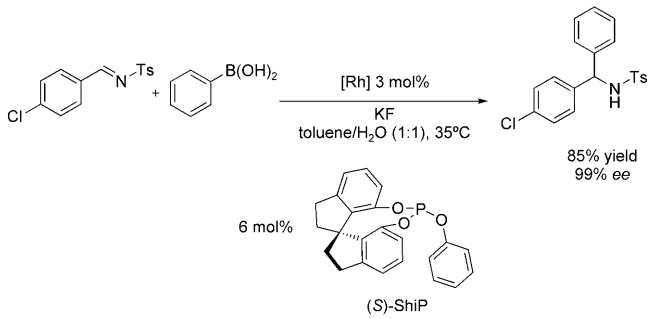
Scheme 3. Asymmetric arylation of an *N*-dpp activated imine with a boronic acid derivative.[10]

Chiral phosphites

As far as we are aware, there has been only one report on the use of chiral phosphite ligands in the catalytic asymmetric arylation of imines with boronic acids.

As the development of an efficient and general method for the synthesis of optically active diarylmethylamines remains a distinct challenge, Zhou and coworkers performed the enantioselective arylation of *N*-tosylimines with arylboronic acids in aqueous media. A novel spiro monophosphite based ligand known as (*S*)-ShiP (Scheme 4) was used.[12] Some good results were achieved after optimizing the reaction with the rhodium precatalyst [Rh(acac)(C_2H_4)$_2$] and with KF as base (Scheme 4).

A study using other chiral ligands (like a spiro monodentate phosphine, a phosphoramidite, and a phosphonite) gave poorer results than for (*S*)-ShiP. Both (*R*)-MeO-MOP and (*S*)-BINAP (Figure 3), which were also screened, were found to be less efficient for this reaction, both in terms of reactivity and



Scheme 4. Rh-Catalyzed arylation of 4-chlorophenyltosylimine with phenylboronic acid.[12]

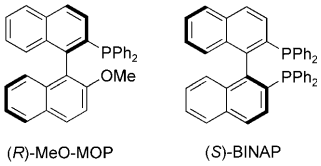


Figure 3. Some of binaphthol-based ligands used by Zhou and coworkers.[12]

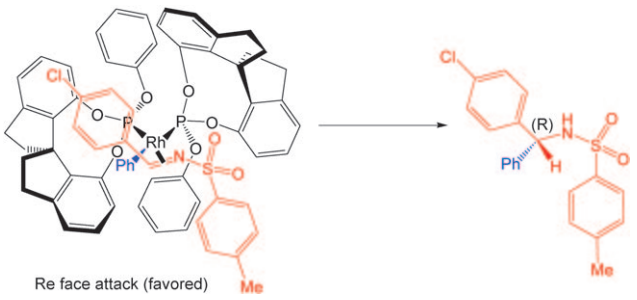
enantioselectivity. The authors proposed, on the basis of an analysis of the crystal structure of $[Rh((S)\text{-ShiP})_2(COD)]^+$ (COD = cyclooctadiene), that the Rh catalyst formed from (*S*)-ShiP should have a large dihedral angle in the back-bone, which is crucial for efficient control of enantioselectivity in this reaction.

Some very good results were produced by using 3 mol% of $[Rh(acac)(C_2H_4)_2/(S)\text{-ShiP}]$ and applying the optimized protocol (Scheme 4) with a variety of aromatic imines (Table 4). A stereorecognition model was proposed by the authors based on the crystal structure of the catalyst $[Rh((S)\text{-ShiP})_2(COD)]^+$ (Scheme 5). These workers proposed that there was favorable coordination by the imine substrate to the metal center, on

Table 4. Asymmetric arylation of imines using (*S*)-ShiP and Rh^I catalysts by Zhou and coworkers.[12]

Entry	$Ar^1CH{=}NTs$ (Ar^1)	$Ar^2B(OH)_2$ (Ar^2)	Yield[a] [%]	*ee*[b] [%]
1	4-ClC_6H_4	Ph	85	93 (*R*)
2	4-FC_6H_4	Ph	80	93 (*R*)
3	4-BrC_6H_4	Ph	82	93 (*R*)
4	4-MeC_6H_4	Ph	77	94 (*R*)
5	4-$MeOC_6H_4$	Ph	65	93 (*R*)
6	3-$MeOC_6H_4$	Ph	72	96 (*R*)
7	2-ClC_6H_4	Ph	79	95 (*R*)
8	2-BrC_6H_4	Ph	76	93 (*R*)
9	2-MeC_6H_4	Ph	73	95 (*R*)
10	2-$MeOC_6H_4$	Ph	67	92 (*R*)
11	Naph	Ph	76	96 (*R*)
12	2-Fur	Ph	84	85 (*R*)
13	Ph	4-FC_6H_4	56	94 (*S*)
14	Ph	4-MeC_6H_4	75	92 (*S*)
15	Ph	4-$MeOC_6H_4$	70	95 (*S*)
16	Ph	3-$MeOC_6H_4$	68	91 (*S*)
17	Ph	2-MeC_6H_4	65	93 (*S*)

[a] Isolated yield. [b] Determined by chiral stationary phase HPLC. (Fur = Furanyl).



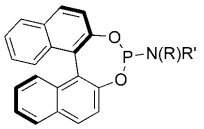
Scheme 5. Stereorecognition model proposed by Zhou and coworkers for the Rh catalyzed arylation of imines with an (*S*)-ShiP based catalyst (adapted from ref. [12]).

the *Re* face. In contrast, the repulsion between the *p*-chlorophenyl, the tosyl group, and the backbone of the ligand make coordination through the *Si* face unfavorable.

Chiral phosphoramidites

From a synthetic point of view, the methodologies presented till now seem to have some inherent drawbacks or limitations. The group of Minnard investigated a more efficient and versatile synthetic method for this transformation, which uses a new type of catalyst.[13a]

Chiral monodentate phosphoramidites (**9**) (Figure 4) were used, owing to their low cost and commercial availability. This class of ligands have already been applied with success in the rhodium-catalyzed conjugate addition of arylboronic acids to enones.[13b] The important issues addressed in this study were: i) The dioxane solvent (a toxic solvent commonly used in this reaction) was substituted by acetone and ii) the chiral phosphoramidite ligand (**9b**) was used (Figure 4), which affords a catalyst that is compatible with a wide range of functional groups (Table 5). Dimethylsulfamoyl aldimines were used as the substrates as they are easy to prepare[14] in similar yields to those of the tosylimine substrates already referred to. Additionally the dimethylsulfamoyl protecting/activating groups were easier to remove than the tosyl groups.

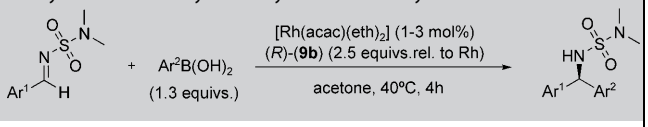


9a: R,R'= Me
9b: R= H, R'= 4-$OMeC_6H_4$

Figure 4. Chiral monodentate phosphoramidites used by Minnard.[13a]

Initial studies conducted on the *p*-chlorobenzaldimine with the phosphoramidite ligand (*R*)-(**9a**) (Figure 4) provided promising results (a yield of 94% and an enantioselectivity of 82% *ee*). Upon changing to ligand (*R*)-(**9b**) (Figure 4), the desired product could be produced in 95% yield in only 4 h (Table 5, entry 1) with an excellent enantioselectivity of 95% *ee*. The study was extended to a range of substrates bearing electron-withdrawing groups, such as: chloro, fluoro, and trifluoromethyl *para*-substituents (Table 5, entries 1–3), that provided high yields and enantioselectivities, using the phosphoramidite ligand (*R*)-(**9b**) (Figure 4). The authors concluded that (*R*)-(**9b**) was the most efficient ligand for a diverse range of functional

Table 5. Enantioselective rhodium/phosphoramidite-catalyzed asymmetric arylation of dimethylsulfamoyl imines with arylboronic acids.[13a]

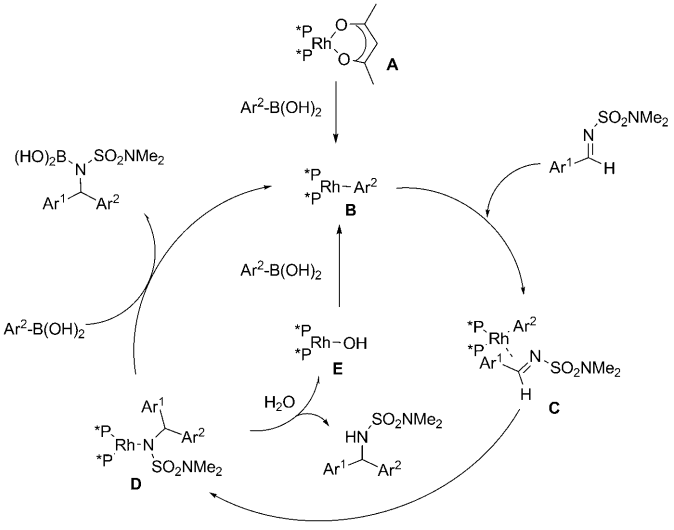


Entry[a]	Ar^1	Ar^2	Yield[b] [%]	*ee*[c] [%]
1	4-ClC_6H_4	Ph	95	95 (*R*)
2	4-FC_6H_4	Ph	81	93 (*R*)
3	4-$CF_3C_6H_4$	Ph	98	94 (*R*)
4	4-$MeOC_6H_4$	Ph	72	90 (*R*)
5	4-MeC_6H_4	Ph	77	92 (*R*)
6	Ph	4-$MeOC_6H_4$	97	92 (*S*)
7	Ph	4-MeC_6H_4	81	94 (*S*)
8	2-MeC_6H_4	Ph	91	87 (*R*)
9	3-FC_6H_4	Ph	81	93 (*R*)
10	2-Thienyl	Ph	81	91 (*R*)

[a] Reactions were performed on a 0.2 mmol scale in the presence of the catalyst generated from 3 mol% $[Rh(acac)(eth)_2]$ and 7.5 mol% monodentate phosphoramidite (*R*)-(**9b**). [b] Yield of isolated product after chromatography. [c] Determined by chiral stationary phase HPLC.

groups. The alternative arylation on unsubstituted benzaldimine using *p*-methoxy and methylphenylboronic acids (Table 5, entries 6, 7, respectively) also proceeded with high yields and enantioselectivities. It was also shown that this methodology is not limited to aldimines made from benzaldehyde derivatives, as it could be performed successfully on a (2-thienyl)carboxaldimine substrate (Table 5, entry 10).[13a]

The proposed mechanism, shown in Scheme 6, suggested that the reaction proceeds by sulfonamido activation of the boron via intermediate **D** rather than by hydrolysis of the sulfonamido group by water to form the intermediate **E**. Deprotection of the *N,N*-dimethylsulfamoyl group by using microwave-assisted heating was performed in good yield, providing the amine chiral product with retention of configuration.



Scheme 6. Proposed mechanism by Minnard and coworkers:[13a] Catalyst precursor (**A**), rhodium aryl complex (**B**), catalyst substrate species (**C**), catalyst product species (**D**), and rhodium hydroxyl complex (**E**).

Marelli et al. conducted some interesting work on the synthesis and application of chiral tropos and atropos phosphorus ligands. These ligands were based on a flexible biphenol or binaphthol unit and a chiral *P*-bound alcohol (phosphites) or secondary amine (phosphoramidites) (Figure 5).[15] A small ligand

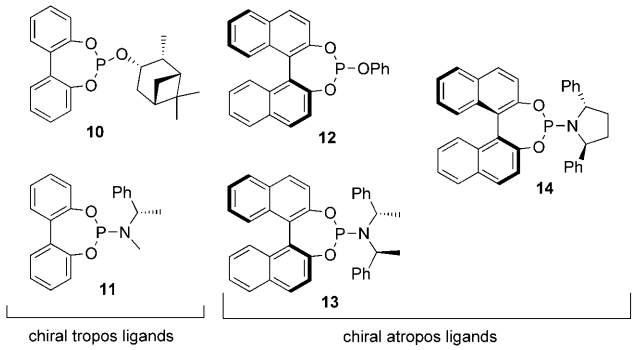
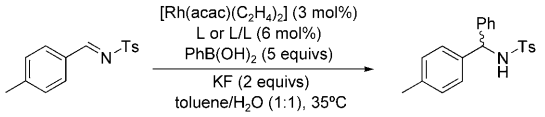


Figure 5. Library of chiral biphenolic phosphite and phosphoramidite [(**10**) and (**11**), tropos)] ligands and binaphtolic phosphite and phosphoramidite [(**12**)–(**14**), atropos] ligands.[15]

library was tested with rhodium as the precatalyst and phenylboronic acid in a binary mixture of toluene and water (Scheme 7). The monodentate ligands were individually applied or as binary mixtures (1:1). Of the ligands tested, the phosphoramidites (**13**) and (**14**) (Figure 5) provided (individually) the best enantioselectivities (90 and 93%, respectively), despite their yields being quite poor to moderate (25 and 45%, respectively). Marelli et al. concluded that the use of a binary mixture of ligands in this kind of catalysis was not useful from a synthetic point-of-view because the enantioselectivities were too low (20–50% *ee*) and they postulated that both ligands are present in the rhodium complex during the enantiodiscriminating step of the reaction.[15]

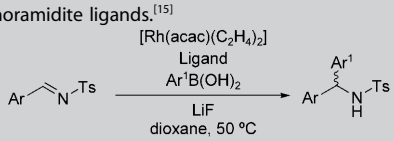


Scheme 7. Screening of tropos and atropos derived Rh catalysts in the catalytic asymmetric *N*-tosylimine arylation reaction.[15]

After conducting some initial screening studies with ligands (**13**) and (**14**) (Figure 5), the optimized conditions were found with a variety of different imine substrates and boronic acids (Table 6). Despite the fact that the catalytic efficiency was only moderate in most cases, an overall review of the results showed that good to excellent enantioselectivities with both electron-withdrawing and electron-donating groups in the phenyl ring of the imine could be obtained. Electron-rich substrates or electron-rich arylboronic acids generally gave higher yields (Table 6, entries 1, 2, 7, 8 and entries 5, 6, 11, 12).

Kurihara et al. prepared the new *N*-linked phosphoramidite *N*-Me-BIPAM (**16**), by reacting the bisBinol substrate (**15**) with

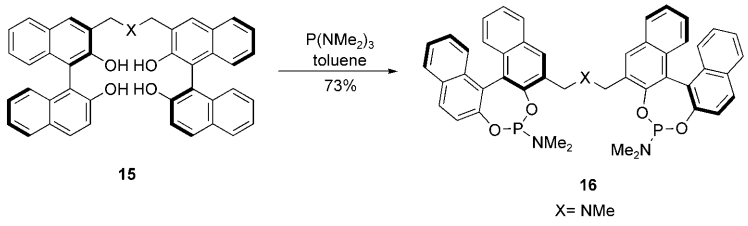
Table 6. Asymmetric arylation of *N*-tosylarylaldimines using chiral binaphtholic phosphoramidite ligands.[15]



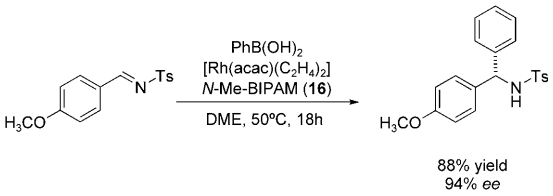
Entry	Ar	Ar^1	Ligand	Yield[a] [%]	*ee*[b] [%]
1	2-MeC_6H_4	Ph	**13**	54	78 (*S*)
2	4-$MeOC_6H_4$	Ph	**13**	40	89 (*S*)
3	1-Naph	Ph	**13**	40	99 (*S*)
4	4-BrC_6H_4	Ph	**13**	16	89 (*S*)
5	Ph	4-MeC_6H_4	**13**	88	87 (*R*)
6	Ph	4-$MeOC_6H_4$	**13**	60	68 (*R*)
7	2-MeC_6H_4	Ph	**14**	42	71 (*S*)
8	4-$MeOC_6H_4$	Ph	**14**	70	81 (*S*)
9	1-Naph	Ph	**14**	32	51 (*S*)
10	4-BrC_6H_4	Ph	**14**	30	87 (*S*)
11	Ph	4-MeC_6H_4	**14**	80	87 (*R*)
12	Ph	4-$MeOC_6H_4$	**14**	85	76 (*R*)

[a] Calculated by ^{1}H NMR analysis of the crude reaction mixture. [b] Both the *ee* values and the absolute configurations were determined by chiral stationary phase HPLC.

$P(NMe_2)_3$ (Scheme 8).[16] On screening the bulky ligand (**16**) in the rhodium(I) catalyzed phenylation of *p*-methoxybenzaldehyde *N*-tosylimine phenylboronic acid, high efficiency and selectivity were revealed (88% yield and 94% *ee*) with [Rh(acac)-$(C_2H_4)_2$] in dimethoxyethane (DME) (Scheme 9).



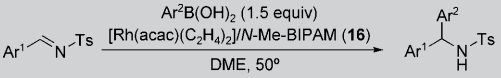
Scheme 8. Synthesis of *N*-Me-BIPAM (**16**) by Kurihara et al.[16]



Scheme 9. Arylation of *p*-metoxybenzaldehyde *N*-tosylimine with phenylboronic acid, $[Rh(acac)(C_2H_4)_2]$ and chiral phosphoramidite ligand (**16**).[16]

In the absence of base, the reaction runs smoothly using only 3 mol% of the catalyst. With these encouraging results, Miyaura's group screened several aryl substituted substrates and boronic acids. Some of the results collected are summarized in Table 7.[16] The overall yield and enantioselectivity was very good, showing no relative difference between electron-donating and electron-withdrawing groups in the aryl rings of the reagents.

Table 7. Arylation of *N*-tosylimines by Kurihara et al.[16]



Entry[a]	Ar^1	Ar^2	Yield [%]	*ee* [%]
1	Ph	4-MeC_6H_4	96	84 (*R*)
2	4-MeC_6H_4	4-$MeOC_6H_4$	92	96 (*R*)
3	4-ClC_6H_4	Ph	98	95 (*S*)
4	3-Br-4-$MeOC_6H_3$	Ph	98	92
5	2-ClC_6H_4	4-$MeOC_6H_4$	99	96 (*S*)
6	2,4-$Cl_2C_6H_3$	Ph	95	85
7	2-Furyl	Ph	89	75 (*S*)
8	2-Benzofuryl	Ph	95	94

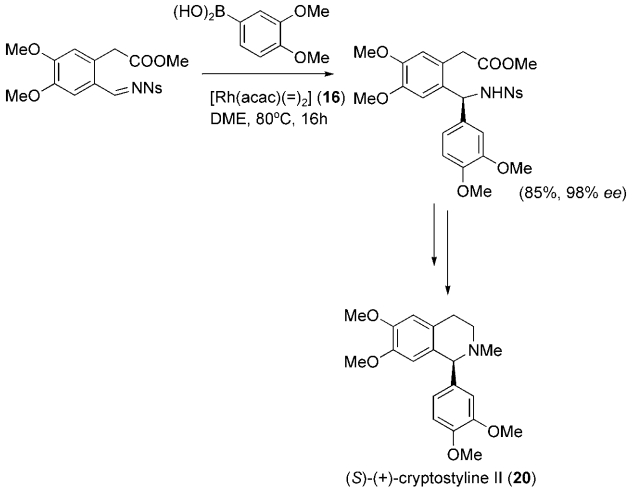
[a] Reaction conditions: 0.5 mmol substrate, 0.75 mmol $Ar^2B(OH)_2$, 3 mol% Rh catalyst and 3.3 mol% *N*-Me-BIPAM (**16**) in DME.

Not all the absolute configurations of the amine products were given (see Table 7). The use of *N*-nosylimines, an interesting group to apply in this kind of catalysis, owing to the mild conditions for deprotection under the same conditions as previously described, gave high enantioselectivities (96–98% *ee*). A broad range of enantiopure diarylmethylamines were easily prepared by using a slight excess of arylboronic acid and a chiral bidentate phosphoramidite ligand, *N*-Me-BIPAM (**16**).

Much more noteworthy was the application of this methodology by this group for the asymmetric synthesis of the neuropharmacological compound (*S*)-(+)-cryptostyline II (Scheme 10), thus showing the great potential of this methodology for the synthesis of important biologically active chiral amine targets.[16]

Chiral *P,O* ligands

In 2004, Tomioka and coworkers investigated hemilabile chiral *P,O*-ligands (**17**) and (**18**) (Figure 6) for the asymmetric arylation of *N*-tosylarylaldimines with or-



Scheme 10. Application of the catalytic asymmetric arylation of an imine in the total synthesis of (*S*)-(+)-cryptostyline II (**20**) by Miyaura's group.[16]

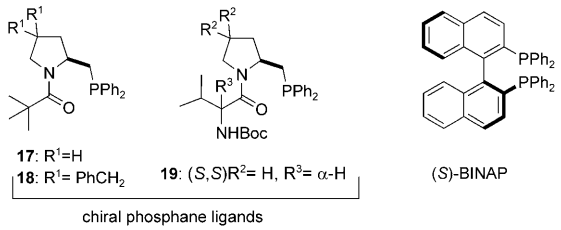
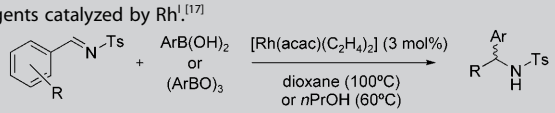


Figure 6. Chiral *P,O*-ligands (**17**)–(**19**) and (*S*)-BINAP screened by Tomioka and coworkers.[17]

ganoboron reagents.[17] Unfortunately, both of the ligands were ineffective for this kind of reaction, providing almost racemic products (Table 8, entries 1 and 2). (*S*)-BINAP (Figure 6) (used only for comparison) also gave only a moderate enantioselectivity of 34% *ee*. The ligand (**19**) was produced by making appropriate structural changes in the architecture of the former ligands by replacing the pivaloyl group by a commercially available α-aminoacid, which gave a ligand with an additional stereogenic centre. Good to excellent yields (72–99%, Table 8, entries 4–8) and moderate to good enantioselectivities (52–80% *ee*, Table 8, entry 4–8) were produced. A study directed at tuning the structure of the imine to improve the stereoselectivity was also conducted. As can be seen in Table 8 (entries 5 and 6), the enantioselectivity was found to be influenced significantly by the position of the substituents in the phenyl ring. Imines with 2 and 3-methyl substituents gave better enantioselectivities than those with 4-methyl substituents. With a trimethylsilyl (TMS) group in the 2-position (Table 8, entry 7) the enantioselectivity could be improved to 80% *ee*. On switching to phenylboroxine as the source of boron, the yield increased to 95% despite the enantioselectivity remaining constant (Table 8, entry 8). This was probably due to a reduction in the hydrolysis of the imine substrate to the aldehyde precursor.

Table 8. Asymmetric arylation of *N*-tosylarylaldimines with boron reagents catalyzed by Rh[I].[17]



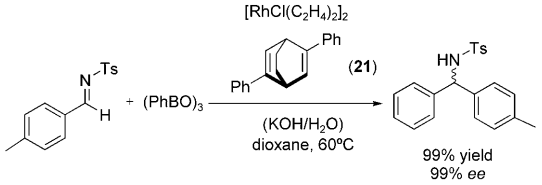
Entry	Imine (R)	Boron	L[a]	Solvent	Yield [%]	*ee*[b] [%]
1	4-Me	$PhB(OH)_2$	**17**	dioxane	80	2
2	4-Me	$PhB(OH)_2$	**18**	dioxane	20	6
3	4-Me	$PhB(OH)_2$	**20**	dioxane	88	34
4	4-Me	$PhB(OH)_2$	**19**	dioxane	95	52
5	3-Me	$PhB(OH)_2$	**19**	dioxane	99	56
6	2-Me	$PhB(OH)_2$	**19**	dioxane	99	74
7	2-TMS	$PhB(OH)_2$	**19**	*n*-PrOH	72	80
8	2-TMS	$(PhBO)_3$	**19**	*n*-PrOH	95	80
9	2-TMS	$(3\text{-MeOPhBO})_3$	**19**	*n*-PrOH	87	90
10	2-TMS	$(3\text{-ClPhBO})_3$	**19**	*n*-PrOH	99	94

[a] Ligand (3.3 mol%). [b] Determined by chiral stationary phase HPLC.

Tomioka and coworkers conducted further studies with electron-donating groups in the phenyl ring of the boron reagent and the results were quite encouraging.[17] The best result was produced by using ligand (**19**) (Figure 6), and 3-chloroboroxine (Table 8, entry 10), to give the *N*-tosylamine in 99% yield and 94% *ee*. If the 2-TMSPh derived tosylimine was used with the boroxines $(3\text{-MeOC}_6H_4BO)_3$ and $(3\text{-ClC}_6H_4BO)_3$ respectively, the enantioselectivities could be increased to 90 and 94% *ee* (Table 8, entries 9, 10).

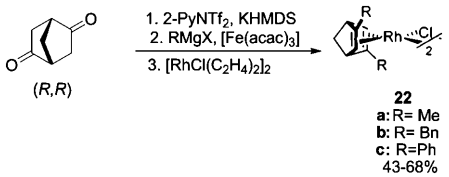
Chiral Olefins

Hayashi's group reported the use of a C_2-symmetric bicyclo-[2.2.2]octadiene (Scheme 11, **21**) chiral ligand in the rhodium catalyzed asymmetric arylation of *N*-tosylarylaldimines.[18] High enantioselectivities were achieved using this type of ligand. On using *p*-methyltosylaldimine and phenylboroxine (Scheme 11) it was possible to obtain the amine product in a yield of 99% and an enantioselectivity of 99% *ee*. Arylation of the aromatic imines, which contained triflouromethyl, methoxyl, and dimethylamino at the *para*-position of the phenyl ring, gave the corresponding amines in high yields and enantioselectivities of over 95% *ee*.



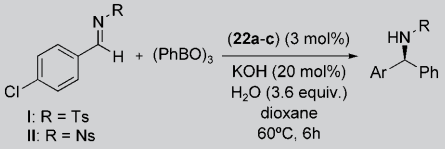
Scheme 11. Rhodium catalyzed asymmetric arylation using ligand (**21**) and (*R,R*)-Ph-bod* reported by Hayashi's group.[18]

Hayashi and Berthon–Gelloz synthesized and fully characterized two new rhodium complexes bearing chiral methyl and phenyl 2,5-disubstituted bicyclo[2.2.1]heptadiene ligands. These were produced from easily accessible chiral bicyclo-[2.2.2]hepta-2,5-dienes (Scheme 12, (**22a**–**c**)).[19] The catalytic activity of these new complexes for the arylation of *N*-tosyl and *N*-nosyl aldimines was investigated (Table 9). The results for both the methyl- (**22a**) and benzyl-substituted (**22b**) ligands (Table 9, entries 1 versus 2 and 4 versus 5) were quite similar for both imine substrates. The best result in terms of yield and enantioselectivity was produced by using the phenyl ligand (**22c**) for both imine substrates (Table 9, entries 3, 6). Hayashi and Berthon–Gelloz have revealed that chiral dienes show better selectivity and catalytic activity, compared to



Scheme 12. New C_2-symmetric byciclo[2.2.1]hepta-2,5-dienes (**22a–c**) developed by Hayashi and Berthon-Gelloz.[19]

Table 9. Asymmetric catalytic arylation of *N*-tosylarylaldimines catalyzed by catalyst (**22a–c**).[19]

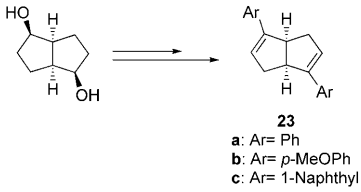


Entry[a]	Imine	Catalyst	Yield[b] [%]	*ee*[c] [%]
1	**I**	**22a**	96	89
2	**I**	**22b**	98	92
3	**I**	**22c**	96	99
4	**II**	**22a**	93	82
5	**II**	**22b**	88	81
6	**II**	**22c**	92	98

[a] Reaction conditions: (0.10 mmol, 1 equiv), $(PhBO)_3$ (0.12 mmol, 3.6 equiv), (**22a–c**) (3 mol% Rh) and 3.1 M aq KOH (0.02 mmol, 6.4 μL, 0.2 equiv) in 1,4-dioxane (0.4 mL) at 60 °C for 6 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC.

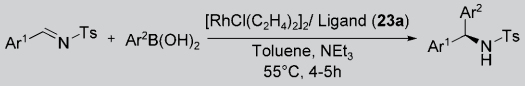
chiral phosphines in the Rh-catalyzed version of this reaction.[19]

Wang and coworkers have developed a new diene ligand (**23**) with a nonbridged bicyclic [3.3.0] skeleton produced from enantiomerically enriched octahydropentalene-1,4-diol (Scheme 13).[20] Screening studies with this ligand afforded promising results. A yield of 85% and an enantioselectivity of 98% *ee* were achieved with the ligand bearing the phenyl groups (**23a**) (Scheme 13). A range of *N*-tosylarylaldimines with diverse steric and electronic properties were tested with several arylboronic acids affording the desired products with extremely high enantioselectivities (98–99% *ee*, Table 10). Apparently there were significant advantages on changing the electronic properties of the aromatic ring in either the substrate or in the arylboronic acid, including the use of other aromatic rings, such as furanyl, thiophenyl, or naphthyl in the substrate (Table 10, entries 8, 14–16, 20). After establishing that the chiral diene ligand (**23a**) could be used as an efficient ligand in this specific reaction, Wang's group extended this methodology for the synthesis of *N*-tosylphthalimidines (**24**) and also for asymmetric reactions, such as the 1,4-addition to α,β-unsaturated ketones and arylation of *N*-nosylimines. The corresponding products (Figure 7, **25** and **26**, respectively) were synthesized in promising yields and enantioselectivities.[20]



Scheme 13. Synthesis of the chiral diene ligand (**23**) made by Wang and coworkers.[20]

Table 10. Catalytic asymmetric arylation of *N*-tosylarylaldimines with chiral olefin ligand (**23a**) and arylboronic acids.[20]



Entry[a]	Ar^1	Ar^2	Yield[b] [%]	*ee*[c] [%]
1	Ph	4-$MeOC_6H_4$	85	98 (*R*)
2	4-FC_6H_4	4-$MeOC_6H_4$	90	99 (*S*)
3	4-ClC_6H_4	4-$MeOC_6H_4$	85	98 (*S*)
4	4-MeC_6H_4	4-$MeOC_6H_4$	92	99 (*R*)
5	2-$MeOC_6H_4$	4-$MeOC_6H_4$	85	99 (*S*)
6	2-MeC_6H_4	4-$MeOC_6H_4$	93	99 (*S*)
7	2-ClC_6H_4	4-$MeOC_6H_4$	65	99 (*S*)
8	1-Naph	4-$MeOC_6H_4$	93	99 (*S*)
9	4-ClC_6H_4	Ph	81	99 (*S*)
10	4-BrC_6H_4	Ph	72	99 (*S*)
11	4-$MeOC_6H_4$	Ph	97	99 (*S*)
12	2-MeC_6H_4	Ph	78	99 (*S*)
13	2-ClC_6H_4	Ph	56	99 (*S*)
14	1-Naph	Ph	88	99 (*S*)
15	2-furanyl	Ph	74	99 (*S*)
16	2-thiopheneyl	Ph	93	98 (*S*)
17	Ph	4-MeC_6H_4	81	99 (*R*)
18	4-$MeOC_6H_4$	4-MeC_6H_4	99	98 (*S*)
19	4-$MeOC_6H_4$	4-ClC_6H_4	97	99 (*R*)
20	1-Naph	2-Naph	91	99 (*S*)

[a] Reaction conditions: 0.5 mmol *N*-tosylarylaldimine; 2 equivs. arylboronic acid; 2 equivs NEt_3; 3 mol% precatalyst and 3.3 mol% ligand (**23a**). [b] Isolated yields. [c] Determined by chiral stationary phase HPLC.

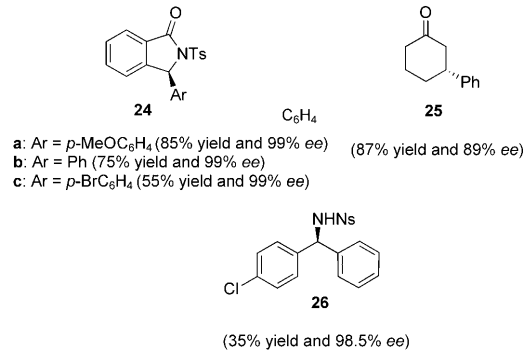


Figure 7. Products of the Rh-catalyzed arylation reaction using the diene ligand (**23a**, Scheme 13).[20]

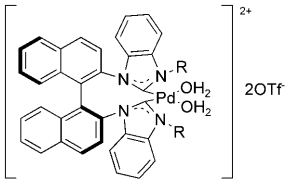
Palladium Catalysts

As far as we are aware, there are very few reports[4b] on the application of palladium catalysts for this particular catalytic enantioselective reaction.

Chiral *N*-heterocyclic carbenes

Motivated by the use of aquo complexes in the synthesis of chiral aryl substituted amines, Ma and coworkers developed for the first time an asymmetric version of this reaction.[21] In the past few years, *N*-heterocyclic carbene (NHC) ligands have shown certain advantages in catalysis because they are stronger σ donors and weaker π acceptors, in comparison to phos-

phine ligands. The stability of these ligands to air/moisture can be a powerful incentive for their use.[22] From a 1,1′-binaphthalenyl-2,2′-diamine (BINAM) backbone, Ma's group created a new chiral C_2-symmetric cationic Pd^{2+}-NHC diaquo complexes (**27**, Figure 8) in a three step pathway. This was applied in the enantioselective arylation of *N*-tosylimines with arylboronic acids under mild conditions.[21]



27

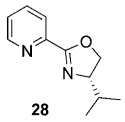
a: R=Me;
b: R=Bn;
c: R=3,5-$Me_2C_6H_3CH_2$;
d: R=Bn;
e: R=Bn.

Figure 8. Chiral cationic NHC-Pd^{2+} diaquo complexes synthesized by Ma and coworkers.[21]

An X-ray structural analysis performed on the crystalline complex (**27a**) revealed the coordination of two water molecules (Figure 8). The arylation of *p*-chlorotosylaldimine with phenylboronic acid and the complex (**27a**) was conducted using a range of conditions. Subsequently a variety of *N*-tosylimines with diverse substitution patterns were tested using phenylboronic acid (Table 11). The results were quite encouraging for this type of complex. High yields (up to 99%) were produced, as well as high enantioselectivities (up to 94% *ee*) independently of the electron donating or electron withdrawing nature of the substituents in the aryl ring. It was observed that an aliphatic imine could also give some encouraging results (Table 11, entry 19). The authors proposed that the mechanism of this catalytic reaction is similar to that presented by Dai and Lu, which used achiral cationic palladium complexes.[23a]

Chiral *N,N* Ligands

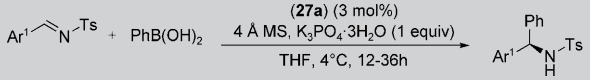
Dai and Lu continued their studies on the arylation reaction and concluded that the use of a ligand is crucial for the attainment of the desired product, owing to its ability to stabilize the divalent palladium species, which can inhibit the coupling reaction between two arylboronic acid molecules that can form an undesired diaryl product.[23b] The authors propose that the ligand influences the electrophilicity of the phenylpalladium species. The asymmetric catalytic version of this reaction was investigated using several aryl substituted imines, boronic acids, and the chiral pyridine-oxazoline ligand (**28**) (Figure 9 and Table 12). *N*-tosylaldimines with strong electron-withdrawing groups and the arylboronic acids with electron-donating groups provided the best results (Table 12, entries 4, 5, 8), whereas *p*-trifluorobenzaldimine, *p*-chlorophenylboronic acid, and *m*-nitrophenylboronic acid failed to react under the conditions investigated (Table 12, entries 3, 6, 9).



28

Figure 9. Chiral pyridine-oxazoline ligand used by Dai and Lu.[23b]

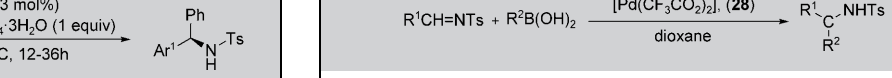
Table 11. Catalytic asymmetric arylation of *N*-tosylimines with Pd complex (**27a**) and phenylboronic acid.[22]



Entry	Ar^1	Yield[a] [%]	*ee*[b] [%]
1	4-ClC_6H_4	99	90 (*S*)
2	3-ClC_6H_4	97	82 (*S*)
3	2-ClC_6H_4	99	90 (*S*)
4	4-BrC_6H_4	64	60 (*S*)
5	3-BrC_6H_4	85	94 (*S*)
6	2-BrC_6H_4	93	84 (*S*)
7	4-FC_6H_4	99	94 (*S*)
8	2,4-$Cl_2C_6H_3$	96	90 (*S*)
9	2,3-$Cl_2C_6H_3$	96	86 (*S*)
10	4-MeC_6H_4	99	90 (*S*)
11	4-$MeOC_6H_4$	99	88 (*S*)
12	2-$MeOC_6H_4$	99	92 (*S*)
13	4-$NO_2C_6H_4$	99	84 (*S*)
14	3-$NO_2C_6H_4$	99	81 (*S*)
15	2-$NO_2C_6H_4$	85	85 (*S*)
16	1-Naph	95	90 (*S*)
17	2-turanyl	99	80 (*S*)
18	2-thiophenyl	87	83 (*S*)
19	$CH_3CH_2CH_2$	64	66 (*S*)

[a] Isolated Yields. [b] Determined by chiral stationary phase HPLC.

Table 12. Asymmetric catalytic addition of arylboronic acids to *N*-tosylaldimines using Pd and ligand (**28**).[23b]



Entry[a]	R^1	R^2	Yield[b] [%]	*ee*[c] [%]
1	4-$NO_2C_6H_4$	Ph	71	85
2	4-$MeOC_6H_4$	Ph	23	88
3	4-$CF_3C_6H_4$	Ph	–	–
4	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	65	78
5	4-$NO_2C_6H_4$	4-MeC_6H_4	42	77
6	4-$NO_2C_6H_4$	4-ClC_6H_4	–	–
7	Ph	β-Naph	84	89
8	Ph	4-$MeOC_6H_4$	68	86
9	Ph	3-$NO_2C_6H_4$	–	–

[a] (0.25 mmol) substrate, (0.5 mmol) arylboronic acid, (5 mol%) [Pd-$(CF_3CO_2)_2$], (6 mol%) ligand (**28**) in dioxane (1 mL), 95 °C, 4 days. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC.

Chiral diphosphines

In 2010, Marques and Burke reported for the first time the application of chiral diphosphines in the palladium catalyzed asymmetric arylation of *N*-tosylimines.[24] Several commercial diphosphine ligands (Figure 10) with $[Pd(OAc)_2]$ as the palladi-

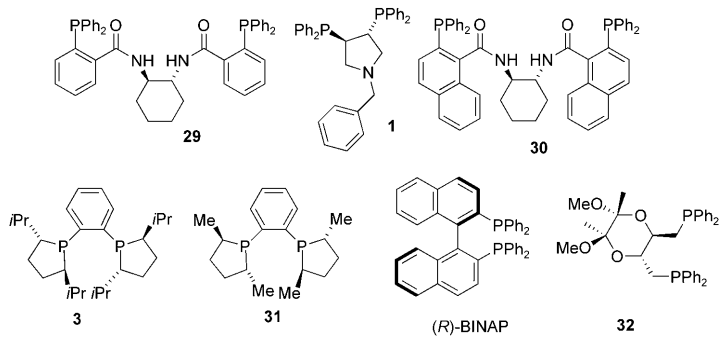
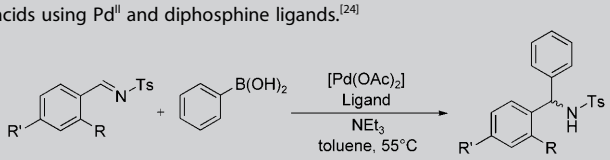


Figure 10. Chiral diphosphine ligands screened by Marques and Burke.[24]

um source and both *o*- and *p*-chlorotosylarylaldimine as substrates were screened under the conditions described in Table 13. A maximum yield of 77% was attained (Table 13, entry 12), with *o*-chlorotosylarylaldimine. Regarding the enantioselectivity some very good to excellent *ee* values were achieved (Table 13, entry 8, for instance).

Table 13. Asymmetric phenylations of *N*-tosylimines with phenylboronic acids using Pd^{II} and diphosphine ligands.[24]



Entry[a]	Substrate	Ligand	Yield[b] [%]	*ee*[c] [%]
1	R = Cl; R′ = H	**29**	27	82 (*R*)
2	R = Cl; R′ = H	**1**	57	72 (*R*)
3	R = H; R′ = Cl	**1**	< 10	12 (*R*)
4	R = Cl; R′ = H	**30**	22	69 (*S*)
5	R = H; R′ = Cl	**30**	16	29 (*S*)
6	R = Cl; R′ = H	**3**	21	92 (*S*)
7	R = H; R′ = Cl	**3**	–	–
8	R = Cl; R′ = H	**31**	41	> 99 (*S*)
9	R = H; R′ = Cl	**31**	19	11 (*S*)
10	R = Cl; R′ = H	*(R)*-BINAP	29	< 5 (*S*)
11	R = H; R′ = Cl	*(R)*-BINAP	10	< 10 (*S*)
12	R = Cl; R′ = H	**32**	77	42 (*R*)
13	R = H; R′ = Cl	**32**	22	41 (*R*)

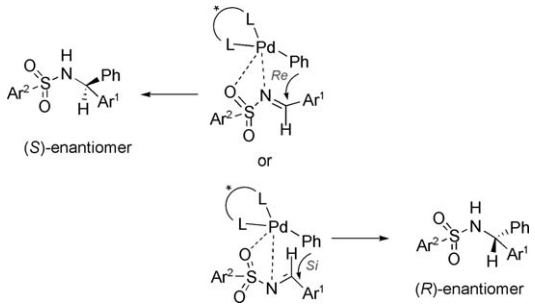
[a] Reaction conditions: (3 mol%) $[Pd(OAc)_2]$, (3.3 mol%) phosphine ligand, $PhB(OH)_2$ (2 equiv) and NEt_3 (2 equiv). [b] Isolated yield. [c] Determined by chiral stationary phase HPLC.

To rationalize the configuration of the major amine product, a working model was proposed. It was presumed that the diphosphine ligands **30**, **3**, **31**, and *(R)*-BINAP (Figure 10) coordinate to both the Pd precatalyst and the substrate (Scheme 14), which introduces the phenyl ring by means of a *Re*-face attack with preferential formation of the (*S*)-enantiomer. In the case of the phosphine ligands **29**, **1**, or **32** (commercially known as DioxPhos) the opposite occurs to give preferential formation of the (*R*)-enantiomer (Scheme 14).

To reduce substrate hydrolysis, some reactions using phenylboroxine (see for example Scheme 11) as the phenyl source were conducted. The results were promising using ligand **32** (Figure 10). Both the yield and the enantioselectivity improved significantly (99% yield, 64% *ee*), compared to the same reaction with phenylboronic acid (Table 13, entry 12).

Outlook

The catalytic enantioselective synthesis of aryl and diarylmethylamines using organoboron reagents and Rh or Pd metal catalysts was discussed in this review. The use of easily prepared imines and commercially available cheap and diverse arylboronic acid reagents



Scheme 14. Working model proposed by Marques and Burke to explain the disparate stereochemical outcomes using different types of diphosphine ligands.[24]

can be used to transform suitably activated/protected imines to a plethora of chiral primary amine products. The method chosen is highly suitable for the rapid combinatorial synthesis of large libraries of biologically active chiral compounds, for use in high-throughput screening studies, owing to the large amount of chemical diversity available through variation of both the substrate and boron-reagent structure. Chiral phosphines, monophosphites, phosphoramidites dienes, and chiral NHCs, have successfully been applied as ligands in this specific reaction and were described in this review.

Thus far only chiral NHCs have been applied in the Pd catalyzed asymmetric arylation of imines. Although, preliminary results from our laboratory show that chiral Rh-NHC complexes can successfully catalyze this reaction.[25]

In the case of rhodium catalysis, there are two specific methods that stand out: the method developed by Minnard[13a] that uses chiral phosphoramidite ligands in conjunction with low equivalents of boronic acids, in acetone (a relatively non-toxic solvent) under mild conditions, to convert dimethylsulfamoyl imines to chiral dimethylsulfamoyl amines (see Table 5). Excellent yields and enantioselectivities were achieved. The groups of both Hayashi and Wang have demonstrated the effectiveness of using chiral diene ligands.[19,20] In the case of the latter group for which *N*-tosylarylaldimines were used as substrates, excellent yields and enantioselectivities were produced for a diverse range of substrates, with electron donating and electron withdrawing substitution groups in the aryl moiety (see Table 10).[20]

In the case of chiral palladium catalysts, few studies have yet been reported. The method developed by Ma, using cationic chiral NHC ligands in aqueous media with a range of *N*-tosylarylaldimines as substrates gave the corresponding amine products in excellent yields and enantioselectivities (see Table 11).[21] Ours was the first group to report the use of Pd-diphosphine type catalysts for this particular transformation.[24]

Concerning the substrate scope, in most cases aromatic imines were used, but, Ellman made a significant breakthrough with aliphatic imine substrates by producing very good results, in terms of yield and enantioselectivity.[10] We believe that this substrate type needs to be fully explored, as it should serve as a key reaction in the synthesis of various amine containing natural products and bio-active compounds. Within our group we are continuing our studies with the asymmetric version of this reaction in an endeavor to expand its scope and application. Other metal catalysts, like ruthenium (which shows potential) are currently being investigated.[25]

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Keywords: arylation · asymmetric catalysis · chiral amines · transition metals

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