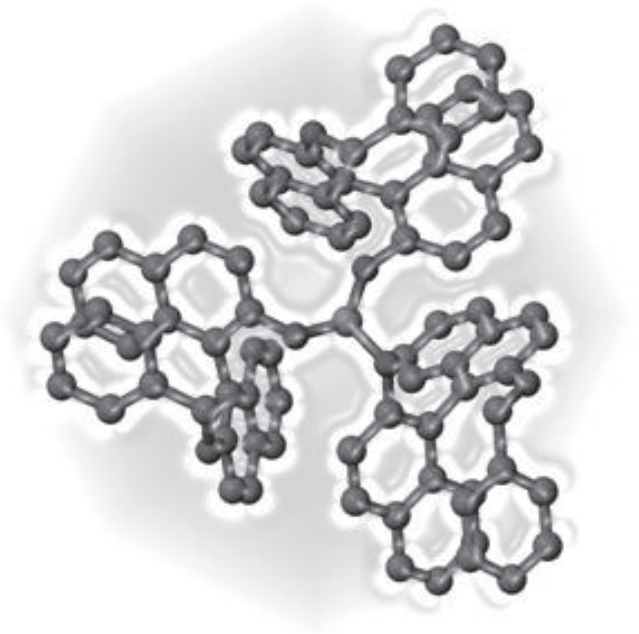


Rui Miguel Barroso Carrilho

BINAPHTHYL-BASED HELICAL MONOPHOSPHITES
A NEW CONCEPT OF PHOSPHORUS LIGANDS IN HOMOGENEOUS CATALYSIS

Tese de Doutoramento (Pré-Bolonha) em Química, área de Química Macromolecular, orientada pela Professora Doutora Maria Miguéns Pereira e pelo Professor Doutor László Kollár, e apresentada à Faculdade de Ciências e Tecnologia da Universidade de Coimbra

2013

· U C ·

Universidade de Coimbra

Universidade de Coimbra
Departamento de Química – Faculdade de Ciências e Tecnologia

BINAPHTHYL-BASED HELICAL MONOPHOSPHITES
A New Concept of Phosphorus Ligands in Homogeneous Catalysis

Rui Miguel Barroso Carrilho

Tese de Doutoramento (Pré-Bolonha) em Química, área de Química Macromolecular, orientada pela Professora Doutora Maria Miguéns Pereira e pelo Professor Doutor László Kollár, e apresentada à Faculdade de Ciências e Tecnologia da Universidade de Coimbra.

Coimbra, 2013

“One thing I have learned in a long life: that all our science, measured against reality, is primitive and childlike and yet it is the most precious thing we have.”

Albert Einstein (1879-1955)

Com amor, para a Renata e a Inês

Agradecimentos/Acknowledgments

Chega ao fim mais um capítulo.
O que parecia ser infindável passou, afinal, num abrir e fechar de olhos.

Gostaria, em primeiro lugar, de prestar uma palavra de especial agradecimento à Professora Doutora Mariette Pereira, a minha orientadora e a pessoa presente em todo o meu percurso académico. Recordando os nove anos que envolveram o estágio de Licenciatura, o Mestrado, Projetos de Investigação e o trabalho de Doutoramento apresentado nesta dissertação, congratulo-me e sinto-me agradecido pela rigorosa orientação científica, pelo apoio e dedicação ao supervisionamento do trabalho, e pela amizade.

To Professor László Kollár, I would like to sincerely thank the admirable scientific supervising, all the support and friendship during my stay in Pécs. Köszönöm!
I would also like to thank all my Hungarian colleagues and friends, who made me feel that Pécs was my second home, and who often stopped their own works to support me, especially to Zsolt Csók, Tamás Kégl, Attila Takács and Orsi Kovács.
All I can say is "*Muito obrigado e até sempre*!"

Quero agradecer ao Professor Doutor Guillermo Muller e ao Doutor Arnald Grabulosa, da Universidade de Barcelona pela forma calorosa com que me receberam no seu laboratório, assim como pela importante colaboração em torno dos trabalhos de hidrovinilação.

Agradeço as preciosas colaborações da Professora Doutora Maria José Moreno, da Faculdade de Farmácia da Universidade de Coimbra e do Professor Doutor Juan Carlos Bayón, da Universidade Autónoma de Barcelona, pela contínua colaboração desde o início deste trabalho, através de frutíferas discussões científicas.

Ao Professor Doutor Enrique Pandolfi, à Professora Doutora Valeria Schapiro e à Doutora Viviana Heguaburu da Universidad de La Republica de Montevideo (UDELAR), pela excelente colaboração e pela cedência dos substratos derivados de conduritol.

Ao Professor Doutor Rui Brito e ao Pedro Cruz do serviço de Ressonância Magnética Nuclear do Centro de Química de Coimbra (CCC-NMR), agradeço a colaboração na obtenção dos espectros de RMN.

À Professora Doutora Teresa Roseiro e à Professora Doutora Ermelinda Eusébio agradeço a colaboração na obtenção e tratamento dos dados cristalográficos, assim como nos estudos de espectroscopia de infravermelho.

À Professora Doutora Elisa Serra, à Professora Doutora Dina Murtinho e à Dra. Sílvia Gramacho, agradeço a atenção dispensada na obtenção da análise elemental, polarimetria e dos espectros de massa, respetivamente.

A todos os colegas de laboratório que comigo se cruzaram ou ainda cruzam, Andreia Peixoto, Artur Abreu, Mónica Silva, Mário Calvete, Carlos Monteiro, Sara Pinto, Vanessa Simões, Ana Almeida, Ângela Neves, César Henriques, Nuno Gonçalves, Gonçalo Costa, Roberto Dias, Álvaro Batista e Lucas Dias. Obrigado pela colaboração, pelo alegre convívio diário, pelo espírito de entreajuda em todos os momentos, e também de solidariedade, em alturas menos encorajantes.

Gostaria ainda de agradecer o apoio financeiro da Fundação para a Ciência e a Tecnologia (FCT), através do Projeto PTDC/QUI-QUI/112913/2009, e da cedência da bolsa de doutoramento SFRH/BD/60499/2009.

Para além das pessoas que estiveram diretamente envolvidas no trabalho, não posso deixar de dedicar umas breves palavras a todos os amigos e família, pela constante presença na minha vida, ainda que, alguns deles, distantes fisicamente.

Em especial, aos meus pais, por serem ao longo da vida os pilares sobre os quais formei o meu carácter e ergui a minha força.

À Renata e à Inês, por serem as minhas fontes de inspiração. Por tudo o que me têm ensinado, pela alegria, pelo amor, por toda a compreensão e ajuda no dia-a-dia, agradeço-vos do fundo do coração e dedico-vos este trabalho.

Rui Miguel B. Carrilho

Setembro de 2013

TABLE OF CONTENTS

Abstract

The work presented in this dissertation was guided toward the synthesis of BINOL-based helical monophosphite ligands containing different OR pendant groups, presenting C_3-symmetry, for the development of new homogeneous catalysts. Their structures have been selected based on recent studies, in which high enantioselectivities were reported, using transition metal complexes with monodentate ligands and/or heterobidentate hemilabile ligands able to establish secondary interactions with the metal center.

Chapter 1 presents a critical review of the literature, essentially focused on the main themes developed in the course of the experimental work.

In **Chapter 2** the development of a family of enantiomerically pure monophosphite ligands containing three units of (*S*)- or (*R*)-BINOL derivatives is described. Their syntheses involved BINOL mono-etherification via *Mitsunobu reaction*, with different alcohols, as methanol, benzyl alcohol, diphenylmethanol and adamantan-1-ol, leading to isolated yields of 84%, 87%, 63% and 52%, respectively. For the synthesis of a mono-ester analogue, the reaction of BINOL with adamantanoyl chloride was performed, with 82% isolated yield. From phosphorylation of the resulting mono-protected BINOL derivatives with PCl_3, the synthesis of chiral tris-binaphthyl monophosphites was achieved, with yields ranging from 76-83%, after purification and isolation procedures. In this section, the preparation of 2'-(benzyloxy)-3-methyl-1,1'-binaphthyl-2-ol and 2'-(benzyloxy)-3'-methyl-1,1'-binaphthyl-2-ol is also described, with isolated yields of 48% and 33%, respectively. All products were characterized by nuclear magnetic resonance spectroscopy and mass spectrometry.

In **Chapter 3**, studies on the application of the chiral tris-binaphthyl monophosphite ligands, previously developed, are presented in asymmetric catalytic reactions, including rhodium-catalyzed hydroformylation and palladium-catalyzed hydrovinylation. Concerning the hydroformylation of aryl olefins, the studies indicated that, in the case of disubstituted double bonds, the activity and selectivity of Rh(I)/monophosphite complexes strongly depend on the structure of the OR group at the ligand, with Rh/tris[(*R*)-2'-(1-adamantyloxy)-1,1'-binaphthyl-2-yl]phosphite being

the most active (TOF=260 h^{-1}, 84% regioselectivity), and Rh/tris[(*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl]phosphite being the most regioselective catalytic system (TOF=197 h^{-1}, 89% regioselectivity). These works were further supplemented with kinetic studies involving the catalytic system Rh/tris[(*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl]phosphite in the hydroformylation of *trans*-β-methylstyrene. In spite of the high activities and selectivities, none of the catalytic systems has achieved enantiomeric excesses above 20%. Furthermore, Rh/monophosphite catalysts were able to promote the diastereoselective hydroformylation of compounds with potential biological activity, namely the steroid 17β-acetoxyandrost-4-ene, achieving 4β-formyl-17β-acetoxy-5β-androstane as major product (86% chemoselectivity, 100% regioselectivity and 70% diastereoselectivity).

The synthesis and characterization of allylpalladium/monophosphite complexes was performed (in 50-71% isolated yields), as well as their evaluation in the asymmetric hydrovinylation of styrene. All catalytic systems led to high chemoselectivity for 3-phenylbut-1-ene (>85%) without occurrence of homodimerization reactions and with only slight isomerization. In general, the palladium complexes containing BINOL-based monophosphite derivatives with ether groups gave moderate to high enantioselectivities (40-71% ee). However, the most remarkable outcome was achieved with the complex containing the ligand tris[(*S*)-2'-(1-adamantanoyloxy)-1,1'-binaphthyl-2-yl]phosphite, which resulted in one of the most enantioselective palladium-based catalytic systems reported so far in hydrovinylation of styrene, with 92% ee.

In **Chapter 4**, optimization studies of palladium-catalyzed aminocarbonylation reactions were carried out, aiming the synthesis of carboxamides, keto-carboxamides and bis-carboxamides with potential biological activity. The aminocarbonylation of iodobenzene and 1-iodo-cyclohexene as model substrates was performed using palladium complexes formed *in situ* with the tris-binaphthyl monophosphite ligands, leading to active catalytic systems. After optimization of reaction conditions towards the selective formation of keto-carboxamides, the synthesis and isolation of cyclohexenyl-glyoxylamides with unprecedented structures, *N-tert*-butyl-2-(cyclohex-1-enyl)-2-oxoacetamide, 1-cyclohexenyl-2-morpholinoethane-1,2-dione and 1-

cyclohexenyl-2-(piperidin-1-yl)ethane-1,2-dione were performed, with isolated yields varying from 60 to 66%. Then, using Pd/triphenylphosphine catalysts, the synthesis of a family of monocarboxamide-carbasugars was developed from the aminocarbonylation of bromo- or iodo-conduritol derivatives, with isolated yields varying from 50 to 85%. Furthermore, it should be highlighted the pioneering application of this catalytic reaction for the synthesis of a series of dicarboxamides, by using, for the first time, different diamines as nucleophiles. This atom economic methodology allowed synthesizing, in a single step, relevant molecules such as steroid dimers containing dicarboxamide bridges with diverse structures, in isolated yields up to 95%.

In **Chapter 5**, the techniques and instrumentation used are described, as well as the characterization of all products synthesized during the experimental work.

Keywords: BINOL; monophosphite; C_3-symmetry; rhodium; palladium; homogeneous catalysis; hydroformylation; hydrovinylation; aminocarbonylation.

Resumo

O trabalho apresentado nesta dissertação orientou-se no sentido de desenvolver métodos de síntese de monofosfitos derivados do BINOL contendo diferentes grupos OR, apresentando estrutura helicoidal e simetria C_3, para preparar novos catalisadores para reações homogéneas. As estruturas dos catalisadores escolhidos basearam-se em trabalhos recentes, nos quais se observou elevada enantiosseletividade utilizando complexos de metais de transições com ligandos monodentados e/ou ligandos hemilábeis heterobidentados com possibilidade de estabelecerem interações secundárias com o centro metálico.

No **Capítulo 1** apresenta-se uma revisão crítica da literatura focalizada essencialmente nas principais temáticas desenvolvidas no decurso do trabalho experimental.

No **Capítulo 2** encontram-se descritos os métodos de síntese de uma família de monofosfitos enantiomericamente puros contendo três unidades de derivados de (*S*)- ou (*R*)-BINOL. A sua síntese iniciou-se com a monoeterificação do BINOL com diferentes álcoois, via *reação de Mitsunobu*, nomeadamente com metanol, álcool benzílico, difenilmetanol e adamantan-1-ol, tendo-se obtido, rendimentos de produtos isolados de 84%, 87%, 63% e 52%, respetivamente. Para a síntese de um derivado monoesterificado, recorreu-se à reação do BINOL com cloreto de adamantanoílo, tendo-se obtido um rendimento de 82%. Da reação dos resultantes derivados monoprotegidos de BINOL com PCl_3, resultou a síntese de monofosfitos quirais com simetria C_3, com rendimentos compreendidos entre 76-83%, após purificação cromatográfica e isolamento. Neste capítulo descreve-se ainda a preparação de 2'-(benziloxi)-3-metil-1,1'-binaftil-2-ol e 2'-(benziloxi)-3’-metil-1,1'-binaftil-2-ol, com rendimentos de 48% e 33%, respetivamente. Todos os produtos foram caracterizados por espetroscopia de ressonância magnética nuclear e espetrometria de massa.

No **Capítulo 3**, apresentam-se os estudos da aplicação dos monofosfitos quirais desenvolvidos neste trabalho em reações de catálise assimétrica, nomeadamente de hidroformilação catalisada com complexos de ródio e de hidrovinilação catalisada por complexos de paládio.

No que diz respeito à hidroformilação de derivados do estireno, os estudos indicaram que, no caso de olefinas dissubstituídas, a atividade e seletividade dos complexos de ródio/monofosfito depende fortemente na estrutura do grupo OR do ligando, sendo o sistema catalítico Rh/tris[(*R*)-2'-(1-adamantiloxi)-1,1'-binaftil-2-il]fosfito o mais activo (TOF=260 h^{-1}, 84% de regiosseletividade) e o Rh/tris[(*R*)-2'-(benziloxi)-1,1'-binaftil-2-il]fosfito o mais regiosseletivo (TOF 197 h^{-1}, 89% de regiosseletividade). Estes trabalhos foram ainda complementados com estudos cinéticos envolvendo o sistema catalítico Rh/tris[(*R*)-2'-(benziloxi)-1,1'-binaftil-2-il] fosfito na hidroformilação de *trans*-β-metilestireno. Apesar das elevadas atividades e seletividades, nenhum dos sistemas catalíticos conduziu à obtenção de excessos enantioméricos superiores a 20%. Estes estudos permitiram ainda promover a hidroformilação diastereosseletiva de compostos com potencial atividade biológica, nomeadamente do esteróide 17β-acetoxiandrost-4-eno, tendo-se obtido como produto maioritário 4β-formil-17β-acetoxi-5β-androstano (86% quimiosseletividade, 100% de regiosseletividade e 70% de diastereosseletividade).

Os estudos prosseguiram com a síntese e caracterização de complexos de paládio-alilo/monofosfito (com rendimentos entre 50-71%) e sua avaliação na reação de hidrovinilação do estireno. Todos os sistemas catalíticos conduziram a uma elevada quimiosseletividade para a formação de 3-fenilbut-1-eno (> 85%), sem ocorrência de reações homodimerização e baixa isomerização. Salienta-se que, de uma forma geral os complexos de paládio contendo fosfitos derivados do BINOL com grupos éter deram origem a enantiosseletividades moderadas a altas (40-71% ee), enquanto que do complexo contendo o ligando tris[(*S*)-2'-(1-adamantanoiloxi)-1,1'-binaftil-2-il]fosfito resultou um dos sistemas de paládio mais enantiosseletivos, descritos na literatura, na reação de hidrovinilação do estireno (92% ee).

No **Capítulo 4**, efetuaram-se estudos de otimização de reações de aminocarbonilação catalisadas por complexos de paládio/ligando de fósforo, tendo em vista a síntese de produtos com potencial atividade biológica, nomeadamente carboxamidas, ceto-carboxamidas e dímeros de bis-carboxamidas. Os catalisadores de paládio/monofosfito gerados *in situ* permitiram efectuar a aminocarbonilação de substratos modelo, como iodobenzeno e 1-iodo-ciclo-hexeno. Após otimização das

condições de reação, foi possível isolar e caracterizar os compostos do tipo ceto-carboxamida, *N*-*tert*-butil-2-(ciclohex-1-enil)-2-oxoacetamida, 1-ciclohexenil-2-morfolinoetano-1,2-diona e 1-ciclohexenil-2-(piperidin-1-il)etano-1,2-diona, com rendimentos isolados entre 60-66%. Utilizando catalisadores de Pd/trifenilfosfina, desenvolveu-se também a síntese de uma família de monocarboxamidas derivadas de conduritol, através de reações de aminocarbonilação dos respetivos bromo- ou iodo-alcenos, com rendimentos de produtos isolados entre 50-85%. É ainda de salientar o uso desta reação catalítica para a preparação de uma série de dicarboxamidas, utilizando, pela primeira vez, diaminas como nucleófilos. Este processo catalítico com elevada economia atómica permitiu sintetizar, num só passo, moléculas tão relevantes quanto dímeros de esteroides, contendo pontes de dicarboxamida com estruturas diversificadas, com rendimentos de produtos isolados até 95%.

No **Capítulo 5**, são descritas as técnicas utilizadas bem como as caracterizações de todos os produtos sintetizados no decorrer do trabalho experimental que conduziu à escrita desta dissertação.

Palavras-chave: BINOL; monofosfito; simetria C_3; ródio; paládio; catálise homogénea; hidroformilação; hidrovinilação; aminocarbonilação.

Abbreviations and Nomenclature

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
AcO	acetoxy
Ad	1-adamantyl
Ar	aryl
[α]	specific rotation
BINOL	1,1'-binaphthyl-2,2'-diol
BINOL-MOM	2,2’-bis(methoxymethoxy)-1,1'-binaphthyl
Bn	benzyl
brs	broad signal (in nuclear magnetic resonance spectroscopy)
Bu	butyl
COSY	correlation spectroscopy in nuclear magnetic resonance
Cy	cyclohexyl
δ	chemical shift (in nuclear magnetic resonance spectroscopy)
d	doublet
dba	dibenzylideneacetone
dcpp	1,3-bis(dicyclohexylphosphino)propane
dppp	1,3-bis(diphenylphosphino)propane
dd	doublet of doublets
dt	doublet of triplets
DEAD	diethyl azodicarboxylate
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

DTGS	deuterated triglycine sulfate
ee	enantiomeric excess
Elem. Anal.	elemental analysis
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
FID	flame ionization detector
GC	gas chromatography
GC-MS	gas chromatography coupled with mass spectrometry
HP-NMR	high-pressure nuclear magnetic resonance spectroscopy
HMBC	heteronuclear multiple-bond correlation spectroscopy in nuclear magnetic resonance
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy in nuclear magnetic resonance
i-Pr	isopropyl
IR	infrared spectroscopy
J	scalar coupling in nuclear magnetic resonance
m	multiplet
M^+	molecular ion
m/z	mass/charge relation
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethoxyl
Mp	melting point
MS	mass spectrometry
NaBARF	sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate
NOESY	nuclear overhauser effect spectroscopy in nuclear magnetic resonance

^{13}C NMR	carbon 13 nuclear magnetic resonance spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
^{31}P NMR	phosphorus 31 nuclear magnetic resonance spectroscopy
OAd	adamantyloxy
OBn	benzyloxy
OMe	methoxy
OTBS	*tert*-butyldimethylsilyloxy
OTBDPS	*tert*-butyldiphenylsilyloxy
OTf	triflate (trifluoromethanesulfonate)
Ph	phenyl
P(O-*o*-^{t}BuC$_6$H$_4$)$_3$	tris(*orto*-*tert*-butylphenyl)phosphite
PPh$_3$	triphenylphosphine
ppm	parts per million
p-TsOH	*para*-toluenesulfonic acid
RT	room temperature
s	singlet
SDD	Stuttgart/Dresden basis set
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
TOF	turnover frequency
Ts	tosyl (*para*-toluenesulfonyl)
UFF	universal force field

Nomenclature

In this dissertation the IUPAC[1] recommendations of 1993 were followed to number and name all compounds. By way of example, the numbering and nomenclature of one of each family of compounds synthesized is presented below.

Accordingly to IUPAC regulations, the absolute *R* or *S* configurations of axially chiral 1,1´-binaphthyl molecules were assigned, accordingly to the Cahn–Ingold–Prelog *R*–*S* notation system (**Fig. I**).[2]

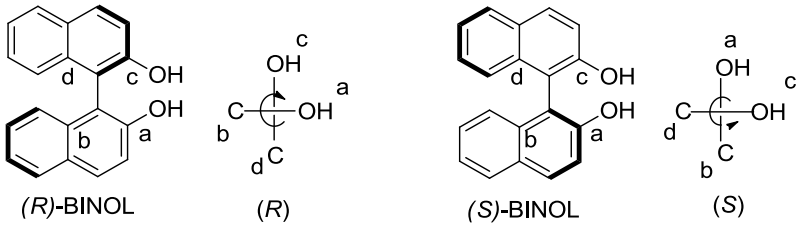
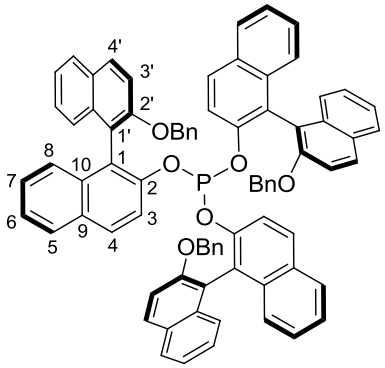


Fig. I – Determination of absolute configuration of BINOL, accordingly to Cahn–Ingold–Prelog *R*–*S* notation system.

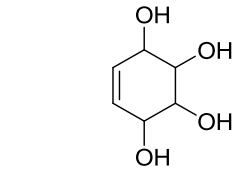
The adopted nomenclature of tris-binaphthyl monophosphites was based on the above mentioned regulations (**Fig. II**).



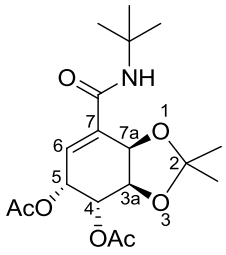
Tris[(*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl]phosphite

Fig. II – Nomenclature of a tris-binaphthyl monophosphite.

The nomenclature of cyclohexenetetraol (trivial name: *conduritol*) derivatives was based on IUPAC recommendations for polycyclic systems with fused rings (**Fig. III**).[3]



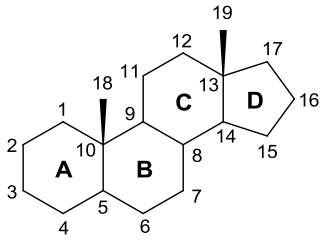
cyclohex-5-ene-1,2,3,4-tetraol
(Conduritol)

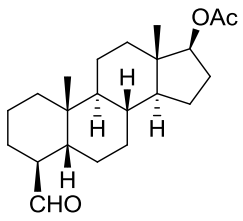


(3a*R*,4*R*,5*R*,7a*R*)-7-(*tert*-butylcarbamoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate

Fig. III – General structure of conduritol and adopted nomenclature for a conduritol-carboxamide derivative.

The steroidal compounds, belonging to androstane series, were named according to the accepted IUPAC nomenclature (**Fig. IV**).[4] The substituents on the same side as the two angular methyl groups at C-10 and C-13 are designated by β substituents, while the others are α substituents. The hydrogen atoms at the stereogenic centers are in 8β, 9α, and 14α positions.





4β-formyl-17β-acetoxy-5β-androstane

Fig. IV – Numbering of the steroidal skeleton and nomenclature of a formyl androstane derivative.

---

[1] R. Panico, W. H. Powell, J.-C. Richer, *A Guide to IUPAC Nomenclature of Organic Compounds (recommendations 1993)*, Blackwell Science, **1993**.

[2] M. M. Pereira, M. J. F. Calvete, A. R. Abreu, R. M. B. Carrilho, *Synthesis of binaphthyl based monophosphorus ligands* in *Advances in Chemistry Research, Vol. 19* (ed. James C. Taylor), Nova Publishers, New York, **2013**.

[3] G. P. Moss, *Pure & Appl. Chem*. **1998**, *70*, 143.

[4] G. P. Moss, *Pure & Appl. Chem*. **1989**, *61*, 1783.

CHAPTER 1

INTRODUCTION AND SCOPE

1.1 Homogeneous catalysis

The term *catalysis* was introduced by Berzelius in the 19th century, who observed alterations in substances when they were brought in contact with small amounts of certain species once called "*ferments*". Some years later, in 1895, Ostwald defined catalyst as *a substance that changes the rate of a chemical reaction without appearing itself as a product*.[1] Currently, a catalyst can be considered as a *chemical substance that increases the rate at which a chemical reaction approaches equilibrium without becoming itself permanently involved*.[2] A catalyst provides a new reaction pathway for a given reaction with a low activation barrier, which may involve different intermediates and several steps, in order to bring the reagents together in a reactive state. Nowadays, catalysis plays a fundamental role in academia as well as in industry, since a large part of the bulk and fine chemicals production is essentially based on catalytic processes.[3]

Homogeneous catalysis is, by definition, a system in which the reagents and catalyst components are all brought together in one only phase (generally, the liquid phase). However, it may involve the use of different types of catalysts: transition metal complexes – *organometallic catalysis*;[4] organic compounds – *organocatalysis*[5] or enzymes – *enzymatic catalysis*.[6]

Catalysis with transition metal complexes is an area of intense research that has grown drastically in the last decades. This growing interest was demonstrated by the recent attribution of three Chemistry Nobel Prizes in this field.[7] In 2001, it was divided, one half jointly to William S. Knowles and Ryoji Noyori *"for their work on chirally catalyzed hydrogenation reactions"* and the other half to K. Barry Sharpless *"for his work on chirally catalyzed oxidation reactions".* In 2005, Yves Chauvin, Robert H. Grubbs and Richard R. Schrock were jointly awarded *"for the development of the metathesis method in organic synthesis"*. More recently, in 2010, the works of Richard F. Heck, Ei-ichi Negishi and Akira Suzuki on *"palladium-catalyzed cross couplings in organic synthesis"* were recognized.[7]

An organometallic catalyst consists of a central metal surrounded by organic (and/or inorganic) ligands (**Figure 1.1**). To bring the reactants together in a reactive state, a metal centre must have a vacant site, to which a substrate may coordinate. The efficiency of an organometallic catalyst is determined by the reaction rates and the selectivity towards a certain product, and lies in the relative ease of catalyst modification by changing the ligands environment.

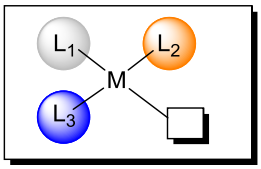


Figure 1.1 – General structure of an organometallic catalyst.

Thus, to perform the rational design of a new catalyst, the selection of the metal and the ligands are both of great relevance. The choice of the metal is generally determined by the envisaged catalytic reaction, based on prior knowledge, or by screening *via* "trial and error". In addition, the adjustment on the metal reactivity

towards a given catalytic reaction can be performed by the coordination of donor ligands to the metal centre. The σ-donor and π-acceptor properties as well as the steric effects imposed by the ligands on the metal centre strongly influence the catalytic performance. It must be noted that the ligand properties are a combination of the donor atom nature with the backbone structure, which is frequently of great importance for stereo-inductive effects and fine-tuning of asymmetric catalytic reactions (**Figure 1.2**).[8]

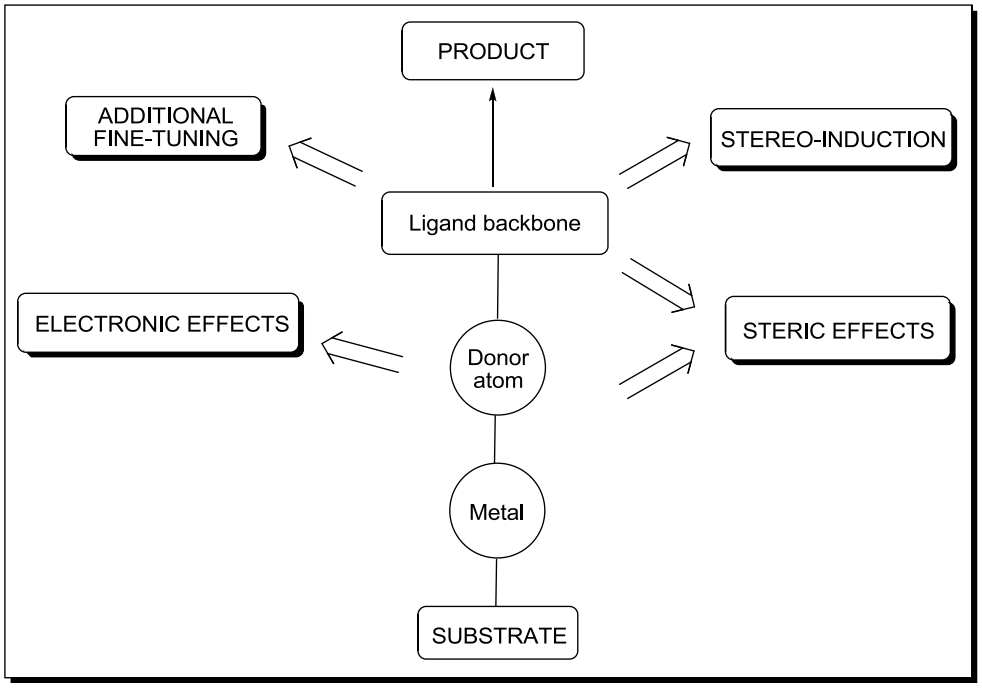


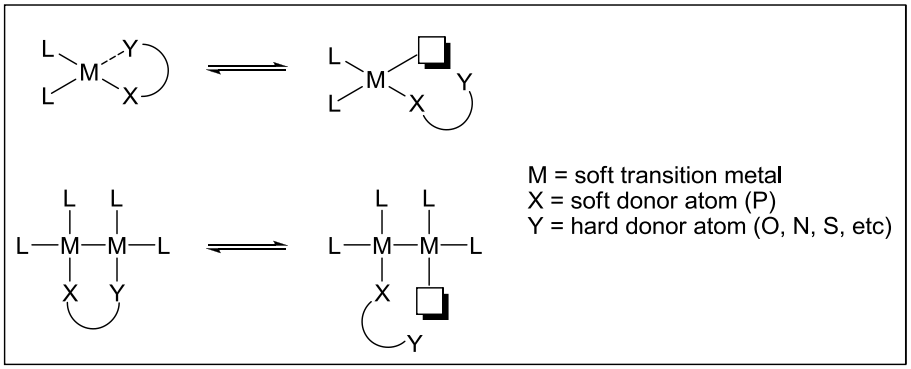
Figure 1.2 – Schematic representation of the several parameters involved in catalyst design and optimization. (Adapted from [8])

An enormous variety of ligands of different type and with different structures has been reported in recent literature: mono-, bi- and polydentate ligands, ligands based on single donor or heterodonor atoms, chiral or achiral and ligands with steric and electronic constraints. Among them, phosphorus (III) compounds can be considered as one of the most important class of ligands, due to their remarkable coordination ability with a range of transition-metal complexes, which led to an extraordinary development of homogeneous catalysis.[8,9]

1.2 Hemilabile phosphorus ligands

Hybrid ligands that contain significantly different chemical functions such as hard and soft donors (often called *hemilabile* ligands) have found increasing use in catalysis, due to their possible dynamic behavior in the metal–ligand interactions.[10] Hemilabile ligands possess at least two different types of bonding groups, whereby one is a labile donor toward substitution, while the other is an "inert" donor atom, which remains anchored to the metal. Therefore, *hemilability* is not an intrinsic property of the sole ligand, since it implies the metal–ligand couple.

Hemilabile ligands can generate accessible coordination vacancies or protect active catalytic sites through a functional "*on-off*" chelating effect with the metal center (**Scheme 1.1**).[11]

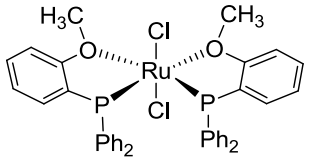


Scheme 1.1

In addition, they can also play important roles in the stabilization of highly unsaturated intermediates, in the interactions with reactive polar species, or even in the activation of substrates.[12] This multifunctional character has been demonstrated to significantly influence the catalytic activity and selectivity in several reactions, such as hydrovinylation,[13] hydrogenation of alkenes,[14] transfer hydrogenation[15] and alkyne hydration.[15]

The concept of *hemilability* was first introduced by Jeffrey and Rauchfuss in 1979,[16] referring to the coordination mode of polydentate chelate ligands bearing two types of bonding groups, in ruthenium(II) complexes. The studies on structure and reactivity of **1.1**, containing a *o*-(diphenylphosphino)anisole ligand revealed that the

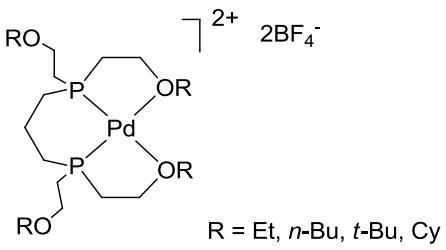
Ru–O bonds were significantly longer than Ru–P bonds, indicating that oxygen atoms were only weakly bonded. The complex was highly reactive toward a number of ligands (such as CO) while remained remarkably stable in presence of oxygen and heat.



1.1

Since then, a large number of hemilabile ligands have been reported. In current years, special attention has been paid to the synthesis,[17] coordination chemistry[18,19,20] and catalytic applications of hemilabile ligands. During a catalytic process, the metal catalyst can suffer a change in the oxidation state, which may consequently weaken or even break the bond to the labile donor atom, producing a vacant coordination site. In general, with low-valent late transition metals, phosphorus atoms usually bind strongly to the soft metal center, while the hard donor atoms (O, N or S) are generally weakly bounded, which allow, by decoordination, the binding of substrates that induce ulterior reactivity. Among hemilabile phosphorus ligands, several functionalized phosphino-ether[21] and phosphino-carbonyl compounds[22] have been intensively studied as heterobidentate ligands with late transition metals, including ruthenium,[23,24] rhodium,[25,26,27] iridium[28] and palladium.[29,30]

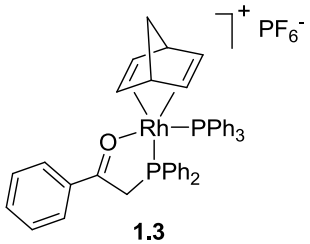
Palladium(II) complexes of ether diphosphine hemilabile ligands **1.2** were originally applied as catalysts in copolymerization reactions between carbon monoxide, ethylene and propene leading to synthesis of polyketones with high molecular weight.[29]



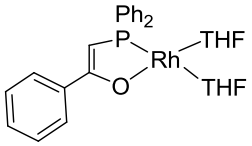
R = Et, *n*-Bu, *t*-Bu, Cy

1.2

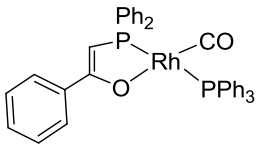
Ligands with carbonyl moieties are also a common type of hemilabile *P*,*O* ligands. These are able of undergoing conversion to enolate moieties upon deprotonation, which usually form substitutionally inert chelates.[31] Some examples include the cationic rhodium(I) β-keto phosphine complex **1.3**, and the neutral enolate-phosphine complexes **1.4**, **1.5** and **1.6**.[22] The cationic complexes bearing a keto-phosphine ligand provided access to active catalysts in the catalytic hydrogenation of 1-hexene and to active enolate complexes in the transfer dehydrogenation of cyclooctane.[22]



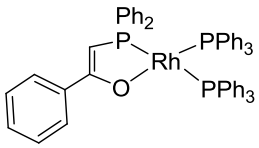
1.3



1.4

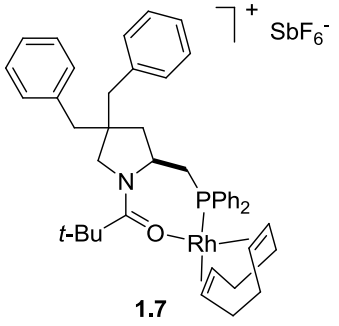


1.5



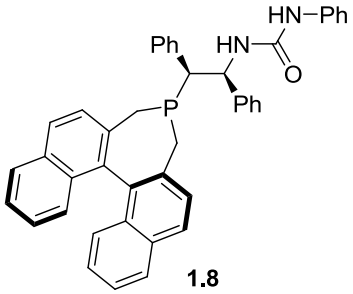
1.6

The synthesis of rhodium(I) complex **1.7**, containing an amido-monophosphine ligand was reported by Tomioka.[32] Its structural features, clarified by NMR, IR and X-ray, revealed that the monophosphine behaves as a hemilabile ligand whose phosphorus atom strongly bonds to rhodium(I), while the amide carbonyl oxygen atom has a fluxional process involving dissociation and recoordination, leading to a highly enantiodiscriminative species in asymmetric 1,4-addition of aryl boronic acids to cycloalkenones (with up to 97% ee).[32]

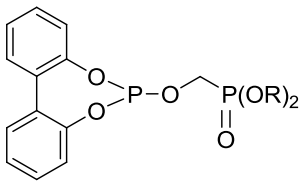


1.7

Recently, Reek[33] reported the synthesis of ureaphosphine ligands, which coordinate in a *P*,*O*-bidentate fashion to rhodium(I). The Rh(I) complex of ligand **1.8** gave high conversions and enantioselectivities up to 88% in the asymmetric hydrogenation of cyclic enamides.



1.8



1.9

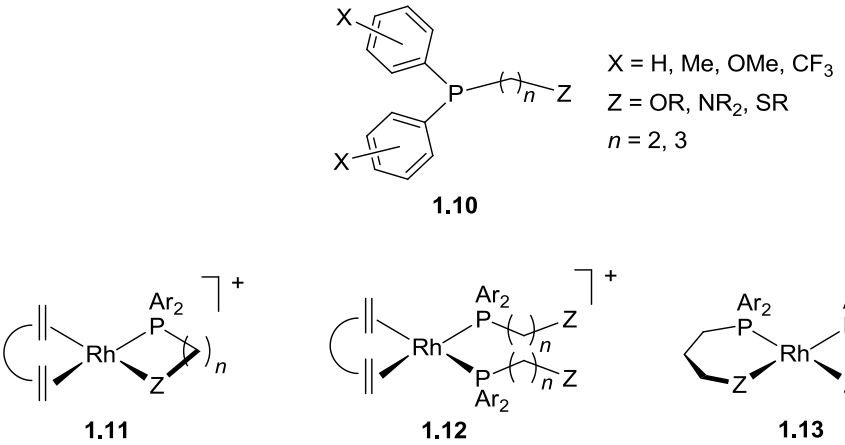
R = Et, *i*-Pr, Cy

Although less frequent, there are also a few examples of hemilabile phosphites,[34] whose metal complexes have been used in catalysis. Based on previous studies of Rh(I)/phosphonated phosphine complexes as hydroformylation catalysts,[35,36] Abbayes reported the first examples of potentially hemilabile phosphite-phosphonate ligands **1.9**, which were evaluated in Rh-catalyzed hydroformylation of styrene.[34] In these ligands, the phosphonate moiety was envisaged to provide an "*on-off*" chelating effect by coordination/decoordination with rhodium, while the phosphorus atom of the phosphite moiety was intended to be permanently anchored to the metal.[34,36] The resulting complexes, especially those with bulkier substituents, provided remarkable catalytic activities in the hydroformylation of styrene at room temperature, with up to 91% conversion in 18h, and an excellent *iso*-regioselectivity of 97%.[34]

Furthermore, *P*,*N*-donor molecules have also been subject of recent studies as hemilabile ligands, in the past few years.[37,38,39] For instance, cationic rhodium(I) complexes bearing nitrogen-containing monophosphine,[40] bis(phosphine) and bis(phosphinite)[41] ligands provided active and selective catalysts in styrene hydroformylation[40,41] and hydroaminomethylation.[42] Other amine functionalized hemilabile phosphines were reported to have remarkable efficiency in Suzuki coupling reaction of aryl chlorides, where the presence of potentially donating nitrogen atoms has demonstrated to have a critical role in the catalytic activity.[43] Furthermore, it has

been shown that rhodium(I) complexes modified with *P*,*N*- hemilabile tetraphosphine complexes were active hydroformylation catalysts.[44] More recently, Cowie[45] reported the synthesis of mono- and binuclear rhodium complexes containing hemilabile *P*,*N*-ligands, and explored their application as catalysts in styrene silylation.[46]

In a pioneering work, Jiménez and Pérez-Torrente[12,47,48] have reported the synthesis and characterization of cationic square-planar rhodium(I) complexes **1.11**, **1.12** and **1.13**, which contained diverse functionalized *P*,*O*-, *P*,*N*- and *P*,*S*- hemilabile phosphine ligands of type **1.10**.



These complexes were used as efficient catalysts for the oxidative amination of styrene with piperidine, where the *P*,*O*-coordinated catalyst precursors of type **1.13**, which contained two 3-ethoxypropyl-functionalized phosphines in a *cis* arrangement, presented outstanding activities, with unprecedented turnover frequencies of up to 80 h^{-1}, and excellent enamine selectivity (up to 96%). This superior performance was attributed to the higher ability of these ligands to show a dynamic "*on-off*" effect in the key catalytic intermediates, due to interactions of the oxygen atom with the rhodium center, thereby forming a six-membered metallocyclic ring. In addition, the steric and electronic effects introduced by the alkoxy moieties seemed also to be important in the protection/deprotection of the active catalytic sites.[12,47] The same authors also reported the use of the cationic rhodium complexes as catalysts for polymerization reaction of phenylacetylene, in which a superior performance was shown by complexes of type **1.11** containing a *P*,*N* functionalized phosphine ligand.[48]

1.3 Phosphorus ligands with C_3-symmetry

It is widely recognized that the presence of rotational symmetry in chiral ligands and metal complexes may increase the selectivity in chemical reactions.[49]

For more than three decades, the design and synthesis of chiral ligands has been predominantly focused on bidentate chelating ligands with C_2-symmetry, or sets of C_1-symmetric monodentate ligands that arrange themselves to generate essentially a similar active space as chelates, which have been considered essential for efficient asymmetric induction.[50,51] However, the exploitation of C_3 symmetry in the design of chiral ligands for asymmetric homogeneous catalytic transformations is currently the focus of considerable research efforts and conceptual debate.[52,53] The recent reviews written by Moberg[54] and Gibson[55] provide accurate and detailed information regarding the application of chiral C_3-symmetric molecules in asymmetric catalysis .

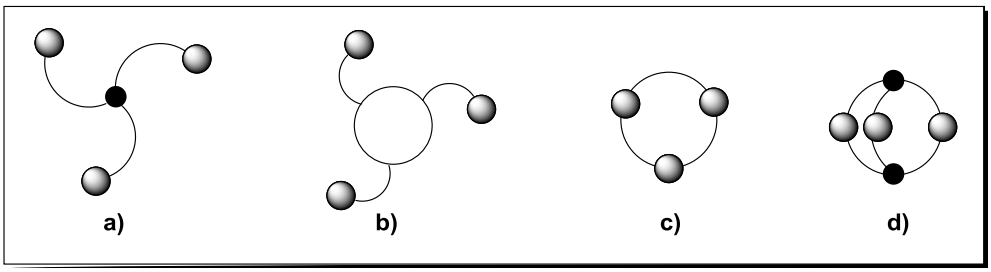


Figure 1.3 – Topologies of structures with C_3 symmetry.[54]

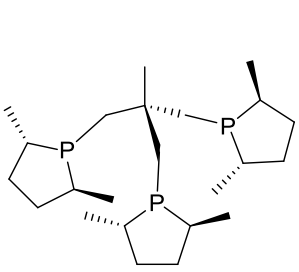
A molecule with C_3 symmetry can have different typical topologies: it may be acyclic (a), exocyclic (b), macrocyclic (c) or bicyclic (d) (**Figure 1.3**).[54] In all of these types, the presence of a chiral center is commonly a requirement for dissymmetry. However, some molecules are known in which dissymmetry is caused by axes of chirality. In these cases, chirality may be originated by the direction of the substituents arrangements. A further possible arrangement possessing C_3 symmetry based on a chirality axis is a triple helix, in which the asymmetric folding of the strands is induced by their stereogenic centers.

A significant number of ligands with C_3 symmetry have been synthesized and, in some cases, applied in catalysis. It was found that chiral and tripodal C_3-symmetric ligands are highly effective in enantioselective catalytic reactions involving octahedral

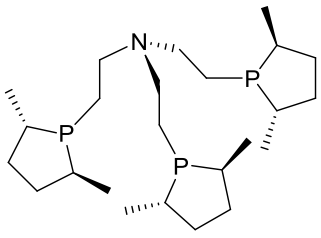
complexes, in which the presence of homotopic coordination can be considered the reason of their favorable properties.[54,56] In addition to efficient catalytic applications, threefold symmetrical molecules have also demonstrated to play important roles in several applications and are believed to have high potential in diverse fields, such as in molecular recognition,[57,58] nanoarchitecture[59] and nonlinear optics.[60] Among C_3-symmetric ligands, are found triols,[61] pyridine derivatives,[62] tris-oxazolines,[63,64] as well as phosphorus based ligands[65-78] which will be focused with more detail in this section.

In general, most of C_3-symmetric chiral phosphorus ligands are tripodal phosphines or monophosphine ligands containing threefold rotational axes. Some pioneering examples include the enantiomerically pure tripodal phosphines **1.14** and **1.15**, which were prepared from cyclic lithiophosphanes and the appropriate trichloro compounds.[65] Their cationic rhodium(I) complexes were successfully applied as catalytic precursors in asymmetric hydrogenation of olefins, displaying good catalytic activity and enantioselectivity in the hydrogenation of dimethyl itaconate (up to 95% ee) and of methylacetamido cinnamate (up to 89% ee).[66]

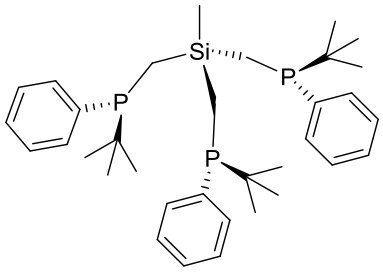
The C_3-symmetric tripodal phosphine **1.16**, which differs from the previous by having the centers of asymmetry on the phosphorus atom, was later synthesized from (*R*)-(*tert*-butyl)(methyl)(phenyl)phosphane–borane through deprotonation, followed by reaction with trichloromethylsilane, and subsequent deprotection.[67] However, its ability as ligand to induce chirality in asymmetric catalysis has not been reported.



1.14



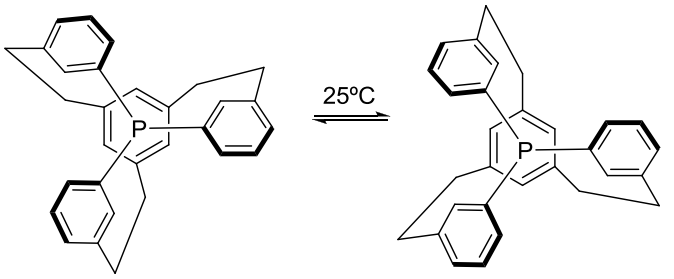
1.15



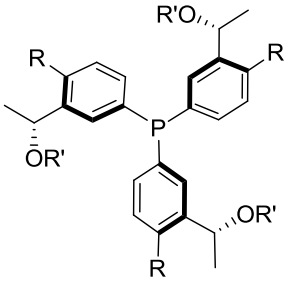
1.16

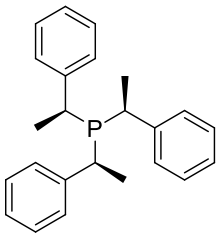
The isomeric monodentate phosphines **1.17** and **1.18**, in which the threefold rotational axis is a chirality axis, could not be resolved due to rapid racemization at room temperature.[68] In an attempt to address this issue, a more recent study has been

focused on C_3-symmetric monodentate phosphine ligands of types **1.19** and **1.20**.[69] The arrangement of the three aromatic groups around the central atom was intended to provide stable enantiomeric propeller-shaped conformations, considering it should supply chiral pockets able of enantiodiscrimination. However, a study of their solid state structures revealed that rotation over the P–aryl bonds enable these ligands to populate conformations that are not perfectly C_3-symmetric. Nevertheless, they were tested in palladium-catalyzed allylation reactions, where enantioselectivities up to 82% were obtained using **1.20b** as ligand.[69]



1.17 **1.18**





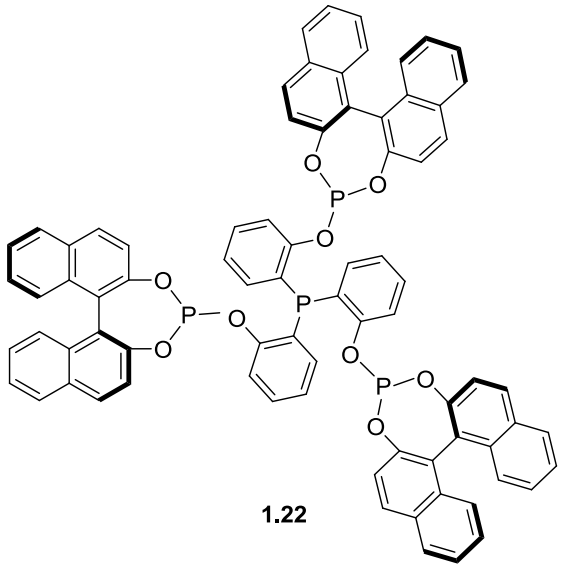
1.19 (R = H) **1.20** (R = OMe) **1.21**

a: R = Me
b: R = Ph
c: R = 2,6-$Me_2C_6H_3$

More recently, the asymmetric synthesis of monophosphine **1.21**, carrying three identical chiral groups on the phosphorus atom was achieved by introduction of two α-methylbenzyl groups, using a nucleophilic Grignard reagent, followed by chiral resolution using (*R*)-α-methylbenzylamine and subsequent introduction of the third chiral group by electrophilic addition of α-methylbenzyl iodide.[70]

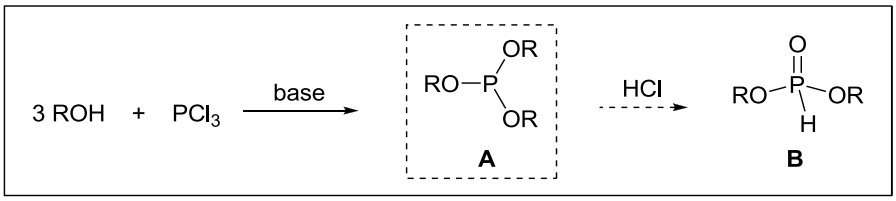
In 1993, Pringle reported the synthesis of the tripodal ligand **1.22**, bearing a triaryl phosphine moiety along with three binaphthyl-based monophosphite units,

through the addition of binaphthyl chlorodioxaphosphepine to triphenylphosphinophenol, in basic medium.[71] This phosphine-phosphite ligand was able to coordinate in a tetradentate mode with Pt(0), leading to a tetrahedral complex, which could be further protonated or methylated, yielding, in both cases, trigonal-bipyramidal complexes, all of them with C_3 symmetry. Curiously, since then, no descriptions regarding their application in catalysis were, however, reported.



1.22

Regarding phosphite ligands with C_3 symmetry, they obviously include the symmetrically trisubstituted monophosphites of general formula $P(OR)_3$, which have been applied as ligands since the early days of homogeneous catalysis, back in the 1960's. This type of ligands can be easily prepared by reaction of an alcohol with phosphorus trichloride (PCl_3) in the presence of a base (**A**, **Scheme 1.2**). The base is used to trap the generated HCl, in the presence of which the phosphite would react to afford the undesired phosphonate (**B**, **Scheme 1.2**).



Scheme 1.2

Symmetrically substituted monophosphite ligands, containing various aliphatic chains, as well as aryl monophosphites containing 2,4-substituted phenyl groups and also naphthyl groups (**Figure 1.4**) have been extensively used in homogeneous catalysis.[72,73,74] An interesting variation of these ligands was the inclusion of fluorinated alkyl chains,[75] which allowed their solubility in supercritical CO_2, leading to efficient biphasic systems with the advantageous possibility of catalyst recycling.

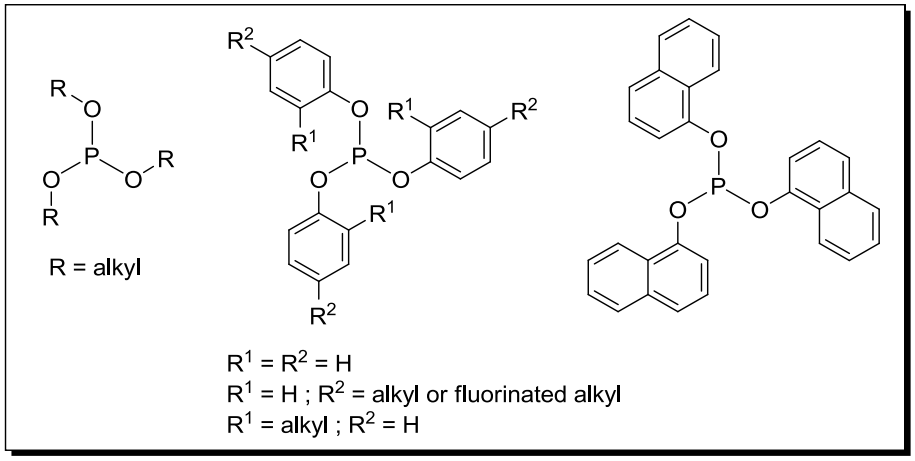
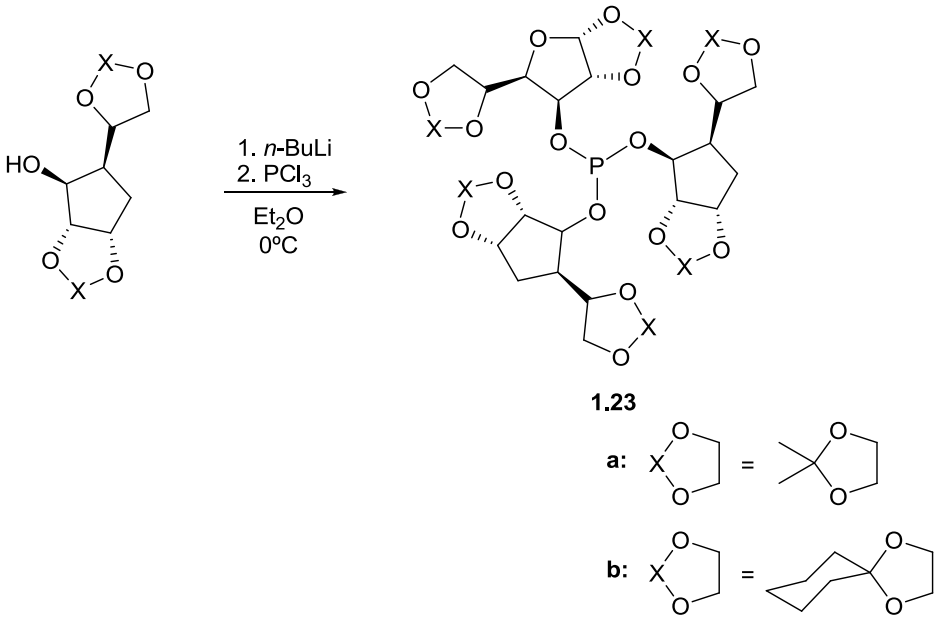


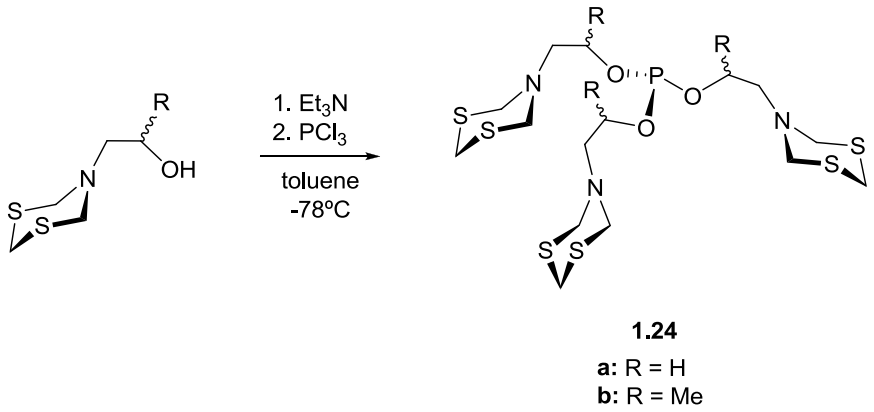
Figure 1.4 – General structures of most common trisubstituted monophosphites.

Despite the numerous examples of trisubstituted monophosphites, the syntheses of C_3 symmetry chiral phosphite ligands and their applications in asymmetric catalysis were scarcely reported. Some of the most representative examples include the chiral monodentate phosphites **1.23a** and **1.23b**, containing three identical D-glucofuranose units distributed around a C_3 symmetry axis, providing a highly symmetric environment.[76,77] The synthesis of the isopropylidene derived **1.23a** and its coordination studies with Cu(I) were firstly reported by Stolmàr *et al*.[76] The ligand was prepared by deprotonation of the carbohydrate precursor with *n*-BuLi as base, generating the corresponding lithium salt, followed by treatment with PCl_3 (**Scheme 1.3**). Later, Pizzano described the synthesis of the bulkier cyclohexylidene analogue **1.23b**.[77] The Rh(I) complexes of both monophosphites **1.23a** and **1.23b** have been evaluated in the asymmetric hydrosilylation of acetophenone, where variable enantioselectivities (0-58% ee) were achieved, depending on the phosphite nature and the ligand to metal molar ratio.[77]



Scheme 1.3

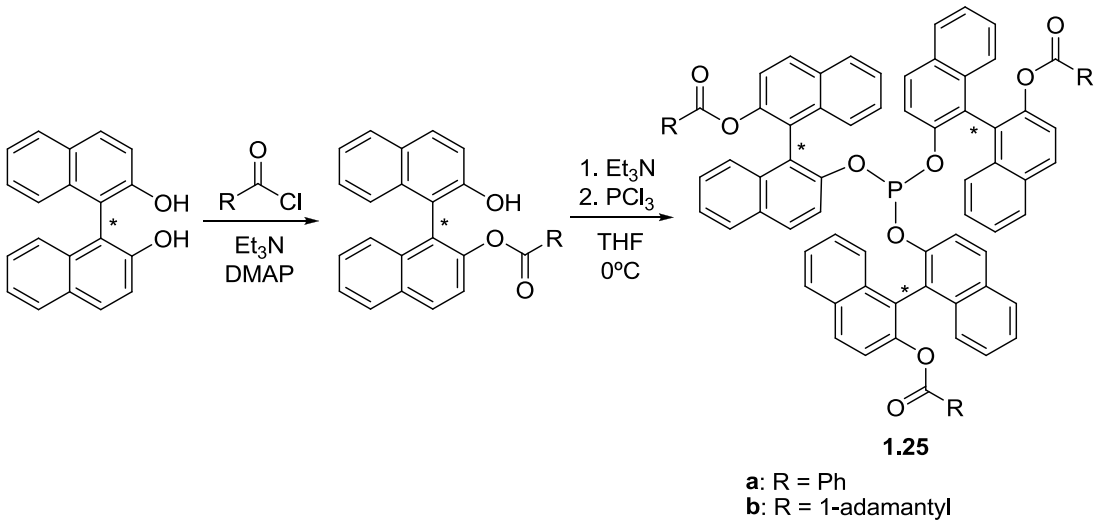
More recently, the monophosphites **1.24a** and **1.24b** derived from different ethanoldithiazinanes were synthesized (**Scheme 1.4**). Molecular modeling studies showed that these tripodal phosphites adopted a preferential conformation, which led to formation of cavities.[78] However, there are no available reports regarding their catalytic applications, until now.



Scheme 1.4

Chiral monophosphites based on the binaphthyl backbone[79,80,81,82] have earned a prominent status, owing to their remarkable efficiency as ligands in asymmetric catalytic reactions, such as the hydrogenation of olefins[83] and allylic substitutions.[84]

In 2009, Reetz described the synthesis of symmetrically substituted tris-binaphthyl chiral monophosphites with helical C_3 symmetry.[85] The ligands containing a benzoyl group (**1.25a**) or an adamantanoyl group (**1.25b**) were synthesized through acylation of (*R*)- or (*S*)-BINOL with benzoyl and adamantanoyl chlorides, respectively, followed by phosphorylation of the corresponding mono-esters with PCl_3, in basic medium (**Scheme 1.5**). Their potentialities as ligands have been exclusively studied in the Rh-catalyzed hydrogenation of homoallylic alcohols, where the use of the sterically hindered adamantanoyl helical derived **1.25b** yielded up to 98% ee.[85] Furthermore, a partially hydrogenated H_8-BINOL analogue of **1.25b** has been applied as ligand in gold-catalyzed enantioselective [4+2] cycloaddition reactions of dienyl-allenes, yielding the chiral cyclization products with up to 92% ee.[86]

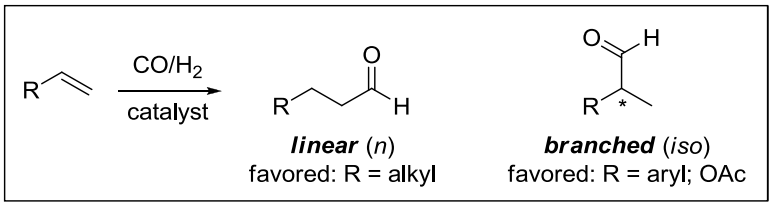


Scheme 1.5

It should be mentioned that these studies were published in parallel with the experimental work described in this dissertation,[87] which is also focused on the development of C_3-symmetry binaphthyl-based monophosphites, containing different pendant hemilabile groups (with ether or ester functionalities), as well as their applications as ligands in a series of asymmetric and non-asymmetric homogeneous catalytic processes, such as rhodium-mediated hydroformylation, palladium-catalyzed hydrovinylation and aminocarbonylation reactions.

1.4 Asymmetric hydroformylation

Hydroformylation – also called *oxo-reaction* – is the addition of hydrogen (H_2) and carbon monoxide (CO) (known as *synthesis gas* or *syngas*), across the π system of a C=C double bond, in the presence of a catalyst (**Scheme 1.6**).[88] The reaction yields the linear and/or the branched aldehydes (the latter containing an asymmetric center), having one carbon atom more than the starting olefin. As a pure addition reaction, in which all raw materials are incorporated in products, the catalytic hydroformylation meets all requirements of a process with total atomic economy.[89]



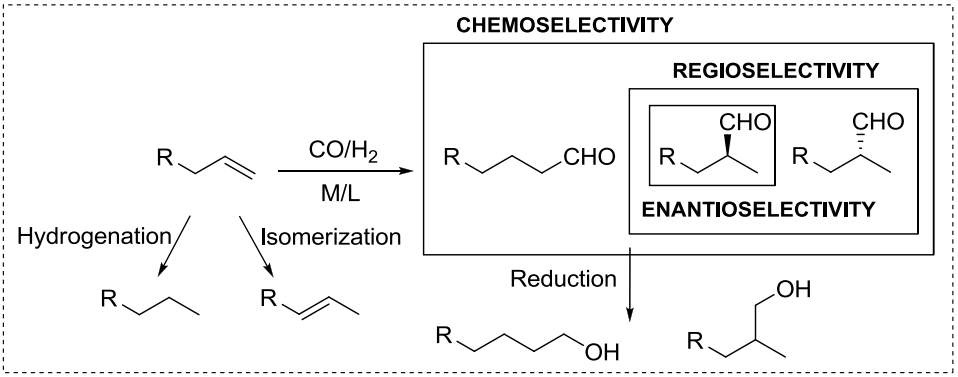
Scheme 1.6

The ratio of linear to branched products formed (*n*/*iso* ratio) has got huge scientific and industrial relevance and may be controlled by the substrate structure or through the use of modulated catalytic systems.[88] The design and synthesis of hydroformylation catalysts has been mainly focused on two distinct strategies: i) developing catalytic systems with high regioselectivity for preferential formation of the linear aldehydes or; ii) developing chiral ligands that lead preferentially to branched aldehydes, containing a new chiral center.

Since its discovery in 1938,[90] the catalytic hydroformylation has turned into the largest scale industrial method of homogeneous catalysis,[91] with production capacities of more than nine million tons/year, being currently one of the most important industrial processes for production of linear aldehydes (with applications in polymer and detergent industries).[92] Nevertheless, industrial application of the asymmetric hydroformylation reaction, leading to chiral branched aldehydes, is still a challenge due to limitation of catalysts regarding the substrate scope, and to the fact that most of chiral ligands are expensive and/or difficult to synthesize.[92]

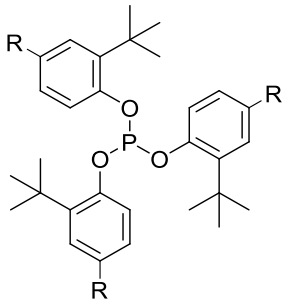
Nowadays, the enormous potential of the hydroformylation reaction can be illustrated by the current interest shown by both academia and industry, resulting in numerous recent publications,[93] including several books[88] and reviews[92,94,95,96,97,98] on the matter. So, a brief perspective is herein presented, giving particular emphasis to the application of the most relevant ligands, considered as historical landmarks.

The asymmetric version of the hydroformylation reaction offers great potential for preparing, in one step, enantiomerically pure aldehydes from olefins.[99,100,101,102] However, to turn it into a viable synthetic alternative for the industrial production of enantiopure fine chemicals,[103,104] the simultaneous control of chemo-, regio- and enantioselectivity (**Scheme 1.7**), while maintaining high activity is one of the most challenging issues to be addressed at both academic and industrial levels.



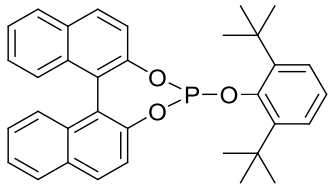
Scheme 1.7

Regarding the chemoselectivity for aldehydes, one can consider that the problem was overcome by the discoveries of Wilkinson,[105] which led to the replacement of cobalt catalysts by more active and chemoselective phosphine-modified rhodium catalysts. Soon after Wilkinson's work, Pruett and Smith have introduced the use of phosphites as rhodium ligands.[106] Later, in the 1980's, van Leeuwen had discovered a peculiar effect of bulky aryl monophosphites (**1.26**),[73] whose rhodium complexes led to very high rates, chemo- and regioselectivities, including in the hydroformylation of disubstituted olefins, allowing the possibility of using milder reaction conditions.[73] Bryant and co-workers at Union Carbide have expanded this work, first by developing other bulky monophosphites (such as **1.27**)[107] and later by focusing on diphosphites.[108]



1.26

a: R = H
b: R = Me



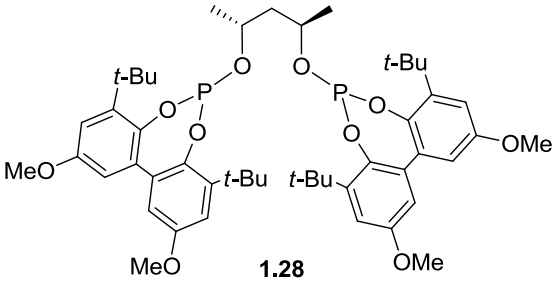
1.27

Concerning enantioselectivity, a long way has been threshed until now, being the most successful systems based, generally, on bidentate chelating phosphorus ligands. The first enantioselective systems in hydroformylation (with up to 90% ee) were reported by Stille and Consiglio, by the use of square-planar complexes of platinum containing chiral diphosphines.[109] However, these catalysts suffered several disadvantages such as low reaction rates, tendency to hydrogenate the substrates and low regioselectivity for the branched products. These issues were mainly overcome by Rh-based catalysts, but only moderate enantioselectivities were obtained using rhodium(I)/diphosphine complexes, being the highest ee (up to 60%) reported in the hydroformylation of styrene with bis-2,4-diphenylphosphinopentane as ligand.[110]

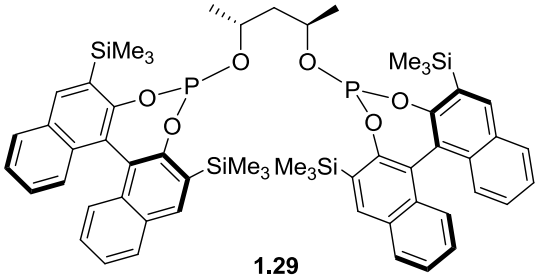
Later on, higher enantioselectivities have been accomplished, using more sophisticated diphosphite,[111] phosphine–phosphite,[112] bis-phospholane,[113] bis-diazophospholane[114] and aminophosphane-phosphinite (AMPP)[115] ligands, with some of the most relevant examples being presented below.

An important advance was achieved by the introduction of bulky diphosphites derived from homochiral (2*R*,4*R*)-pentane-2,4-diol, reported by Babin and Whiteker at Union Carbide.[116] The best results were achieved with Chiraphite **1.28**, which led to 99% regioselectivity for the branched aldehyde, and up to 90% ee in the Rh-catalyzed hydroformylation of styrene. The excellent enantioselectivity obtained with this type of diphosphite ligands was attributed to formation of eight-membered chelates with rhodium(I), through a bis-equatorial coordination mode. The group of van Leeuwen developed a series of similar diphosphite ligands, in which the bisphenol groups were replaced by (*R*)- or (*S*)-binaphthyl units.[117] The highest enantioselectivity (87% ee) in

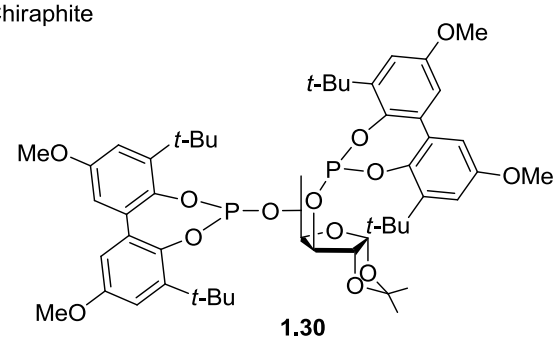
the asymmetric hydroformylation of styrene was obtained with the ligand **1.29**, derived from (*2R,4R*)-pentane-2,4-diol and (*S*)-binaphthyl derivatives containing bulky trimethylsilyl substituents at the 3- and 3'-positions.[117b] Another relevant class of diphosphite ligands are those based on carbohydrate backbones, developed by Claver.[118] The rhodium(I) complex of **1.30**, containing a three-carbon bridge, achieved 93% ee, together with 98% of *iso*-regioselectivity, in styrene hydroformylation.



1.28
Chiraphite

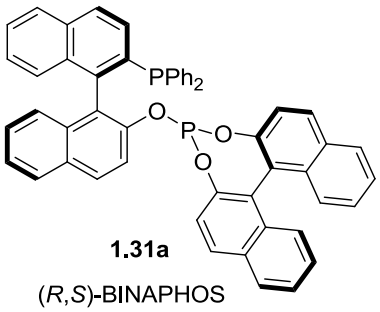


1.29



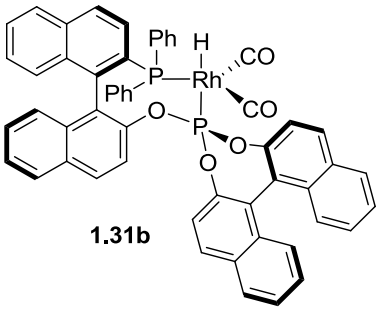
1.30

The major breakthrough in asymmetric hydroformylation came from Takaya's laboratory with the synthesis of (*R*,*S*)-BINAPHOS **1.31a**.[112] This paradigmatic ligand was found to lead to high enantioselectivities for a variety of olefins. Up to 95% ee together with 91% regioselectivity towards the branched product was obtained in the hydroformylation of styrene, and more than 90% ee with a range of other substrates, such as functionalized and internal alkenes.[119] HP-NMR studies showed that the C_1-symmetric ligand **1.31a** coordinate to Rh(I) in equatorial-axial fashion, in which the more σ-donor phosphine P atom sits in the plane with the CO ligands, while the more π-accepting phosphite P atom binds apical to the hydride, and no interchange is observed at any temperature (**1.31b**). This unique dissymmetric environment in a single catalytically active species seems to be an important factor for the high enantioselectivity obtained.



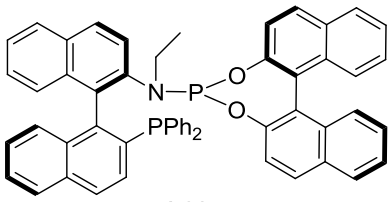
1.31a

(*R*,*S*)-BINAPHOS



1.31b

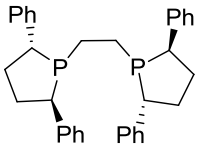
More recently, Zhang and coworkers synthesized the mixed phosphine–phosphoramidite ligand (*R*,*S*)-YANPHOS **1.32**,[120] from the chiral NOBIN (2-amino-2'-hydroxy-1,1'-binaphthyl). The crowded *N*-substituent was intended to supply a conformationally rigid structure able to provide a deeper and more closed chiral pocket than the corresponding BINAPHOS complex, expecting it could lead to improved asymmetric induction. The YANPHOS ligand produced indeed a better performance than BINAPHOS, in terms of conversions and enantioselectivity, for a number of substrates,[121] under mild conditions, providing 99% ee along with 90% iso-regioselectivity, in the Rh-catalyzed hydroformylation of styrene.[120,121]



1.32

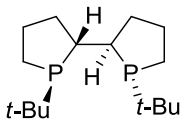
(*R*,*S*)-YANPHOS

Furthermore, the application of bisphospholane ligands, such as Ph-BPE (**1.33**), Tangphos (**1.34**) and the phosphacyclic diphosphine Binapine (**1.35**), which were originally developed for asymmetric hydrogenations, has been reported by Klosin *et al.*, achieving up to 94% ee in the Rh-catalyzed hydroformylation of several olefins.[113,114] The same authors reported the use of bis-diazaphospholane ligand **1.36** in the asymmetric hydroformylation of styrene, vinyl acetate and allyl cyanide, achieving for these substrates 89%, 96% and 87% ee, respectively.[122]



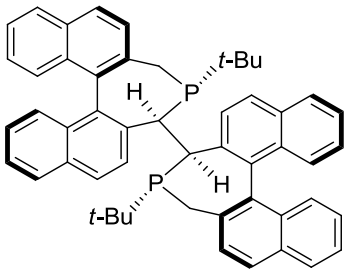
1.33

(*R*,*R*)-Ph-BPE



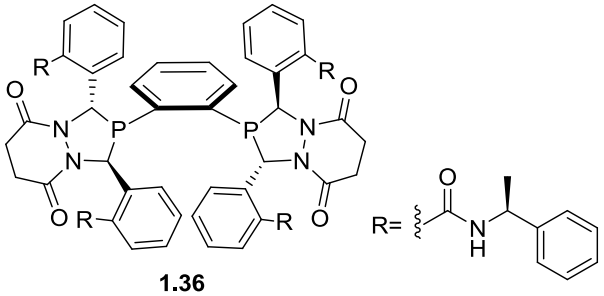
1.34

(*S*,*S*,*R*,*R*)-Tangphos



1.35

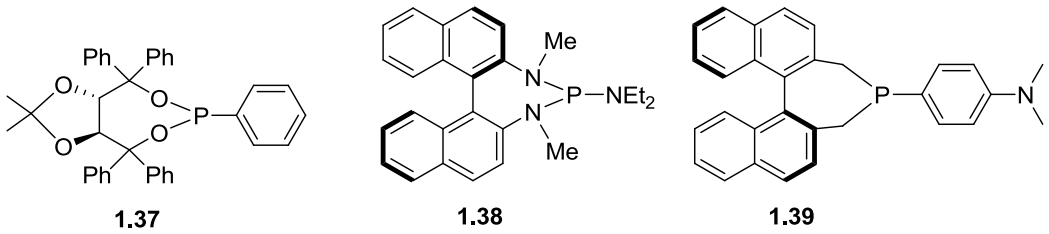
(*R*)-Binapine



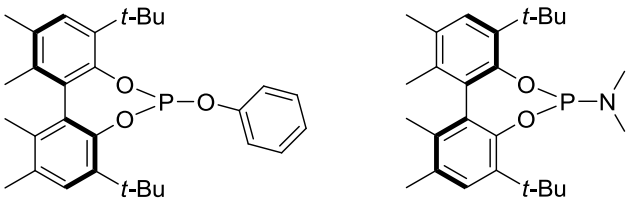
1.36

Despite the evident triumph of bidentate ligands, there are also a few reports concerning the use of rhodium(I) complexes containing monodentate phosphorus donor ligands in enantioselective hydroformylation. Indeed, they were often able to provide higher catalytic activity than their bidentate counterparts, however only moderate enantioselectivities have been achieved so far.

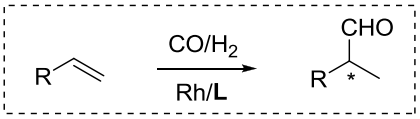
Some examples of employed monodentate chiral phosphorus ligands include the TADDOL-based phosphonite **1.37**,[123] which provided very good regioselectivity (95%) but induced only 20% ee, and the binaphthyl-based diazaphospholidine **1.38**,[124] which gave up to 37% ee in the Rh-catalyzed asymmetric hydroformylation of styrene. Recently, Beller reported the use of several monodentate phosphepine ligands.[125] The best enantioselectivity was achieved with **1.39** (48% ee), which albeit modest, is the highest ever recorded in the asymmetric hydroformylation of styrene with a monodentate ligand.[125] The monophosphite ligand **1.40** was applied in the Rh-catalyzed asymmetric hydroformylation of styrene and allyl cyanide, providing high activities and regioselectivities, although with moderate enantioselectivities (38% and 43% ee, respectively, for each substrate).[126] Furthermore, Ojima and coworkers reported the use of biphenyl-based phosphoramidite **1.41** in Rh-catalyzed asymmetric hydroformylation of allyl cyanide,[127] which led to the highest enantiomeric excess (80% ee) ever reported for this reaction with a monodentate chiral ligand (**Scheme 1.8**).



1.37 **1.38** **1.39**



1.40 **1.41**



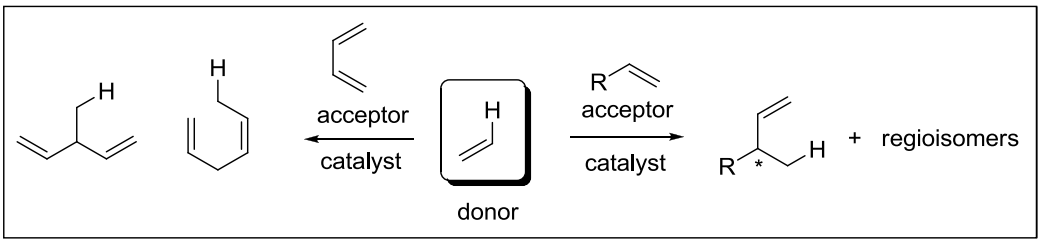
	Ligand (**L**)	Regio (%)	ee (%)
R = Ph	**1.37**	95	20
	1.38	78	37
	1.39	96	48
	1.40	94	38
R = CH_2CN	**1.40**	84	43
	1.41	96	80

Scheme 1.8

These promising results, although fairly distant from those obtained with bidentate ligands, indicate that achieving high enantioselectivities through the use of monodentate ligands is possible, but still remains a great challenge. Thus, one of the main goals of this work consisted on the application of monophosphite ligands in Rh-catalyzed hydroformylation reactions, whose results are presented in Chapter 3, section 3.2.

1.5 Asymmetric hydrovinylation

The hydrovinylation reaction can be defined as the addition of ethylene to the double bond of an alkene, in presence of a metal catalyst. It can also be regarded as the heterocodimerization of ethylene with another olefin.[13,128,129] From a purely formal perspective, ethylene can be viewed as the donor molecule, while the other alkene as the acceptor. If the acceptor is an unconjugated olefin, the reaction is a 1,2-hydrovinylation, while the addition of ethylene over a 1,3-diene moiety can result either in 1,2- or a 1,4-hydrovinylations (**Scheme 1.9**).



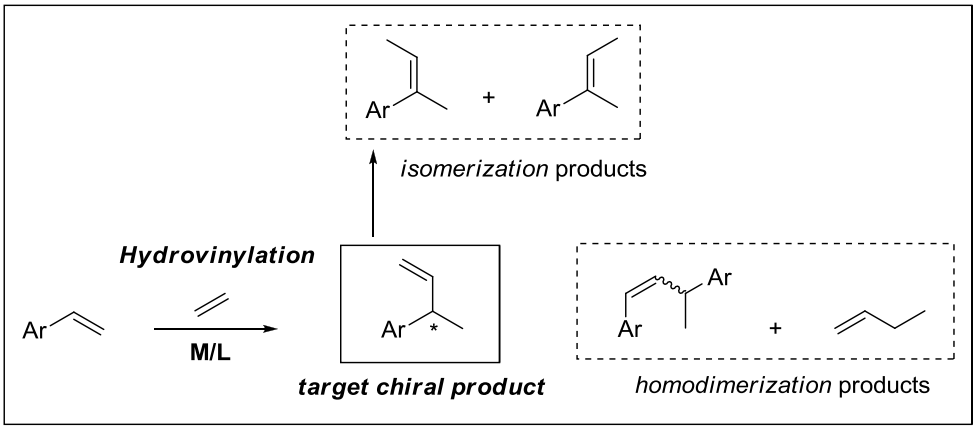
Scheme 1.9

The catalytic hydrovinylation was first reported back in 1965, by Alderson *et al.* who described the use of hydrated rhodium and ruthenium chloride complexes to perform the codimerization of ethylene, at high pressures, with a variety of olefins, including styrene and butadiene.[130] In early studies, in addition to rhodium, other metals such as ruthenium, cobalt, palladium, and nickel were also used. However, in most cases, low selectivities were obtained due to isomerization of the initially formed 3-arylbut-1-enes and oligomerization of the starting olefins.[131,132,133]

The asymmetric version of the hydrovinylation reaction[134,135] was early explored by Wilke and coworkers in 1972, who described the hydrovinylation of 1,3-cyclooctadiene, norbornene and norbornadiene with Ni(II) systems.[136] Other works on enantioselective hydrovinylation have been carried out, using cobalt[137,138] and ruthenium[139] complexes. However, Ni(II)[140,141] and Pd(II)[142,143] organometallic precursors modified with *P*-donor ligands have been the most representative and extensively studied systems, clearly being the ones which provide the highest activities and selectivities.[13,135]

The scope of the hydrovinylation reaction is often limited by the nature of the olefin since excellent regio- and stereoselectivity can be exclusively achieved with conjugated dienes[138] and strained olefins[144] as substrates, or via intramolecular reactions.[145] The excellent reaction yields using nickel systems led to the proposal of a protocol for the synthetic application of the process.[146,147,148] The reaction has been employed in the stereoselective construction of benzylic all-carbon quaternary stereocenters,[149,150,151] a structural motif present in several pharmacologically relevant compounds. Furthermore, it has also been recently used in the total synthesis and functionalization of natural products such as terpene[152] and steroidal derivatives.[153,154]

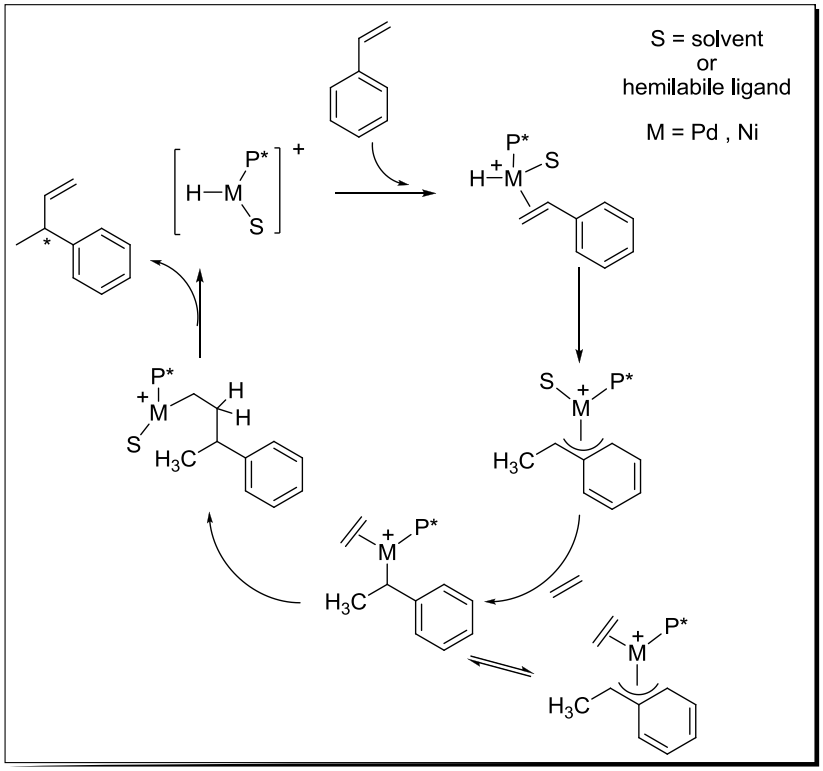
When applied to vinyl arenes, the generation of a new stereogenic carbon atom may provide a short route to 3-arylbut-1-enes, the olefinic precursors of enantiopure 2-arylpropionic acids.[155,156] In general, the excellent regioselectivities obtained are originated by the allylic nature of the intermediates. However, possible side-reactions can often occur, such as the subsequent product isomerisation to more stable 2-arylbut-2-enes, as well as competitive homodimerization reactions (**Scheme 1.10**).



Scheme 1.10

Therefore, the control of the chemo- and enantioselectivity are both critical aspects and the main challenges regarding this catalytic process. The use of chiral monophosphorus ligands revealed to be a crucial feature to promote the enhancement of the activity and enantioselectivity while chelating diphosphines and other bidentate ligands have shown to inhibit the reaction.[148,157]

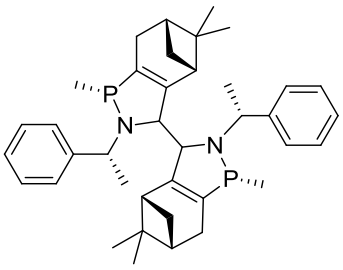
Most of the mechanistic works on catalytic hydrovinylation, usually performed with styrene as model substrate, have showed that there are no fundamental differences between Ni and Pd complexes and therefore both metals are often treated together.[13] It has been largely accepted that the mechanism involves an extremely reactive unsaturated cationic metal hydride intermediate, which is produced by reaction of an allylic metal halide with a weakly coordinated anion, and stabilized with solvent, the substrate or hemilabile ligands. This coordinates and inserts styrene, giving a η^3-benzylic intermediate, while subsequent ethylene coordination, insertion into the metal-carbon bond and β-elimination releases the product and regenerates the hydride, closing the catalytic cycle (**Scheme 1.11**).



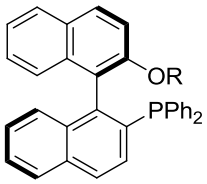
Scheme 1.11

The reaction's enantioselectivity is usually determined by the coordination of the catalyst to one of the enantiotopic faces of the vinylarene, since apparently the subsequent ethylene insertion is non-reversible, under typical conditions. Therefore, to reach high enantioselectivities it is convenient that the monophosphorus ligand offers substituents capable of exhibiting secondary interactions with the metal.[158,159]

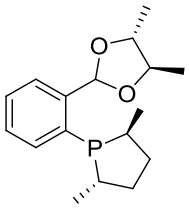
The first breakthrough in asymmetric hydrovinylation came with the discovery of a very complex 1,2-diazaphospholene **1.42** ligand by Wilke,[160] prepared in a multistep process from (*R*)-myrtenal and (*R*)-1-phenylethylamine. This ligand, containing twelve stereogenic centers was used in combination with allyl-nickel halide dimers and organoaluminium Lewis acids, leading to an exceptional 93% ee in the hydrovinylation of styrene. These results were the best in hydrovinylation for many years. The efficiency of the Wilke's catalyst was also demonstrated in supercritical CO_2[161] and in ionic liquid/CO_2 systems, which allowed the catalyst recycling and selective removal of the product from the reaction mixture.[162] However, the ligand **1.42** demonstrated limited possibilities of development, owing to difficult synthetic procedures. Furthermore, other diastereomers of the ligand and ''simplified'' monomeric versions of it have been found to produce very poor catalytic systems.[163] At the end of the 1990's decade, new protocols avoiding the use of the problematic organoaluminium reagents and new ligands capable of inducing exceptional activities and enantioselectivities began to be developed.[146,147,148]



1.42
97% selectivity
93% ee



1.43
R = H, Me, Bn, *i*-Pr, C(O)CH_3
up to 93% selectivity
up to 80% ee

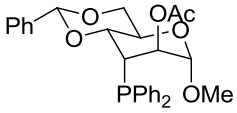


1.44
99% selectivity
91% ee

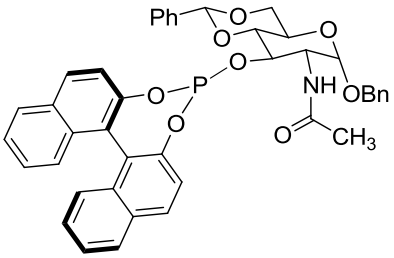
Monophosphine ligands, such as 2-diphenylphosphino-2'-alkoxy-1,1'-binaphthyl (MOP type[164]) derivatives **1.43** have been early applied by RajanBabu in Ni(II) catalyzed hydrovinylation reactions of vinylarenes,[165] with enantioselectivities varying between moderate and good. Synergistic effects between coordination ability of the stabilizing anion and the presence of a hemilabile group in the ligand were found to be crucial to achieve a good catalytic performance. Later, the same author described the efficient application of fine-tuned phospholanes with hemilabile pendant groups, designed on

the basis of working models for asymmetric induction.[166] The secondary interactions with the metal have demonstrated again to be decisive in the hydrovinylation of prototypical vinylarenes, with the Ni-complex of ligand **1.44** having achieved excellent selectivity for the desired 3-arylbutenes (>99%) and up to 91% ee.

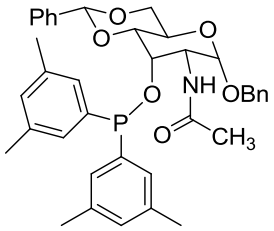
The carbohydrate-derived phosphine **1.45**,[167] phosphite **1.46**[168] and phosphinite **1.47**[168] ligands also gave important contributions in hydrovinylation of several vinylarenes and norbornene, being the most remarkable result achieved with the nickel(II) complexes of phosphinite **1.47**, which afforded 89% of chemoselectivity and 81% ee in the hydrovinylation of styrene.[167,168]



1.45
99% selectivity
42% ee

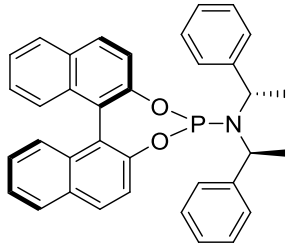


1.46
95% selectivity
62% ee

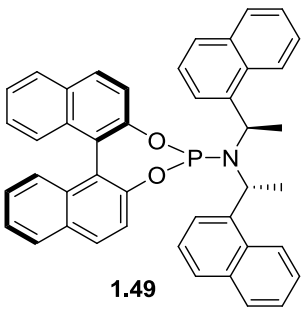


1.47
89% selectivity
81% ee

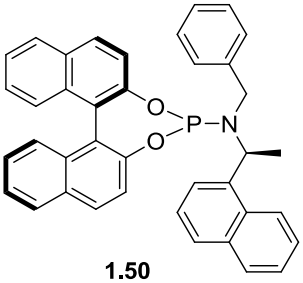
However, the most enantioselective hydrovinylation catalytic systems reported so far have been developed by the groups of Rajanbabu[169] and Leitner,[170,171,172] with the use of binaphthyl-based phosphoramidite ligands. The nickel complexes of **1.48**, **1.49** and **1.50** achieved chemoselectivities above 99% and enantiomeric excesses higher than 90%, using a diversity of aryl olefins as substrates, whose hydrovinylation products have been used in concise syntheses of biologically relevant targets.[173,174]



1.48

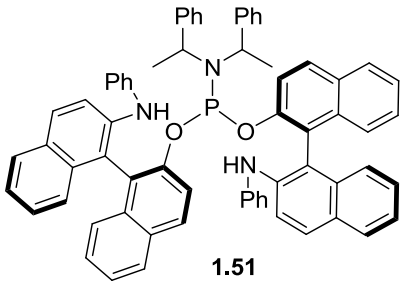


1.49



1.50

In 2013, Franciò[175] reported the use of phosphoramidite ligand **1.51**, containing three non-bridged substituents at phosphorus, including two oxygen-bounded NOBIN moieties with pendant nitrogen atoms, in the enantioselective hydrovinylation of styrene. The ligand **1.51** gave rise to active Ni(II) catalysts, leading to almost perfect selectivity (99%) and ee up to 91%.



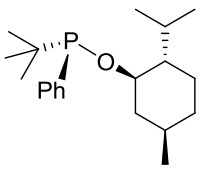
1.51

99% selectivity
91% ee

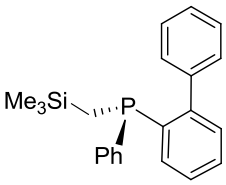
Although initial studies on Pd-based systems were reported to produce extensive polymerization and a significant amount of linear products,[132,176] recent works carried out by the groups of Muller[177,178] and Vogt[142] proved that Pd complexes with suitable ligands are also competent systems for asymmetric hydrovinylation.

Most of these systems consisted of allyl-palladium complexes containing chiral monodentate ligands, which were often able to operate at room temperature. This constitute the most important advantage of Pd-based systems over nickel(II) catalysts, which albeit being more active, usually require very low temperatures (below 0°C) to achieve high chemo- and enantioselectivities. Another remarkable benefit of palladium-based systems with chiral monophosphorus ligands is the lack of ethylene dimerization, as result of the formation of very stable Pd-allylic intermediates that favor coordination and insertion of the vinylarene at the beginning of the catalytic cycle, over the coordination of less sterically hindered ethylene.

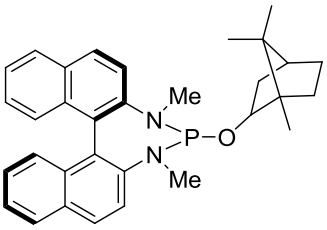
Among the most efficient catalysts, palladium π-allylic complexes of *P*-chiral phosphinite **1.52**,[142] phosphine **1.53**[179] and binaphthyl-based diamidophosphite **1.54**[180] led to very high chemoselectivities and gave up to 86%, 83% and 90% ee, respectively, in the hydrovinylation of styrene.



1.52
94% selectivity
86% ee

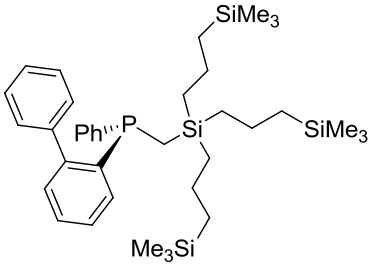


1.53
98% selectivity
83% ee



1.54
93% selectivity
90% ee

Furthermore, dendritic materials functionalized with *P*-stereogenic phosphines have been recently applied in Pd-catalyzed hydrovinylation.[181,182] The palladium complex of the carbosilane dendron **1.55** achieved high chemo- and enantioselectivity (up to 82% ee) in the hydrovinylation of styrene, however with no clear improvements with respect to the corresponding mononuclear complex.



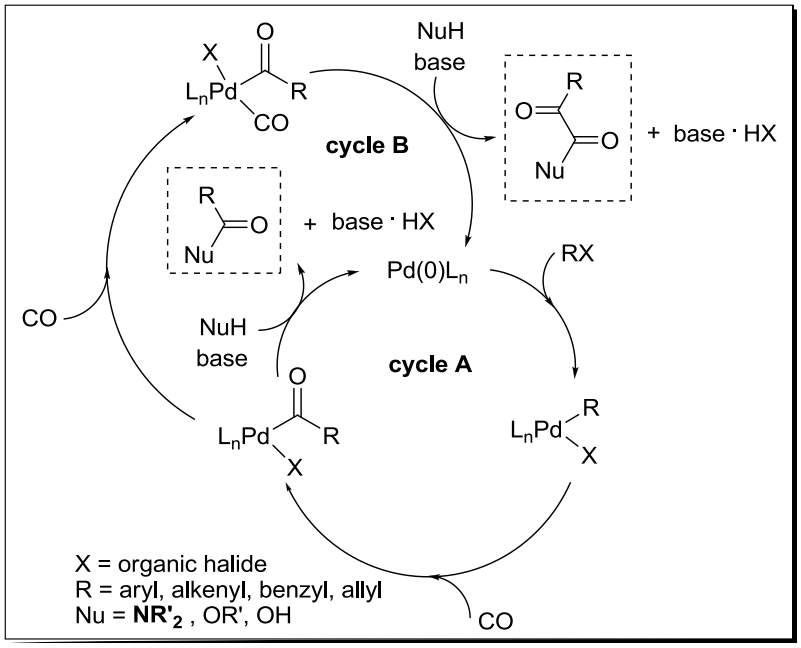
1.55
97% selectivity
82% ee

In sum, the design and synthesis of phosphorus ligands with specific electronic and steric requirements are essential aspects in the development of active and selective hydrovinylation catalytic systems, which relies on ligand tuning to bring about optimum results. Although a huge body of work on the chemistry of phosphine, phosphinite, phosphoramidite and aminophosphine ligands has been carried out, there are only few examples on the use of monophosphite ligands in asymmetric hydrovinylation reactions. Furthermore, ligands containing potentially hemilabile groups may offer great opportunities for increasing the enantioselectivity of the process, as result of the possible dynamic interaction with the metal center. Therefore, studies on the synthesis of allyl-palladium complexes containing *P*,*O*-monophosphites and their application in styrene hydrovinylation are described in Chapter 3, section 3.3.

1.6 Catalytic aminocarbonylation

The term carbonylation covers a large number of closely related reactions that have in common the incorporation of a carbonyl group into a substrate by the addition of CO to an aryl-, benzyl- or vinyl halide (or *pseudohalide*), generally catalyzed by palladium complexes, in the presence of a nucleophile (**Scheme 1.12**).[183]

Palladium-catalyzed carbonylation reactions were first reported by Heck[184] almost 40 years ago. Since then, carbonylation has become a valuable tool for organic synthesis, being extensively applied to generate a range of carbonyl compounds, including various carboxylic acid derivatives with high synthetic relevance.[185] The enormous potential of these reactions is illustrated by the large number of reviews published on the subject[186,187,188,189] and an excellent book recently edited by Kollár.[183]



Scheme 1.12

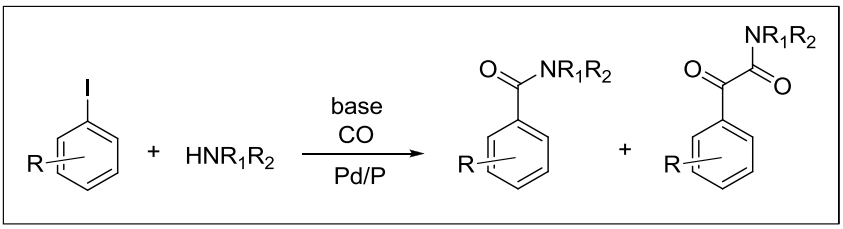
The process follows a general pathway in which the organic halide undergoes oxidative addition with palladium(0), resulting in a palladium(II) complex. The coordination of carbon monoxide and subsequent migratory insertion form an acylpalladium species, which is susceptible to attack by nucleophiles (alcohols, water or amines). In the presence of base, the reaction yields the coupled products, forming

esters from alcohols (*alkoxycarbonylation*), carboxylic acids from water (*hydroxycarbonylation*) or amides in presence of amine nucleophiles (*aminocarbonylation*), while the reductive elimination of HX regenerates the palladium(0) catalyst (**Scheme 1.12**, cycle A). In the cases of double carbonylation,[190,191] which are usually consequence of higher CO pressures, the mechanism proceeds via CO insertion into the Pd–R bond before reductive elimination occurs (**Scheme 1.12**, cycle B). Typically, the reactions require a stoichiometric amount of base to regenerate the catalyst. In line with the C–X bond energy, the rate of the oxidative addition of the organic halide to an electronically unsaturated Pd complex decreases in the order: C–I > C–OTf ≥ C–Br >> C–Cl >> C–F.[192]

Pd-catalyzed aminocarbonylation reactions, in which the nucleophile is an amine, have received significant attention by both academy and industry, since it has become an easy and practical method for the synthesis of amides.[193] Amides constitute, in fact, one of the most important functional groups in contemporary chemistry, being essential for sustaining life, for instance, linking the amino acids in proteins. They are found in numerous natural products and are some of the most prolific moieties in modern pharmaceutical molecules.[194] Despite their obvious importance, the majority of amide bond syntheses require stoichiometric amounts of coupling reagents, making them generally expensive and wasteful procedures.[195] In advantage, the use of amines as nucleophiles, under carbonylation conditions, provides a straightforward route for the desired amide functionality without producing stoichiometric amounts of waste, which constitute a remarkable advance in chemical industry.[186,196] Herein are presented some of the most relevant aspects regarding catalytic aminocarbonylation, giving special emphasis to the catalytic systems used in this reaction and selected examples of its synthetic applications.

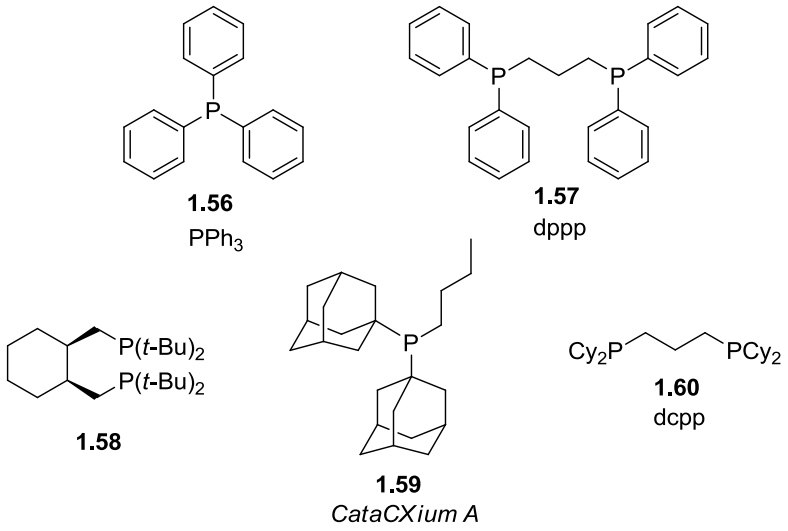
Over the last decades, a large number of aryl and alkenyl halides have been extensively applied as substrates in aminocarbonylation reactions, using a diversity of aliphatic and aromatic primary or secondary amines, as nucleophiles. Among the organic halide derivatives, iodo-aromatics and iodo-alkenes possess a special role due to the presence of a more polarizable iodo leaving group enabling facile reactions under mild reaction conditions.[197]

In general, the reactions of iodoarenes with amine nucleophiles lead to the formation of aryl carboxamides and ketocarboxamides, as a result of competitive aminocarbonylation and double carbonylation processes, respectively (**Scheme 1.13**).



Scheme 1.13

The reaction's selectivity is affected by several factors, such as CO pressure, reaction temperature, the choice of the base used as hydrogen halide scavenger, electronic and steric properties of the amine nucleophile and properties/functional groups of the iodoarenes themselves.[197] Although the structure of the palladium precursor and the properties of the phosphine ligands are considered of minor importance, different precursors have been applied in aminocarbonylation reactions over the years, mostly Pd(II) complexes but also Pd(0) compounds. The active catalytic intermediates are generally obtained from fully formed complexes, such as commercially available $Pd(PPh_3)_4$ and $Pd_2(dba)_3$, which generate the active catalytic intermediates by ligand dissociation or exchange, or they can be prepared *in situ* by the addition of phosphine ligands to a palladium(II) precursor, which are often highly stable, and easier to store and to handle. In most of the cases, palladium complexes containing aryl and alkyl monophosphines, have been successfully used, being Pd/**1.56** considered as the most efficient catalysts for this reaction.[198] The diphosphine **1.57** has also been applied in some cases, however it is known that bidentate ligands often lead to mixtures of amides, keto-amides or dehalogenation products.[199,200] A remarkable exception was recently reported by Claver and Castillón who described the use of *cis*-1,2-bis[(di-*tert*-butylphosphino)methyl]cyclohexane **1.58** in Pd-catalyzed aminocarbonylation of aryl iodides, achieving high activities and up to 99% chemoselectivity toward monocarboxamides, with a range of amine nucleophiles.[201]

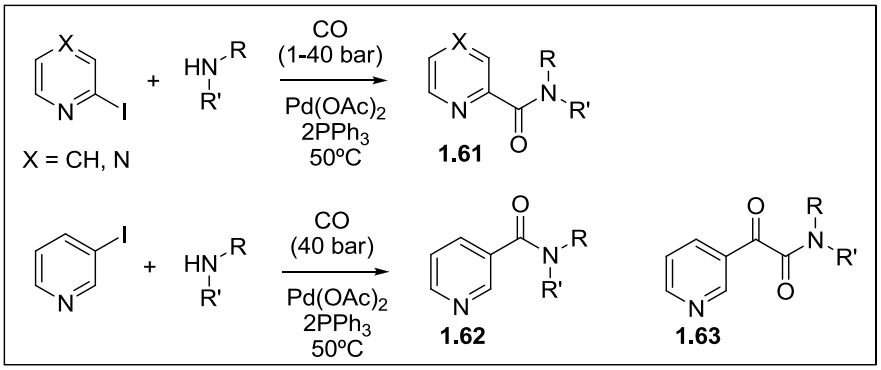


Skoda-Földes and Kollár synthesized ferrocene amides and ferrocene α-ketoamides by Pd-catalyzed aminocarbonylation or double carbonylation of iodoferrocene, respectively, in the presence of $Pd(OAc)_2$/**1.56**, at 40–50 bar CO. The selectivity of the reaction with less sterically hindered secondary amines showed to be highly dependent on the reaction temperature, being the formation of double-carbonylated products favored at 40–60°C, whereas amides were produced almost exclusively at 100°C.[202] Analogous aminocarbonylation reactions of 1,1'-diiodoferrocene led to 1'-iodoferrocenecarboxamides and 1'-iodoferrocenylglyoxylic amide products.[203]

Although the preparation of primary amides via aminocarbonylation is rather restricted due to low nucleophilicity and high toxicity of ammonia, Beller reported the first application of ammonia in palladium-catalyzed aminocarbonylation of aryl halides, where the best results were achieved by the use of a catalytic system consisting of $Pd(OAc)_2$ and commercially available di-1-adamantyl-*n*-butylphosphane (CataCXium A, **1.59**).[204]

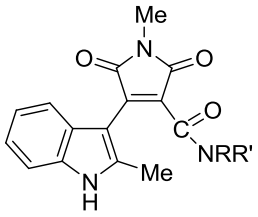
Kollár also described a methodology for the synthesis of primary amides and ketoamides by sequential carbonylation/deprotection, which involved the treatment of aryl and alkenyl iodides with *tert*-butylamine under 1 bar CO, in the presence of $Pd(OAc)_2/PPh_3$. After isolation, the products were heated with *tert*-butyldimethylsilyl triflate to obtain the corresponding primary derivatives.[205]

Palladium-catalyzed aminocarbonylation has proved to be an efficient method for the functionalization of *N*-containing iodo-heteroaromatics.[206] The position of the iodo-substituent relative to the nitrogen atom was a crucial factor for the chemoselectivity towards mono- and di-carbonylated products, with 2-iodopyridine and iodopyrazine giving amides **1.61**, while 3-iodopyridine gave mixtures of carboxamides **1.62** and 2-keto-carboxamides **1.63** (**Scheme 1.14**).[207]



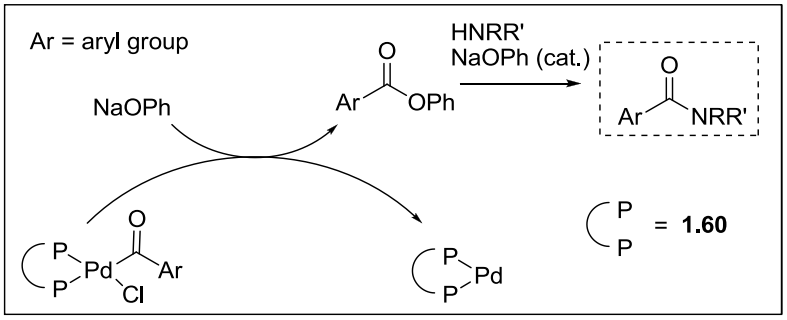
Scheme 1.14

Beller prepared various aromatic and heteroaromatic amides from the corresponding bromoarenes by making use of $Pd(OAc)_2$/**1.59** as catalytic system.[208] Compared to most known carbonylation protocols, the reactions proceeded at low catalyst loadings (<0.5 mol% Pd) to give the desired compounds in excellent yields. More recently, this catalyst was applied to synthesize potentially bioactive 3-aminocarbonyl-4-indolylmaleimides (**1.64**), from 3-bromoindolylmaleimide.[209]



Schnyder and Indolese demonstrated that the scope of the aminocarbonylation could be expanded to the synthesis of unsymmetrical aroyl acyl imides by treating aryl bromides with primary amides or sulfonamides under mild conditions.[210]

Buchwald has recently disclosed the synthesis of a range of aromatic amides through Pd-catalyzed aminocarbonylation of the corresponding aryl chlorides using 1 atm of CO, promoted by the dual role of sodium phenoxide as additive (**Scheme 1.15**).[211] The optimal ligand proved to be the electron rich bulky diphosphine **1.60**, which has been demonstrated to aid both oxidative addition and acyl migration.

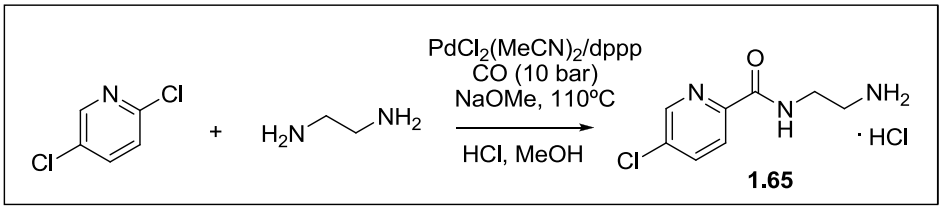


Scheme 1.15

Similarly to aryl halides, halo-alkenes of various structures have been aminocarbonylated, resulting in α,β-unsaturated carboxamides.[212,213] The major difference to the corresponding aromatic substrates lies in the lack of double carbon monoxide insertion, *i.e*., the formation of 2-ketocarboxamides is not observed. For instance, the aminocarbonylation of α-iodostyrene and α,α'-diiodo-1,4-divinylbenzene, in the presence of simple amines and amino acid methyl esters under mild conditions, gave *N*-substituted phenylacrylamides, formed chemoselectively in up to 83% yield.[214]

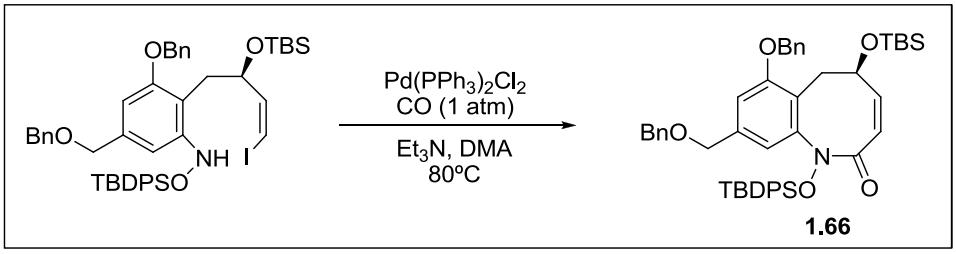
Aminocarbonylation reactions of several aryl and alkenyl halides, triflates and tosylates have been applied in the selective syntheses of numerous biologically active compounds and natural products.[215,216,217] Likewise, various types of complex skeletons were functionalized as well, yielding amide-functionalized compounds with high synthetic relevance, including steroids,[218] alkaloids[219] and indole[220] derivatives.

An important example of the application of aminocarbonylation reactions in industrial processes is the synthesis of *Lazabemide* **1.65**, a monoamine *oxidase* B inhibitor used as an anti-parkinson agent, which is produced in one-step by Hoffmann–La Roche laboratories, through the direct aminocarbonylation of 2,5-dichloropyridine with ethylenediamine, using a palladium/dppp catalyst (**Scheme 1.16**).[221]



Scheme 1.16

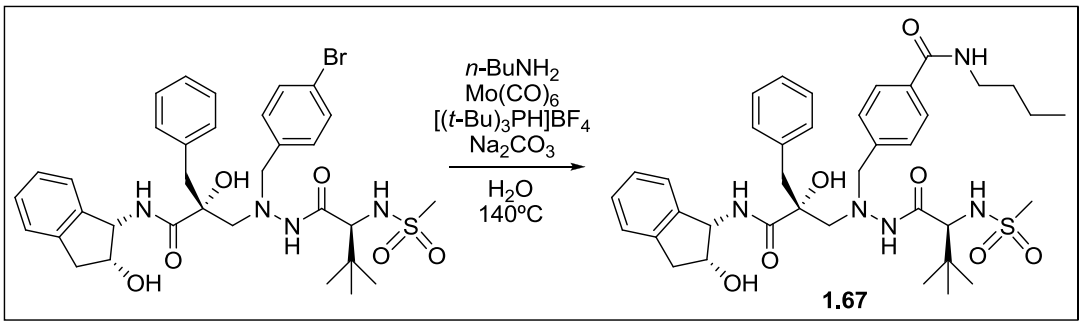
In addition to intermolecular aminocarbonylations, intramolecular reactions are also of enormous interest, since cyclocarbonylation of amino-substituted aryl/vinyl halides enables the synthesis of high valuable lactams.[222] A prominent example of Pd-catalyzed lactamization is found in the synthesis of a benzazocine core of *FR900482* **1.66**, a drug with anticancer activity (**Scheme 1.17**).[223]



Scheme 1.17

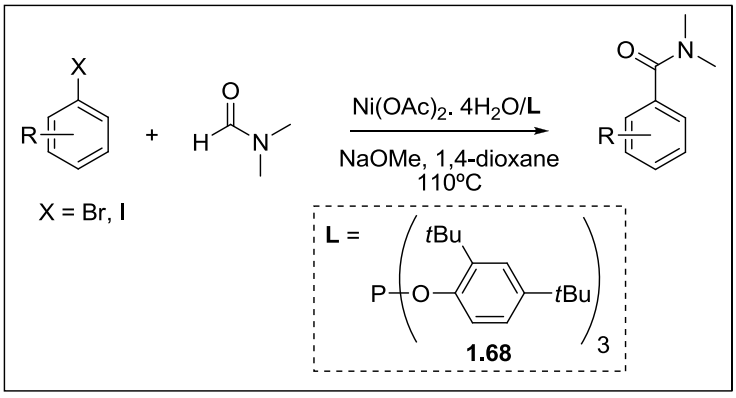
In order to develop environmentally sustainable methodologies for preparation of amides, the use of nonvolatile ionic liquids as reaction media was reported in Pd-catalyzed aminocarbonylation reactions. Some of these catalytic systems achieved higher activities than conventional homogeneous systems under standard conditions, and offered the possibility of recycling and reuse in several consecutive batches, without activity loss.[224,225] Furthermore, efforts have also been proposed to develop methods that suppress the direct use of carbon monoxide. Several metal carbonyls including $Ni(CO)_4$,[226] $Mo(CO)_6$,[227] $Cr(CO)_6$,[227] $W(CO)_6$,[227] carbamoylstannanes[228] and carbamoylsilanes[229] have been used for *in situ* generation of carbon monoxide. Furthermore, transition metal-catalyzed aminocarbonylation using DMF in strongly basic condition as a source of carbon monoxide and dimethylamine, have also been reported both under thermal[230,231] and microwave irradiation.[232] For instance, an

aminocarbonylation procedure performed in aqueous media, using $Mo(CO)_6$ as carbon monoxide source was reported by Larhed, in the microwave assisted synthesis of **1.67**, a novel HIV-1 protease inhibitor (**Scheme 1.18**).[233]



Scheme 1.18

Although the most common aminocarbonylation systems involve palladium/phosphine complexes as catalytic precursors, an efficient nickel-based catalyst has been recently reported, in the aminocarbonylation of different aryl halides using DMF as an amide source, in presence of sodium methoxide and a bulky triarylphosphite **1.68**, as ligand (**Scheme 1.19**).[230,234]



Scheme 1.19

Considering the enormous relevance of aminocarbonylation reactions for generating high valuable amides, it was also one of the main goals of the present work to explore this reaction as a tool for the synthesis of different families of amides, ketoamides and dicarboxamides. The results are presented in Chapter 4.

1.7 Perspectives and aim of the study

Chemical reactions that generate new C–C bonds by incorporation of cheap and abundant feedstock carbon sources (such as carbon monoxide and simple olefins like ethylene) into organic molecules, in an atom-economical mode, are among the most relevant transformations in organic chemistry.

In this context, the development of novel catalytic systems with improved performance for known reactions is one of the key challenges of current chemical research. Although there is no universal approach to the discovery of new molecular catalysts, several parameters must be often optimized in order to achieve the highest levels of reactivity and selectivity, the most crucial of which is perhaps the design of the ligand. Phosphorus (III) compounds can be considered as one of the most important classes of ligands, since they found widespread applications not only in organometallic chemistry but also in homogeneously catalyzed industrial processes. Furthermore, ligands containing electronically divergent donor atoms (*hemilabile*) have been intensively investigated in recent times, since it is desirable that they are able to reversibly open or protect coordination sites and stabilize reactive transition metal species during the course of catalysis.

More than ever, synthetic chemists are faced with the requirement of preparing materials in an enantioselective fashion. The key feature for entering this optically active world is the use of asymmetric catalysis, in which the catalytic core is surrounded by ligands that create a chiral environment for a given reaction. The binaphthyl backbone has emerged as one of the most remarkable chiral building blocks for the synthesis of large libraries of phosphorus compounds, which have attracted considerable attention due to their versatility as ligands in asymmetric catalysis. Among them, binaphthyl-based monophosphite ligands represent an outstanding breakthrough, since their straightforward synthesis and easy structural modifications can offer wide opportunities for catalyst design and fine-tuning.

It is well established that rotational symmetry in chiral ligands and metal complexes may also increase the selectivity in chemical reactions. Although a great part of homogeneous catalyzed reactions make use of C_2-symmetry bidentate phosphorus ligands – the so called *privileged ligands* –, the applications of C_3-

symmetric phosphorus ligands represent a relatively recent and groundbreaking concept, while their use in a wide range of catalytic reactions has been scarcely explored.

The purpose of the work presented herein is the development of C_3-symmetry binaphthyl-based monophosphite ligands containing potentially hemilabile groups, as well as the application of their transition metal complexes as catalysts in homogeneous reactions. Their evaluation in enantioselective C-C bond formation reactions, such as hydroformylation and hydrovinylation of aryl olefins are the main goals, considering that both catalytic reactions comprise great interest for preparation of enantiopure products with enormous academic and industrial relevance. Furthermore, aiming the selective synthesis of different families of carboxamides, ketocarboxamides and dicarboxamides with synthetic importance, aminocarbonylation reactions of aryl and alkenyl halides are also explored in this study. A general overview of the catalytic reactions studied in this dissertation is illustrated in **Figure 1.5**.

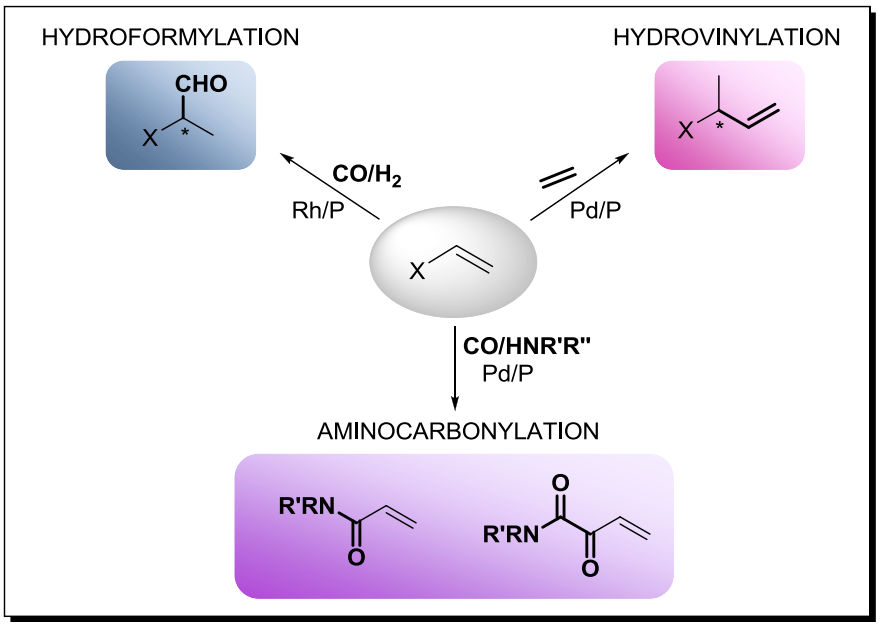


Figure 1.5 – Homogeneous catalytic reactions focused in the present study.

1.8 References

1. P. W. N. M. van Leeuwen, *Homogeneous Catalysis. Understanding the Art*, Kluwer Academic Publishers, Dordrecht, **2004**.

2. K. J. Laidler, *Pure* & *Appl. Chem*. **1996**, *68*, 149.

3. J. L. Figueiredo, M. M. Pereira, J. Faria (Eds.), *Catalysis from Theory to Application. An Integrated Course*, Coimbra University Press, Coimbra, **2008**.

4. G. Duca, *Homogeneous Catalysis with Metal Complexes*, Springer Series in Chemical Physics, Springer - Verlag Berlin Heidelberg, **2012**.

5. B. List, *Chem. Rev.* **2007**, *107*, 5413.

6. M. H. M. Olsson, W. W. Parson, A. Warshel, *Chem. Rev.* **2006**, *106*, 1737.

7. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/index.html (Accessed on October 25th, **2013**).

8. P. C. J. Kamer, P. W. N. M. van Leeuwen (Eds.) *Phosphorus (III) Ligands in Homogeneous Catalysis. Design and Synthesis*, Wiley & Sons, Chichester, **2012**.

9. S. Lühr, J. Holz, A. Börner, *ChemCatChem* **2011**, *3*, 1708.

10. P. Braunstein, N. Naud, *Angew. Chem., Int. Ed.* **2001**, *40*, 680.

11. P. Braunstein, *J. Organomet. Chem.* **2004**, *689*, 3953.

12. M. V. Jiménez, M. I. Bartolomé, J. J. Pérez-Torrente, F. J. Lahoz, L. A. Oro, *ChemCatChem* **2012**, *4*, 1298.

13. R. M. Ceder, A. Grabulosa, G. Muller, M. Rocamora, *Catal. Sci. Technol.* **2013**, *3*, 1446.

14. (a) D. Rageot, A. Pfaltz, *Helvetica Chimica Acta* **2012**, *95*, 2176; (b) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *J. Org. Chem.* **2004**, *69*, 2355.

15. (a) D. B. Grotjahn, *Chem. Lett.* **2010**, *39*, 908; (b) D. B. Grotjahn, *Dalton Trans.* **2008**, 6497.

16. J. C. Jeffrey, T. B. Rauchfuss, *Inorg. Chem.* **1979**, *18*, 2658.

17. M. V. Jiménez, J. J. Pérez-Torrente, M. I. Bartolomé, L. A. Oro, *Synthesis* **2009**, 1916.

18. A. de Leon, J. Pons, J. García-Antón, X. Solans, M. Font-Bardia, J. Ros, *Polyhedron* **2007**, *26*, 2498.

19. S. C. N. Hsu, S.-C. Hu, Z.-S- Wu, M. Y. Chiang, M.-Y. Hung, *J. Organomet. Chem.* **2009**, *694*, 1912.

20. A. Caballero, F. A. Jalón, B. R. Manzano, G. Espino, M. Pérez-Manrique, A. Mucientes, F. J. Poblete, M. Maestro, *Organometallics* **2004**, *23*, 5694.

21. A. Bader, E. Lindner, *Coord. Chem. Rev.* **1991**, *108*, 27.

22. P. Braunstein, Y. Chauvin, J. Nähring, A. DeCian, J. Fischer, A. Tiripicchio, F. Ugozzoli, *Organometallics* **1996,** *15,* 5551.

23. E. Lindner, J. Wald, K. Eichele, R. Fawzi, *J. Organomet. Chem.* **2000**, *601*, 220.

24. E. Lindner, S. Pautz, M. Haustein, *Coord. Chem. Rev.* **1996**, *155*, 145.

25. R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2134.

26. J. R. Farrell, A. H. Eisenberg, C. A. Mirkin, I. A. Guzei, L. M. Liable-Sands, C. D. Incarvito, A. L. Rheingold, C. L. Stern, *Organometallics* **1999**, *18*, 4856.

27. J. L. Ruiz, T. Flor, J. C. Bayón, *Inorg. Chem. Commun.* **1999**, *2*, 484.

28. E. Lindner, K. Gierling, B. Keppeler, H. A. Mayer, *Organometallics* **1997**, *16*, 3531.

29. E. Lindner, M. Schmid, P. Wegner, C. Nachtigal, M. Steimann, R. Fawzi, *Inorg. Chim. Acta* **1999**, *296*, 103.

30. J.-C. Shi, D.-X. Wu, T.-B. Weng, M.-C. Hong, Q.-T. Liu, B.-S. Kang, S.-J. Lu, H.-Q. Wang, *J. Chem. Soc., Dalton Trans.* **1996**, 2911.

31. C. S. Slone, D. A. Weinberger, C. A. Mirkin, *Prog. Inorg. Chem.* **1999**, *48*, 233.

32. M. Kuriyama, K. Nagai, K. Yamada, Y. Miwa, T. Taga, K. Tomioka, *J. Am. Chem. Soc.* **2002**, *124*, 8932.

33. J. Meeuwissen, R. J. Detz, A. J. Sandee, B. de Bruin, J. N. H. Reek, *Dalton Trans.* **2010**, *39*, 1929.

34. C. Roch-Neirey, N. Le Bris, P. Laurent, J.-C. Clément, H. des Abbayes, *Tetrahedron Lett.* **2001**, *42*, 643.

35. D. D. Ellis, G. Harrison, A. G. Orpen, H. Phetmung, P. G. Pringle, J. G. de Vries, H. Oevering, *J. Chem. Soc., Dalton Trans.* **2000**, 671.

36. I. Le Gall, P. Laurent, E. Soulier, J.-Y. Salaün, H. des Abbayes, *J. Organomet. Chem.* **1998**, *567*, 13.

37. P. Espinet, K. Soulantica, *Coord. Chem. Rev.* **1999**, *193-195*, 499.

38. R. Romeo, L. M. Scolaro, M. R. Plutino, A. Romeo, F. Nicolo, A. Del Zotto, *Eur. J. Inorg. Chem.* **2002**, *3*, 629.

39. P. Braunstein, F. Naud, A. Dedieu, M. M. Rohmer, A. DeCian, S. J. Rettig, *Organometallics* **2001**, *20*, 2966.

40. I. D. Kostas, C. G. Screttas, *J. Organomet. Chem.* **1999**, *585*, 1.

41. I. D. Kostas, *J. Organomet. Chem.* **2001**, *626*, 221.

42. I. D. Kostas, C. G. Screttas, *J. Chem Res. (S)* **1999**, 630.

43. M. L. Clarke, D. J. Cole-Hamilton, J. D. Woollins, *J. Chem. Soc*., *Dalton Trans*. **2001**, 2721.

44. M. E. Broussard, B. Juma, S. G. Train, W.-J. Peng, S. A. Laneman, G. S. Stanley, *Science* **1993**, *260*, 1784.

45. L. J. Hounjet, M. Bierenstiel, M. J. Ferguson, R. McDonald, M. Cowie, *Dalton Trans.* **2009**, 4213.

46. L. J. Hounjet, R. McDonald, M. J. Ferguson, M. Cowie, *Inorg. Chem.* **2011**, *50*, 5361.

47. M. V. Jiménez, M. I. Bartolomé, J. J. Pérez-Torrente, D. Gómez, F. J. Mondrego, L. A. Oro, *ChemCatChem* **2013**, *5*, 263.

48. M. V. Jiménez, J. J. Pérez-Torrente, M. I. Bartolomé, E. Vispe, F. J. Lahoz, L. A. Oro, *Macromolecules* **2009**, *42*, 8146.

49. C. Moberg, *Isr. J. Chem.* **2012**, *52*, 653.

50. K. Mikami, M. Lautens (Eds.), *New Frontiers in Asymmetric Catalysis*, Wiley & Sons, New Jersey, **2007**.

51. R. Noyori (Ed.), *Asymmetric Catalysis in Organic Synthesis*, Wiley, New-York, **1994**.

52. (a) S. E. Gibson, M. P. Castaldi, *Angew. Chem., Int. Ed.* **2006**, *45*, 4718; (b) M. P. Castaldi, S. E. Gibson, M. Rudd, A. J. P. White, *Angew. Chem., Int. Ed.* **2005**, *44*, 3432; (c) M. P. Castaldi, S. E. Gibson, M. Rudd, A. J. P. White, *Chem. Eur. J.* **2006**, *12*, 138.

53. (a) M. Bonchio, O. Bortolini, G. Licini, S. Moro, W. A. Nugent, *Eur. J. Org. Chem.* **2003**, 507; (b) M. G. Buonomenna, E. Drioli, W. A. Nugent, L. J. Prins, P. Scrimin, G. Licini, *Tetrahedron Lett.* **2004**, *45*, 7515.

54. C. Moberg, *Angew. Chem., Int. Ed.*, **1998**, 37, 248.

55. S. E. Gibson, M. P. Castaldi, *Chem. Commun.* **2006**, 3045.

56. M. F. Cain, D. S. Glueck, J. A. Golen, A. L. Rheingold, *Organometallics* **2012**, *31*, 775.

57. C. Moberg, *Angew. Chem., Int. Ed.* **2006**, *45*, 4721.

58. (a) S. D. Erickson, J. A. Simon, W. C. Still, *J. Org. Chem.* **1993**, *58*, 1305; (b) F. Gasparrini, D. Misiti, C. Villani, *J. Org. Chem.* **1995**, *60*, 4314; (c) D. Q. McDonald, W. C. Still, *J. Am. Chem. Soc.* **1996**, *118*, 2073.

59. (a) J. van Gestel, A. R. A. Palmans, B. Titulaer, J. A. J. M. Vekemans, E. W. Meijer, *J. Am. Chem. Soc.* **2005**, *127*, 5490; (b) J. J. van Gorp, J. A. J. M. Vekemans, E. W. Meijer, *J. Am. Chem. Soc.* **2002**, *124*, 14759.

60. J. J. Wolff, F. Siegler, R. Matschiner, R. Wortmann, *Angew. Chem., Int. Ed.* **2000**, *39*, 1436.

61. (a) G. Bringmann, R.-M. Pfeifer, C. Rummey, K. Hartner, M. Breuning, *J. Org. Chem.* **2003**, *68*, 6859; (b) T. Fang, D-M. Du, S-F. Lu, J. Xu, *Org. Lett.* **2005**, *7*, 2081.

62. A. Togni, L. M. Venanzi, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497.

63. L. H. Gade, S. Bellemin-Laponnaz, *Chem. Eur. J.* **2008**, 14, 4142.

64. J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2005**, *34*, 664.

65. M. J. Burk, R. L. Harlow, *Angew. Chem., Int. Ed. Engl.* **1990**, *27*, 1462.

66. M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron: Asymmetry* **1991**, *2*, 569.

67. T. R. Ward, L. M. Venanzi, A. Albinati, F. Lianza, T. Gerfin, V. Gramlich, G. M. R. Tombo, *Helv. Chim. Acta* **1991**, *74*, 983.

68. C. Bolm, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *29*, 5101.

69. (a) M. T. Powell, A. M. Porte, K. Burgess, *Chem. Commun.* **1998**, 2161; (b) M. T. Powell, A. M. Porte, J. Reibenspies, K. Burgess, *Tetrahedron* **2001**, *57*, 5027.

70. P. Wyatt, H. Eley, J. Charmant, B. J. Daniel, A. Kantacha, *Eur. J. Org. Chem.* **2003**, 4216.

71. M. J. Baker, P. G. Pringle, *J. Chem. Soc., Chem. Commun.* **1993**, 314.

72. M. B. Dinger, M. J. Scott, *Inorg. Chem.* **2001,** *40,* 856.

73. (a) P. W. N. M. van Leeuwen, C. F. Roobeek, *J. Organomet. Chem.* **1983**, *258*, 343; (b) T. Jongsma, G. Challa, P. W. N. M. van Leeuwen, *J. Organomet. Chem.* **1991**, *421*, 121; (c) A. van Rooy, E. N. Orij, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 34.

74. (a) A. F. Peixoto, M. M. Pereira, A. M. S. Silva, C. M. Foca, J. C. Bayón, M. J. S. M. Moreno, A. M. Beja, J. A. Paixão, M. R. Silva, *J. Mol. Catal. A: Chem.* **2007**, *275*, 121; (b) A. A. Dabbawala, H. C. Bajaj, R. V. Jasra, *J. Mol. Catal. A: Chem.* **2009**, *302*, 97.

75. T. Mathivet, E. Monflier, Y. Castanet, A. Mortreux, J.-L. Couturier, *Tetrahedron* **2002**, *58*, 3877.

76. M. Stolmàr, C. Floriani, G. Gervasio, D. Viterbo, J*. Chem. Soc. Dalton Trans.* **1997**, 1119.

77. A. Suárez, A. Pizzano, I. Fernández, N. Khiar, *Tetrahedron: Asymmetry* **2001**, *12*, 633.

78. R. Colorado-Peralta, A. Xotlanihua-Flores, J. C. Gálvez-Ruíz, S. A. Sánchez-Ruíz, R. Contreras, A. Flores-Parra, *J. Mol. Struct.* **2010**, *981*, 21.

79. M. M. Pereira, M. J. F. Calvete, R. M. B. Carrilho, A. R. Abreu, *Chem. Soc. Rev.* **2013**, *42*, 6990.

80. M. M. Pereira, M. J. F. Calvete, A. R. Abreu, R. M. B. Carrilho, in *Advances in Chemistry Research, Vol. 19*, J. C. Taylor (Ed.), Nova Publishers, New York, **2013**, pp. 111-154.

81. (a) M. T. Reetz, G. Mehler, *Angew. Chem., Int. Ed.* **2000**, *39*, 3889; (b) M. T. Reetz, G. Mehler, A. Meiswinkel, T. Sell, *Tetrahedron Lett.* **2002**, *43*, 7941; (c) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem Int. Ed.* **2003**, *42*, 790; (d) M. T. Reetz, L. J. Goossen, A. Meiswinkel, J. Paetzold, J. F. Jensen, *Org. Lett.* **2003**, *5*, 3099.

82. (a) T. Jerphagnon, J. L. Renaud, P. Demonchaux, A. Ferreira, C. Bruneau, *Adv. Synth. Catal.* **2004**, *346*, 33; (b) A. Iuliano, D. Losi, S. Facchetti, *J. Org. Chem.* **2007**, *72*, 8472; (c) X.-P. Hu, J.-D. Huang, Q.-H. Zeng, Z. Zheng, *Chem. Commun.* **2006**, 293; (d) W. Chen, S. M. Roberts, J. Whittall, *Tetrahedron Lett.* **2006**, *47*, 4263.

83. T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101.

84. K. N. Gavrilov, S. E. Lyubimov, S. V. Zheglov, E. B. Benetsky, V. A. Davankov, *J. Mol. Catal. A: Chem.* **2005**, *231*, 255.

85. M. T. Reetz, H. Guo, J.-A. Ma, R. Goddard, R. J. Mynott, *J. Am. Chem. Soc.* **2009**, *131*, 4136.

86. A. Z. González, F. D. Toste, *Org. Lett.* **2010**, *12*, 200.

87. R. M. B. Carrilho, A. R. Abreu, G. Petöcz, J. C. Bayón, M. J. S. M. Moreno, L. Kollár, M. M. Pereira, *Chem. Lett.* **2009**, *38*, 844.

88. C. Claver, P. W. N. M. van Leeuwen (Eds.), *Rhodium Catalyzed Hydroformylation*, Kluwer Academic Publishers, Dordrecht, **2000**.

89. (a) B. M. Trost, *Science* **1991**, *254*, 1471; (b) B. M. Trost, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

90. O. Roelen (Ruhrchemie AG), *German Patent* 849548, **1938**.

91. H.-J. Arpe (Ed.), *Industrial Organic Chemistry 5th Edition*, Wiley-VCH, Weinhem, **2010**.

92. R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675.

93. (a) G. M. Noonan, J. A. Fuentes, C. J. Cobley, M. L. Clarke, *Angew. Chem., Int. Ed.* **2012**, *51*, 2477; (b) T. T. Adint, G. W. Wong, C. R. Landis, *J. Org. Chem.* **2013**, *78*, 4231; (c) S. H. Chikkali, R. Bellini, B. de Bruin, J. I. van der Vlugt, J. N. H. Reek, *J. Am. Chem. Soc.* **2012**, *134*, 6607.

94. M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpainter, *J. Mol. Catal. A: Chem.* **1995**, *104*, 17.

95. C. Claver, M. Diéguez, O. Pàmies, S. Castillón, *Top. Organomet. Chem.* **2006**, *18*, 35.

96. B. Breit, W. Seiche, *Synthesis*, **2001**, 1.

97. F. Ungváry, *Coord. Chem Rev.* **2002**, *228*, 61.

98. J. Pospech, I. Fleischer, R. Franke, S. Buchholz, M. Beller, *Angew. Chem., Int. Ed.* **2013**, *52*, 2852.

99. A. Gual, C. Godard, S. Castillón, C. Claver, *Tetrahedron: Asymmetry* **2010**, *21*, 1135.

100. S. Gladiali, J. C. Bayón, C. Claver, *Tetrahedron Asymmetry*, **1995**, *6*, 1453.

101. F. Agbossou, J.-F. Carpentier, A. Mortreux, *Chem. Rev.* **1995**, *95*, 2485.

102. J. Klosin, C. R. Landis, *Acc. Chem. Res.* **2007**, *40*, 1251.

103. X. Zheng, B. Cao, T. Liu, X. Zhang, *Adv. Synth. Catal.* **2013**, *355*, 679.

104. X. Wang, S. L. Buchwald, *J. Org. Chem.* **2013**, *78*, 3429.

105. (a) D. Evans, J. A. Osborn, G. Wilkinson, *J. Chem Soc. A.* **1968**, 3133; (b) D. Evans, G. Yagupsky, G. Wilkinson, *J. Chem Soc. A.* **1968**, 2660; (c) C. K. Brown, G. Wilkinson, *J. Chem Soc. A.* **1970**, 2753.

106. (a) R. L. Pruett, J. A. Smith, *J. Org. Chem.* **1969**, *34*, 327; (b) R. L. Pruett, J. A. Smith (Union Carbide Corp.), *South African Patent* 6804937, **1968**.

107. E. Billig, A. G. Abatjoglou, D. R. Bryant, R. E. Murray, J. M. Maher (Union Carbide Corp.), *U.S. Patent* 4599206, **1986**.

108. E. Billig, A. G. Abatjoglou, D. R. Bryant (Union Carbide Corp.), *U.S. Patent* 4668651, **1987**.

109. (a) J. K. Stille, H. Su, P. Brechot, G. Parrinello, L. S. Hegedus, *Organometallics* **1991**, *10*, 1183; (b) G. Consiglio, S. C. A. Nefkens, A. Borer, *Organometallics* **1991**, *10*, 2046.

110. A. M. Masdeu-Bultó, A. Orejon, A. Castellanos, S. Castillón, C. Claver, *Tetrahedron: Asymmetry* **1996**, *7*, 1829.

111. M. Diéguez, O. Pàmies, C. Claver, *Tetrahedron: Asymmetry* **2004**, *15*, 2113.

112. (a) N. Sakai, S. Mano, K. Nozaki, H. Takaya, *J. Am. Chem. Soc.* **1993**, *115*, 7033; (b) K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T. Horiuchi, H. Takaya, *J. Am. Chem. Soc.* **1997**, *119*, 4413.

113. A. T. Axtell, J. Klosin, G. T. Whiteker, C. J. Cobley, M. E. Fox, M. Jackson, K. A. Abboud, *Organometallics* **2009**, *28*, 2993.

114. A. T. Axtell, J. Klosin, K. A. Abboud, *Organometallics* **2006**, *25*, 5003.

115. R. Ewalds, E. B. Eggeling, C. H. Alison, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt, *Chem. Eur. J.* **2000**, *6*, 1496.

116. J. E. Babin, G. T. Whiteker (Union Carbide Corp.), *WO Patent* 93/03839, **1993**.

117. (a) G. J. H. Buisman, E. J. Vos, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Chem. Soc., Dalton Trans.* **1995**, 409; (b) G. J. H. Buisman, L. A. van der Veen, A. Klootwijk, W. G. J. de Lange, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt, *Organometallics* **1997**, *16*, 2929.

118. (a) M. Diéguez, O. Pàmies, A. Ruiz, S. Castillón, C. Claver, *Chem. Eur. J.* **2001**, 7, 3086; (b) M. Diéguez, O. Pàmies, A. Ruiz, C. Claver, *New J. Chem.* **2002**, *26*, 827.

119. (a) K. Nozaki, *Chem. Rec.* **2005**, *5*, 376; (b) R. Tanaka, K. Nakano, K. Nozaki, *J. Org. Chem.* **2007**, *72*, 8671; (c) K. Nakano, R. Tanaka, K. Nozaki, *Helv. Chim. Acta* **2006**, *89*, 1681; (d) F. Shibahara, K. Nozaki, T. Hiyama, *J. Am. Chem. Soc.* **2003**, *125*, 8555; (e) K. Nozaki, T. Matsuo, F. Shibahara, T. Hiyama, *Organometallics* **2003**, *22*, 594.

120. Y. Yan, X. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7198.

121. X. Zhang, B. Cao, Y. Yan, S. Yu, B. Ji, X. Zhang, *Chem. Eur. J.* **2010**, *16*, 871.

122. T. P. Clark, C. R. Landis, S. L. Freed, J. Klosin, K. A. Abboud, *J. Am. Chem. Soc.* **2005**, *127*, 5040.

123. J. -I. Sakaki, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1993**, *76*, 2654.

124. M. T. Reetz, H. Oka, R. Goddard, *Synthesis* **2003**, 1809.

125. G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *J. Mol. Catal. A: Chem.* **2008**, *280*, 148.

126. (a) C. J. Cobley, J. Klosin, C. Qin, G. T. Whiteker, *Org. Lett.* **2004**, *6*, 3277; (b) C. J. Cobley, K. Gardner, J. Klosin, C. Praquin, C. Hill, G. T. Whiteker, A. Zanotti-Gerosa, *J. Org. Chem.* **2004**, *69*, 4031.

127. Z. Hua, V. C. Vassar, H. Choi, I. Ojima, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5411.

128. T. V. RajanBabu, *Synlett* **2009**, 853.

129. G. Hilt, *Eur. J. Org. Chem.* **2012**, 4441.

130. T. Alderson, E. L. Jenner, R. V. Lindsey, *J. Am. Chem. Soc.* **1965**, *87*, 5638.

131. L. S. Pu, A. Yamamoto, S. Ikeda, *J. Am. Chem. Soc.* **1968**, *90*, 7170.

132. M. G. Barlow, M. J. Bryant, R. N. Haszeldine, A. G. Mackie, *J. Organomet. Chem.* **1970**, *21*, 215.

133. K. Kawakami, N. Kawata, K. Maruya, T. Mizoroki, A. Ozaki, *J. Catal.* **1975**, *39*, 134.

134. L. J. Goossen, *Angew. Chem., Int. Ed.* **2002**, *41*, 3775.

135. T. V. RajanBabu, *Chem. Rev.* **2003**, *103*, 2845.

136. B. Bogdanovic, B. Henc, B. Meister, H. Pauling, G. Wilke, *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1023.

137. M. M. P. Grutters, J. I. van der Vlugt, Y. Pei, A. M. Mills, M. Lutz, A. L. Spek, C. Müller, C. Moberg, D. Vogt, *Adv. Synth. Catal.* **2009**, *351*, 2199.

138. R. K. Sharma, T. V. RajanBabu, *J. Am. Chem. Soc.* **2010**, *132*, 3295.

139. G. Jiang, B. List, *Chem. Commun.* **2011**, *47*, 10022.

140. B. Saha, T. V. RajanBabu, *J. Org. Chem.* **2007**, *72*, 2357.

141. G. Franciò, F. Faraone, W. Leitner, *J. Am. Chem. Soc.* **2002**, *124*, 736.

142. R. Bayersdörfer, B. Ganter, U. Englert, W. Keim, D. Vogt, *J. Organomet. Chem.* **1998**, *552*, 187.

143. J. Albert, R. Bosque, J. Magali Cadena, S. Delgado, J. R. Granell, G. Muller, J. I. Ordinas, M. Font Bardia, X. Solans, *Chem. Eur. J.* **2002**, *8*, 2279.

144. R. Kumareswaran, M. Nandi, T. V. Rajanbabu, *Org. Lett.* **2003**, *5*, 4345.

145. U. Boothe, H. C. Rudbeck, D. Tanner, M. Johannsen, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3305.

146. N. Nomura, J. Jin, H. Park, T. V. RajanBabu, *J. Am. Chem. Soc.* **1998**, *120*, 459.

147. T. V. RajanBabu, N. Nomura, J. Jin, B. Radetich, H. Park, M. Nandi, *Chem. Eur. J.* **1999**, *5*, 1963.

148. T. V. Rajanbabu, N. Nomura, J. Jin, M. Nandi, H. Park, X. Sun, *J. Org. Chem.* **2003**, *68*, 8431.

149. W. Shi, J. Xie, S. Zhu, G. Hou, Q. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 2780.

150. A. Zhang, T. V. RajanBabu, *J. Am. Chem. Soc.* **2006**, *128*, 5620.

151. C. R. Smith, H. J. Lim, A. Zhang, T. V. RajanBabu, *Synthesis* **2009**, 2089.

152. A. Zhang, T. V. RajanBabu, *Org. Lett.* **2004**, *6*, 3159.

153. Z. He, C. S. Yi, W. A. Donaldson, *Synlett* **2004**, 1312.

154. B. Saha, C. R. Smith, T. V. RajanBabu, *J. Am. Chem. Soc.* **2008**, *130*, 9000.

155. C. R. Smith, T. V. RajanBabu, *Org. Lett.* **2008**, *10*, 1657.

156. C. R. Smith, T. V. RajanBabu, *J. Org. Chem.* **2009**, *74*, 3066.

157. R. Ceder, G. Muller, J. I. Ordinas, *J. Mol. Catal.* **1994**, *92*, 127.

158. J. Joseph, T. V. RajanBabu, E. D. Jemmis, *Organometallics* **2009**, *28*, 3552.

159. M. Hölscher, G. Franciò, W. Leitner, *Organometallics* **2004**, *23*, 5606.

160. G. Wilke, J. Monkiewicz, H. Kuhn, *U.S. Patent* 4912274, **1990**.

161. A. Wegner, W. Leitner, *Chem. Commun.* **1999**, 1583.

162. A. Bösmann, G. Franciò, E. Janssen, M. Solinas, W. Leitner, P. Wasserscheid, *Angew. Chem., Int. Ed.* **2001**, *40*, 2697.

163. K. Angermund, A. Eckerle, F. Lutz, *Z. Naturforsch., B: J.Chem. Sci.* **1995**, *50*, 488.

164. Y. Uozumi, A. Tanahashi, S. Lee, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 1945.

165. M. Nandi, J. Jin, T. V. RajanBabu, *J. Am. Chem. Soc.* **1999**, *121*, 9899.

166. A. Zhang, T. V. RajanBabu, *Org. Lett.* **2004**, *6*, 1515.

167. H. Park, T. V. RajanBabu, *J. Am. Chem. Soc.* **2002**, *124*, 734.

168. H. Park, R. Kumareswaran, T. V. RajanBabu, *Tetrahedron* **2005**, *61*, 6352.

169. W. Liu, T. V. RajanBabu, *J. Org. Chem.* **2010**, *75*, 7636.

170. N. Lassauque, G. Franciò, W. Leitner, *Eur. J. Org. Chem.* **2009**, 3199.

171. N. Lassauque, G. Franciò, W. Leitner, *Adv. Synth. Catal.* **2009**, *351*, 3133.

172. C. J. Diez-Holz, C. Böing, G. Franciò, M. Hölscher, W. Leitner, *Eur. J. Org. Chem.* **2007**, 2995.

173. W. Liu, H. J. Lim, T. V. RajanBabu, *J. Am. Chem. Soc.* **2012**, *134*, 5496.

174. D. J. Mans, G. A. Cox ,T. V. RajanBabu, *J. Am. Chem. Soc.* **2011**, *133*, 5776.

175. M. Schmitkamp, W. Leitner, G. Francio, *Catal. Sci. Technol.* **2013**, *3*, 589.

176. K. Kawamoto, A. Tatani, T. Imanaka, S. Teranishi, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1239.

177. A. Grabulosa, G. Muller, J. I. Ordinas, A. Mezzetti, M. A. Maestro, M. Font-Bardia, X. Solans, *Organometallics* **2005**, *24*, 4961.

178. R. M. Ceder, C. Garcia, A. Grabulosa, F. Karipcin, G. Muller, M. Rocamora, M. Font-Bardia, X. Solans, *J. Organomet. Chem.* **2007**, *692*, 4005.

179. A. Grabulosa, A. Mannu, G. Muller, T. Calvet, M. Font-Bardia, *J. Organomet. Chem.* **2011**, *696*, 2338.

180. I. Ayora, R. M. Ceder, M. Espinel, G. Muller, M. Rocamora, M. Serrano, *Organometallics* **2011**, *30*, 115.

181. L. Rodríguez, O. Rossell, M. Seco, A. Grabulosa, G. Muller, M. Rocamora, *Organometallics* **2006**, *25*, 1368.

182. L. Rodríguez, O. Rossell, M. Seco, G. Muller, *Organometallics* **2008**, *27*, 1328.

183. L. Kollár (Ed.), *Modern Carbonylation Methods*, Wiley-VCH, Weinheim, **2008**.

184. (a) A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327; (b) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem*. **1974**, *39*, 3318; (c) A. Schoenberg, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 7761.

185. R. Skoda-Földes, L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097.

186. R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515.

187. A. Brennführer, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.

188. C. F. J. Barnard, *Organometallics* **2008,** *27,* 5402.

189. X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986.

190. F. Ozawa, T. Sugimoto, T. Yamamoto, A. Yamamoto, *Organometallics* **1984**, *3*, 692.

191. V. de la Fuente, C. Godard, E. Zangrando, C. Claver, S. Castillón, *Chem. Commun.* **2012**, *48*, 1695.

192. B. Cornils, W. A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1*, Wiley - VCH, Weinheim, **1996**.

193. T. Xu, H. Alper, *Tetrahedron Lett.* **2013**, *54*, 5496.

194. (a) B. Malawska, *Curr. Top. Med. Chem.* **2005**, *5*, 69; (b) J. J. Luszczki, M. J. Swiader, K. Swiader, R. Paruszewski, W.A. Turski, S. Czuczwar, *J. Fund. Clin. Pharmacol.* **2008**, *22*, 69.

195. C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405.

196. D. U. Nielsen, R. H. Taaning, A. T. Lindhardt, T. M. Gøgsig, T. Skrydstrup, *Org. Lett.* **2011**, *13*, 4454.

197. R. Skoda-Földes, L. Kollár, *Lett. Org. Chem.* **2010**, *7*, 621.

198. A. Takács, A. Petz, L. Kollár, *Tetrahedron* **2010**, *66*, 4479.

199. M.-Z. Cai, C.-S. Song, X. Huang, *Synth. Commun.* **1997**, *27*, 361.

200. C. F. J. Barnard, *Org. Process Res. Dev.* **2008**, *12*, 566.

201. V. de la Fuente, C. Godard, C. Claver, S. Castillón, *Adv. Synth. Catal.* **2012**, *354*, 1971.

202. (a) Z. Szarka, R. Skoda-Földes, A. Kuik, Z. Berente, L. Kollár, *Synthesis* **2003**, 545; (b) Z. Szarka, R. Skoda-Földes, L. Kollár, *Tetrahedron Lett.* **2001**, *42*, 739.

203. Z. Szarka, A. Kuik, R. Skoda-Földes, L. Kollár, *J. Organomet. Chem.* **2004**, *689*, 2770.

204. X.-F. Wu, H. Neumann, Matthias Beller, *Chem. Eur. J.* **2010**, *16*, 9750.

205. E. Takács, C. Varga, R. Skoda-Földes, L. Kollár, *Tetrahedron Lett.* **2007**, *48*, 2453.

206. (a) A. Takács, A. R. Abreu, A. F. Peixoto, M. M. Pereira, L. Kollár, *Synth. Commun.* **2009**, *39*, 1534; (b) A. Takács, A. Szilágyi, P. Ács, L. Márk, A. F. Peixoto, M. M. Pereira, L. Kollár, *Tetrahedron* **2011**, *67*, 2402.

207. A. Takács, B. Jakab, A. Petz, L. Kollár, *Tetrahedron* **2007**, *63*, 10372.

208. H. Neumann, A. Brennführer, P. Groß, T. Riermeier, J. Almena, M. Beller, *Adv. Synth. Catal.* **2006**, *348*, 1255.

209. A. Brennführer, H. Neumann, A. Pews-Davtyan, M. Beller, *Eur. J. Org. Chem.* **2009**, 38.

210. A. Schnyder, A. F. Indolese, *J. Org. Chem.* **2002**, *67*, 594.

211. J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2007**, *46*, 8460.

212. A. Takács, P. Ács, R. Farkas, G. Kokotos, L. Kollár, *Tetrahedron* **2008**, *64*, 9874.

213. X.-F. Wu, J. Schranck, H. Neumann, M. Beller, *ChemCatChem* **2012**, *4*, 69.

214. A. Takács, R. Farkas, L. Kollár, *Tetrahedron* **2008**, *64*, 61.

215. I. P. Andrews, R. J. Atkins, N. F. Badham, R. K. Bellingham, G. F. Breen, J. S. Carey, S. K. Etridge, J. F. Hayes, N. Hussain, D. O. Morgan, A. C. Share, S. A. C. Smith, T. C. Walsgrove, A. S. Wells, *Tetrahedron Lett.* **2001**, *42*, 4915.

216. T. F. Walsh, R. B. Toupence, J. R. Young, S. X. Huang, F. Ujjainwalla, R. J. DeVita, M. T. Goulet, M. J. Wyvratt Jr., M. H. Fisher, J.-L. Lo, N. Ren, J. B. Yudkovitz, Y. T. Yang, K. Cheng, R. G. Smith, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 443.

217. M. P. Wentland, R. Lou, Y. Ye, D. J. Cohen, G. P. Richardson, J. M. Bidlack, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 623.

218. R. Skoda-Földes, L. Kollár, *Chem. Rev.* **2003**, *103*, 4095.

219. L. Horváth, Z. Berente, L. Kollár, *Lett. Org. Chem.* **2007**, *4*, 236.

220. K. Kumar, A. Zapf, D. Michalik, A. Tillack, T. Heinrich, H. Bottcher, M. Arit, M. Beller, *Org. Lett.* **2004**, *6*, 7.

221. M. Scalone, P. Vogt (Hoffmann–La Roche, Switzerland), *Eur. Patent* 0385210, **1990**.

222. (a) C. Coperet, T. Sugihara, G. Wu, I. Shimoyama, E. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 3422; (b) G. T. Crisp, A. G. Meyer, *Tetrahedron* **1995**, *51*, 5585.

223. B. M. Trost, M. K. Ameriks, *Org. Lett.* **2004**, *6*, 1745.

224. (a) T. Fukuyama, T. Inouye, I. Ryu, *J. Organomet. Chem.* **2007**, *692*, 685; (b) E. Müller, G. Péczely, R. Skoda-Földes, E. Takács, G. Kokotos, E. Bellis, L. Kollár, *Tetrahedron* **2005**, *61*, 797.

225. J. McNulty, J. J. Nair, A. Robertson, *Org. Lett.* **2007**, *9*, 4575.

226. E. J. Corey, L. S. Hegedus, *J. Am. Chem. Soc.* **1969**, *91*, 1233.

227. (a) J. Wannberg, M. Larhed, *J. Org. Chem.* **2003**, *68*, 5750; (b) W. Ren, M. Yamane, *J. Org. Chem.* **2010**, *75*, 8410; (c) B. Roberts, D. Liptrot, L. Alcaraz, T. Luker, M. J. Stocks, *Org. Lett.* **2010**, *12*, 4280.

228. C. M. Lindsay, D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 1* **1988**, 569.

229. R. F. Cunico, B. C. Maity, *Org. Lett.* **2003**, *5*, 4947.

230. J. Ju, M. Jeong, J. Moon, H.M. Jung, S. Lee, *Org. Lett.* **2007**, *9*, 4615.

231. N. Iranpoor, H. Firouzabadi, S. Motevalli, *J. Mol. Catal. A: Chem.* **2012**, *355*, 69.

232. Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6232.

233. X. Wu, J. K. Ekegren, M. Larhed, *Organometallics* **2006**, *25*, 1434.

234. Y. Jo, J. Ju, J. Choe, K. H. Song, S. Lee, *J. Org. Chem.* **2009**, *74*, 6358.

CHAPTER 2

SYNTHESIS OF BINAPHTHYL-BASED MONOPHOSPHITE LIGANDS

2.1 Introduction

Phosphite ligands are extremely attractive as they represent a noteworthy breakthrough in the field of catalysis, particularly in the development of several asymmetric reactions.[1,2] It is well known that phosphites are, in general, easy to prepare from readily available alcohols and phenols, which allow designing and screening libraries of chiral ligands, for optimization of a given catalytic reaction.[1,3] Other advantages of phosphite ligands include their lower sensitiveness to air and to other oxidizing agents, and their high tolerance to parallel synthesis, when comparing with phosphines. In addition, bulky aryl phosphite ligands are less prone to decomposition reactions such as hydrolysis, alcoholysis and the Arbuzov reaction.[4,5] Furthermore, phosphites have a very rich coordination chemistry, being able to coordinate with most of transition metals, and providing particularly stable complexes with those more electron-rich.[3]

Nowadays, the aromatic binaphthyl backbone is considered as one the most versatile chiral building blocks,[6,7] which provided access to a diversity of modular phosphorus ligands with appropriate substituents, functionalities, and accurate elements of symmetry able to differentiate the available space in the vicinity of the metal centre.[8] Therefore, the design of chiral binaphthyl-based monophosphite ligands is a relevant topic, owing to their relatively facile synthesis and modulation, high stability and mainly due to their prominent role recently found in asymmetric catalysis.[8,9,10,11,12]

In this chapter, the synthesis of a family of C_3-symmetry binaphthyl-based monophosphite ligands is described. Their steric bulkiness was intended to provide chemical stability. The potentially hemilabile OR substituents at the chiral binaphthyl backbone were intended to offer the possibility of establish secondary interactions with transition metal complexes and also to perform the fine-tuning of both catalytic activity and selectivity (**Figure 2.1**).

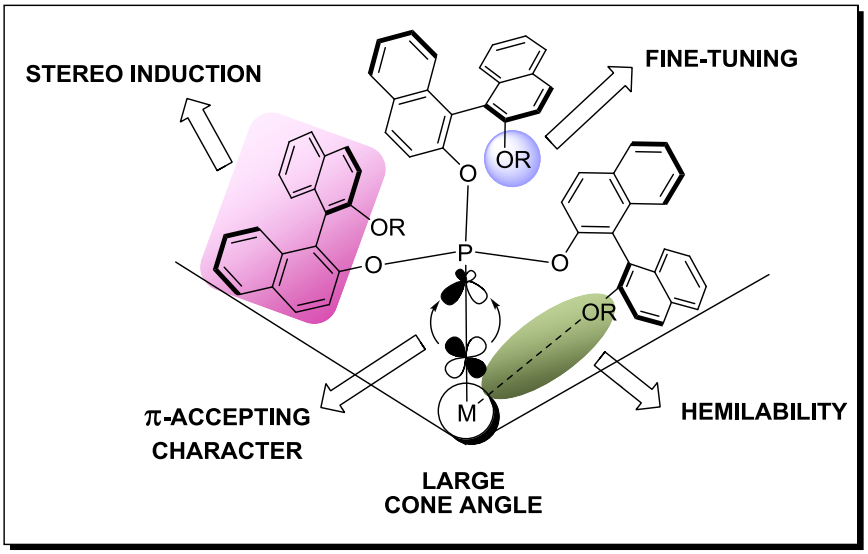
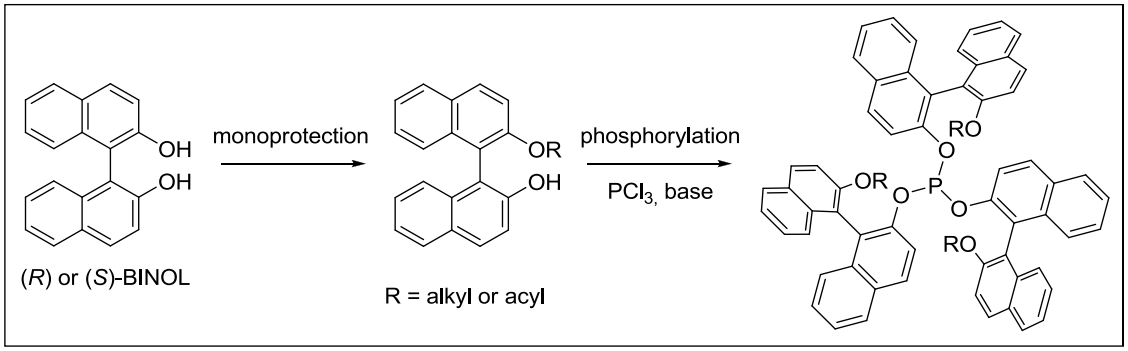


Figure 2.1 – Main features of C_3-symmetry monophosphite ligands developed in this work.

2.2 C_3-symmetry binaphthyl-based monophosphites

The adopted synthetic strategy for preparation of C_3-symmetry binaphthyl-based chiral monophosphites with general formula P(O-BIN-OR)$_3$, (BIN = 2,2'-binaphthyl; R = alkyl or acyl group) consisted in a two-step procedure that included the mono-protection of enantiomerically pure (*S*) or (*R*)-BINOL, followed by PCl_3 phosphorylation, in the presence of a base (**Scheme 2.1**).

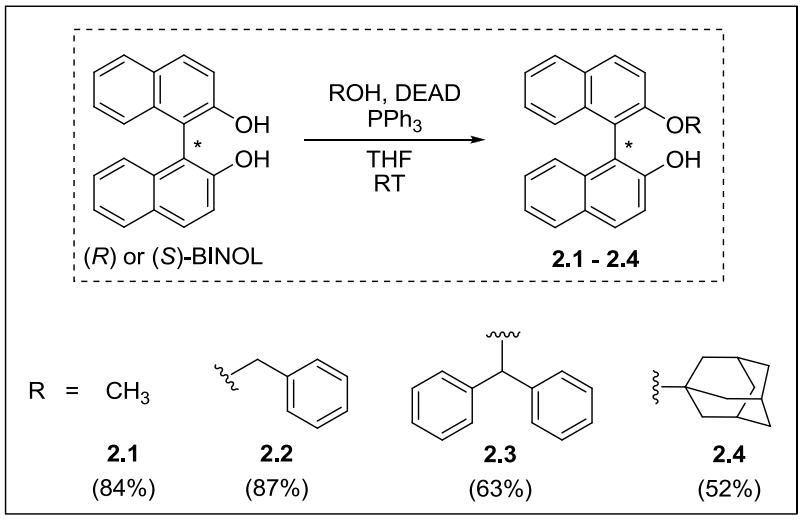


Scheme 2.1

We had formulated that the three aryloxy residues at phosphorus would be "locked" into a screw-like orientation, in order to achieve a single diastereomeric conformer. Aiming this goal, the introduction of substituents in the binaphthyl 2-position was intended to incorporate steric hindrance into the monophosphite ligands, hoping that this would induce helicity and subsequently provide high enantiodiscrimination. Additionally, the incorporation of oxygen atoms could allow hemilabile interactions with the metal, leading to hetero-bidentate complexes, instead of the typical phosphorus mono-coordinated species. As one of the main goals of this work was to evaluate the effects of the OR substituents in the activity and selectivity of the metal/monophosphite catalysts, two different approaches were followed for the synthesis of mono-protected BINOL precursors. The first, based on the *Mitsunobu reaction*,[13] consisted in the mono-etherification of BINOL, with different alcohols, in presence of triphenylphosphine and an azodicarboxylate compound. The second approach consisted on the nucleophilic addition/elimination reaction of an acyl halide with enantiopure BINOL,[14] giving the corresponding mono-ester.

2.2.1 Synthesis of mono-protected BINOL derivatives

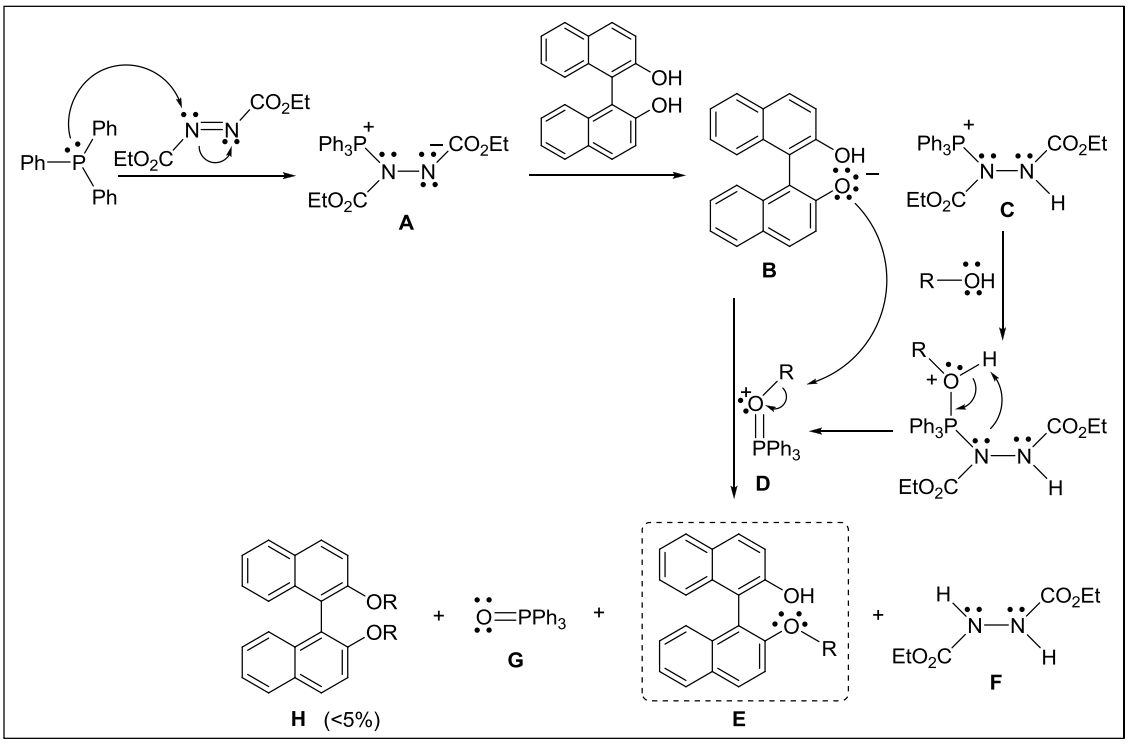
The mono-etherification of enantiopure BINOL took place via *Mitsunobu reaction*,[13] following a slightly modified literature procedure.[15] In order to obtain monophosphite ligands containing structurally different ether substituents and evaluate their effect in catalysis, four different alcohols have been selected to promote the first step of the synthesis: methanol, benzyl alcohol, diphenylmethanol and 1-adamantanol (**Scheme 2.2**).



Scheme 2.2

In a typical procedure, to a stirring solution of (*R*)- or (*S*)-BINOL, triphenylphosphine and the desired alcohol in dry THF, diethyl azodicarboxylate (DEAD) was added dropwise, at 0°C, and the mixture was allowed to warm up to room temperature, under nitrogen atmosphere with magnetic stirring for, approximately, 48h. The reaction's progress was controlled by TLC analysis of samples taken from the reaction mixture. After observing complete (or nearly complete) conversion of reactants into products, the reaction was quenched by water, and subsequently worked-up by standard procedures. The crude mixtures were then purified by column chromatography on silica gel, using mixtures of CH_2Cl_2/*n*-hexane as eluent (exact ratios for purification of each compound are specified in Chapter 5, section 5.2.1).

According to a simplified mechanism,[16,17,18] diethyl azodicarboxylate (DEAD) undergoes nucleophilic attack by triphenylphosphine, giving rise to the corresponding ylide species **A**, which is able to promote deprotonation of one hydroxyl group of BINOL, forming the ionic pair consisting of the species **B** and **C**. In the presence of an alcohol, the oxyphosphonium salt **D** is formed. Finally, upon nucleophilic attack of species **B** to **D**, the desired mono-ether **E** is formed, concomitantly with generation of diethyl hydrazine-1,2-dicarboxylate **F** and triphenylphosphine oxide **G** (**Scheme 2.3**).



Scheme 2.3

Careful procedures have been taken to avoid the presence of water traces, which would consume the reaction intermediate **A**. For instance, the reagents and solvents were appropriately dried and the reaction was carried out under nitrogen atmosphere, using *Schlenk* techniques. Furthermore, the addition of DEAD was done slowly, at 0°C, in order to minimize the bis-ether **H** formation.

As expected, the structure of the alcohol strongly affected the rate of etherification. The BINOL mono-protection reactions with methanol and benzyl alcohol have occurred with nearly complete conversions in 48 h, providing the desired alkyl

mono-ethers **2.1** and **2.2** in 84% and 87% isolated yields, respectively. The reaction proceeded at a much slower rate with diphenylmethanol than with primary alcohols, but **2.3** was still obtained in 63% isolated yield, after 72 h reaction, with full recovery of non-reacted BINOL. However, with the tertiary alcohol, 1-adamantanol, the etherification took place very slowly, giving the BINOL ether **2.4** in only 52% isolated yield, after 96 h reaction (**Scheme 2.2**). Therefore, as previously reported by Takahashi *et al.*,[15] the steric hindrance around the alcohol hydroxyl group had a determinant role in the mono-etherification rates and yields. They were higher with primary alcohols, significantly lower with secondary and even more difficult using tertiary alcohols, due to higher steric impediment. In all cases, the formation of BINOL bis-ethers was negligible (less than 5%). As expected, the isolated yields, using both (*R*)- or (*S*)-BINOL as starting materials, were identical.

All compounds **2.1**-**2.4** have been chemically characterized by NMR, HRMS and elemental analysis, described with detail in Chapter 5, section 5.2.1. As illustrative example, the ^{1}H NMR spectrum of (*S*)-**2.2** is shown in **Figure 2.2**.

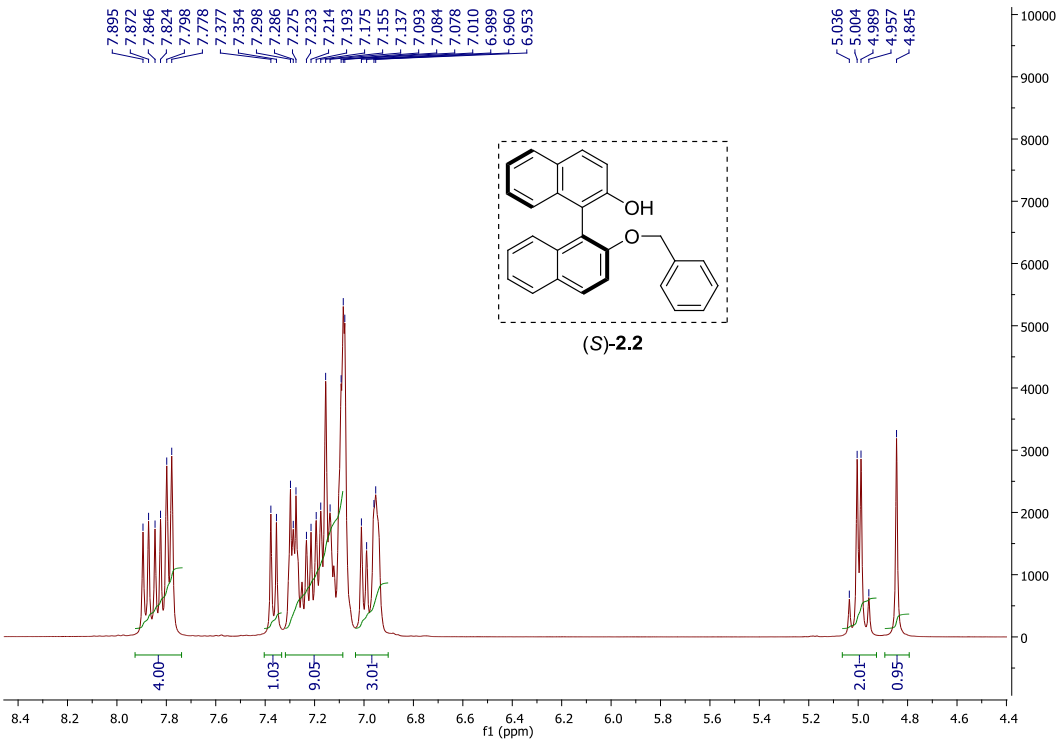


Figure 2.2 – ^{1}H NMR spectrum of (*S*)-2'-(benzyloxy)-1,1'-binaphthyl-2-ol ((*S*)-**2.2**), expansion of 4.40-8.40 ppm region.

The ^{1}H NMR spectrum of (*S*)-**2.2** in $CDCl_3$, at room temperature shows a singlet at δ=4.85 ppm assigned to the hydroxyl proton; at 4.96-5.04 ppm, the two diastereotopic benzylic protons are clearly evidenced by two different doublets coupled to each other (^{2}J = 12.8 Hz), with typical second order effects, resulting in a so-called "AB-quartet". Finally, in the characteristic aromatic region between 6.95 and 7.90 ppm, the signals were assigned to the 17 protons from the phenyl group and the binaphthyl backbone. The full assignment of the aromatic protons was not performed.

After dissolution of compound (*S*)-**2.2** in ethyl acetate (5 mg ml^{-1}), single-crystals suitable for X-ray diffraction were obtained, by slow evaporation of the solvent, at room temperature for 24 h. The corresponding crystal structure is shown in **Figure 2.3**, while the full crystallographic data is presented in **Annex 1**.

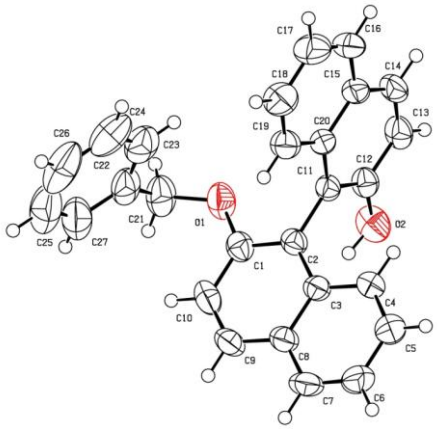
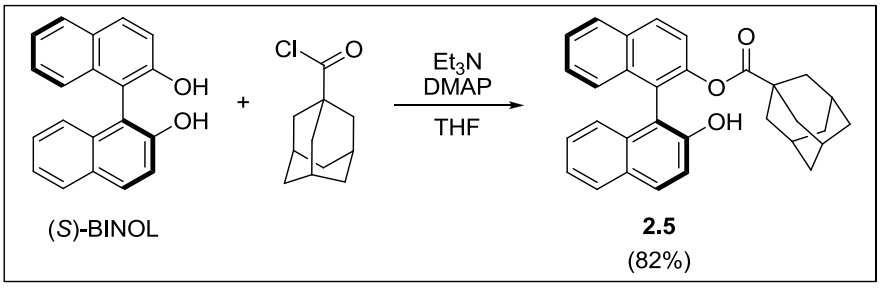


Figure 2.3 – *ORTEPII* plot of the compound (*S*)-**2.2**.

The introduction of an adamantyl ester functionality at the 2-position of BINOL backbone was performed, aiming the preparation of another potentially hemilabile[19] monophosphite ligand, whose catalytic evaluation was performed in the asymmetric Pd-catalyzed hydrovinylation of styrene (Chapter 3, section 3.3). The approach for mono-esterification consisted on the procedure recently reported by Reetz *et al.*,[14] through the nucleophilic addition/elimination reaction between (*S*)-BINOL and the sterically hindered adamantanoyl chloride in basic medium, generating the corresponding enantiopure BINOL mono-ester **2.5**, with concomitant HCl formation, which is trapped by the base Et_3N (**Scheme 2.4**).

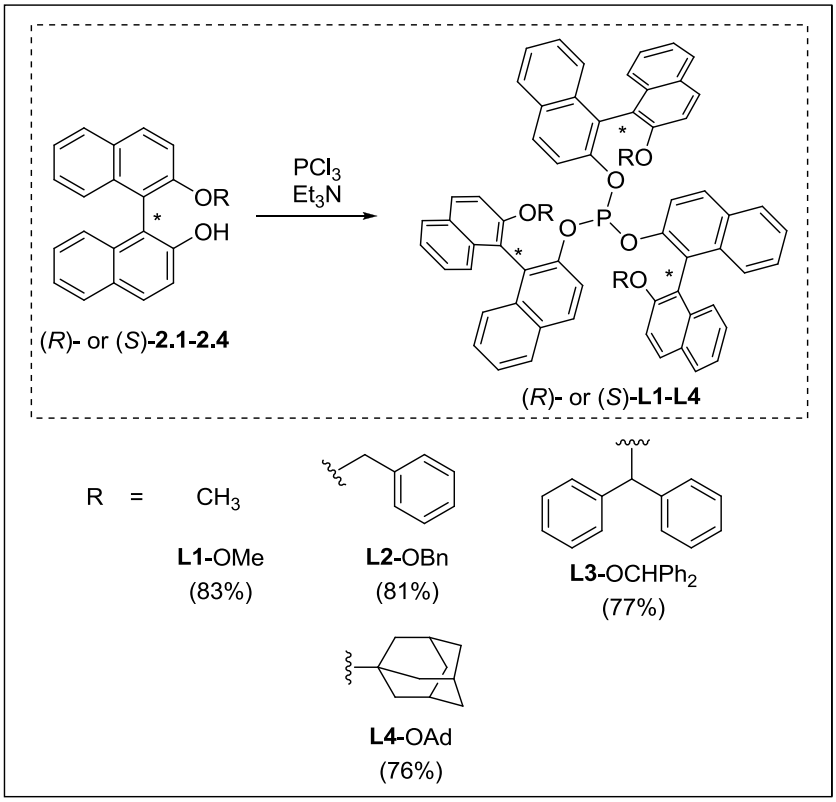


Scheme 2.4

In a standard procedure, a dried round-bottom flask was charged with (*S*)-BINOL, 4-dimethylaminopyridine (DMAP), and triethylamine in anhydrous THF. The mixture was cooled to 0°C and 1-adamantanoyl chloride was added dropwise. Once the addition was complete, the reaction mixture was left at room temperature for 30 h, until nearly complete disappearance of the starting material was observed by TLC. The reaction was quenched with distilled water and after work-up, the crude product was purified by column chromatography on silica gel (dichloromethane/*n*-hexane), providing **2.5** in 82% isolated yield (**Scheme 2.4**). Spectral data was in agreement with the literature.[14] This method provided a more successful strategy to introduce a bulky adamantyl group into the binaphthyl backbone than the *Mitsunobu reaction* approach, as demonstrated by the significantly higher yield (82%) when compared with the previous 52% isolated yield of derivative **2.4**, which might be related to difficulties on the approach of the sterically hindered adamantyl oxyphosphonium salt to the binolate anion.

2.2.2 Synthesis of monophosphite ligands

Following the central objective of preparation of C_3-symmetry binaphthyl-based monophosphites ligands for application in homogeneous catalytic reactions, we proceeded with the second step of their synthesis. This was performed through phosphorylation reactions of each one of the previously obtained mono-protected BINOL derivatives (*R*) or (*S*)-**2.1-2.5** with PCl_3, in the presence of triethylamine (**Scheme 2.5** and **Scheme 2.6**). The procedure was adapted from the literature,[20,21,22,23] however some modifications have been introduced, like the exclusive use of Et_3N as both the base and the reaction solvent.[24]

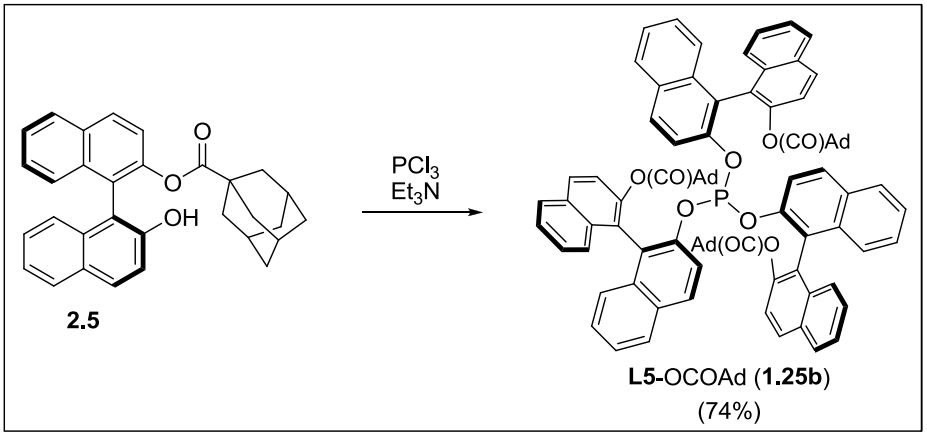


Scheme 2.5

In a typical experiment, a dried Schlenk flask was charged with the desired mono-protected BINOL derivative, which was azeotropically dried with toluene, then placed under nitrogen atmosphere and dissolved in dry triethylamine. The solution was cooled to 0°C, then PCl_3 was slowly added and the mixture was stirred for 3 h. The reaction progress was followed by TLC analysis and ^{31}P NMR spectroscopy from aliquots taken from the reaction mixture. When the emergence of a single ^{31}P NMR signal at the range of 131-136 ppm (typical of aryl monophosphite resonance) was observed, concomitantly with the consumption of the starting material, the solvent was immediately evaporated under reduced pressure. Then, the residue was dissolved in dichloromethane/*n*-hexane (1:1) and the target product was isolated through silica gel column chromatography using a mixture of dichloromethane/*n*-hexane (1:1) as eluent, in all cases, and further purified by recrystallization in diethyl ether/*n*-hexane, always under nitrogen atmosphere.

The ligands tris[(*R*)-2'-methoxy-1,1'-binaphthyl-2-yl]phosphite ((*R*)-**L1**-OMe), tris[(*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl]phosphite ((*R*)-**L2**-OBn), tris[(*R*)-2'-(diphenylmethoxy)-1,1'-binaphthyl-2-yl]phosphite ((*R*)-**L3**-$OCHPh_2$) and tris[(*R*)-2'-(1-adamantyloxy)-1,1'-binaphthyl-2-yl]phosphite ((*R*)-**L4**-OAd) were obtained in 83%, 81%, 77% and 76% isolated yields,[24,25,26] respectively (**Scheme 2.5**). In addition, the monophosphite ligands (*S*)-**L1**-OMe, (*S*)-**L2**-OBn, (*S*)-**L3**-$OCHPh_2$, (*S*)-**L4**-OAd have also been synthesized, from the corresponding (*S*)-BINOL mono-ethers, in similar isolated yields and with spectroscopic data in accordance with the (*R*) analogues.

Following the same procedure, the monophosphite ligand tris[(*S*)-2'-(1-adamantanoyloxy)-1,1'-binaphthyl-2-yl]phosphite (**L5**-OCOAd) was obtained from the corresponding mono-ester **2.5** in 74% isolated yield (**Scheme 2.6**), being the spectroscopic data in agreement with the literature values.[14]



Scheme 2.6

Thus, an almost negligible effect of the mono-protected BINOL derivatives structure was observed on the yields of monophosphite ligands syntheses, being slightly higher when less bulky substituents were used as mono-protecting groups. Furthermore, the use of Et_3N as solvent and, simultaneously, as base in this reaction, has circumvented the use of other hazardous organic solvents, while it also rendered clean and reproducible syntheses. All the monophosphite ligands **L1**-OMe, **L2**-OBn, **L3**-$OCHPh_2$, **L4**-OAd and **L5**-OCOAd have been fully characterized by suitable spectroscopic techniques, described with detail in Chapter 5, section 5.2.2.

The ^{31}P NMR spectra carried out in $CDCl_3$, at room temperature, showed in all cases, a single peak in the range δ = 131-136 ppm, typical of the phosphorus resonance in tris-aryl monophosphite ligands, $\underline{P}(OAr)_3$. As example, the ^{31}P NMR spectrum of (*S*)-**L2**-OBn presenting a singlet at δ = 132.51 ppm (**Figure 2.4**) is illustrative of its high purity.

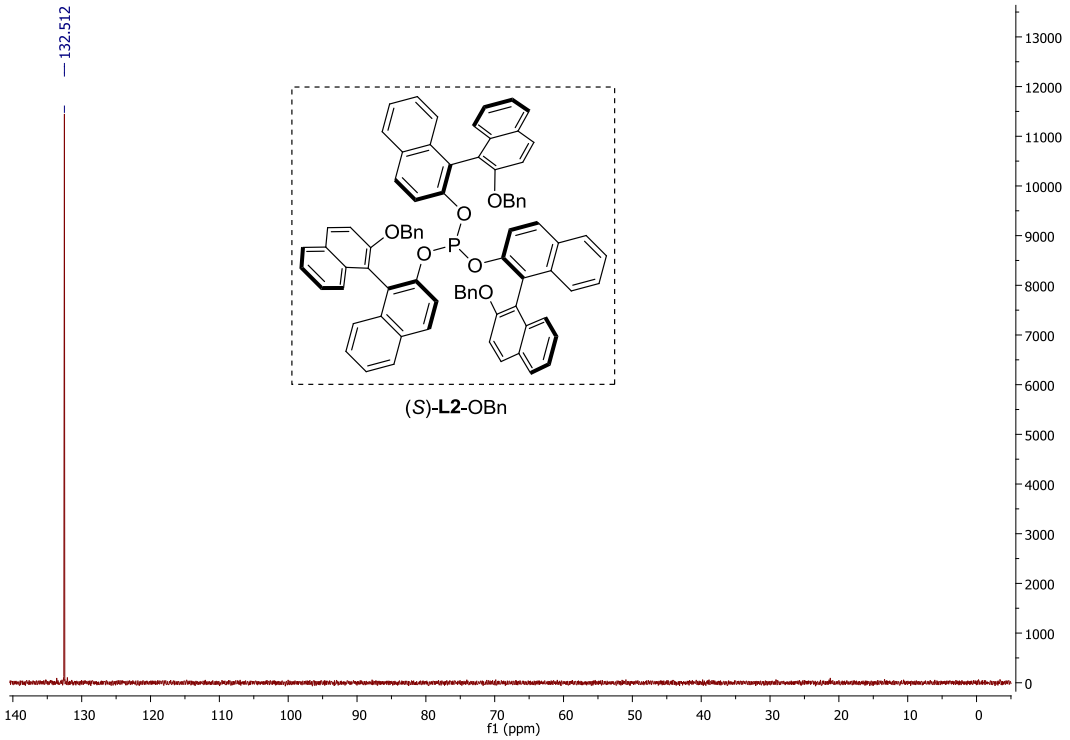


Figure 2.4 – ^{31}P NMR spectrum of tris[(*S*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl] phosphite ((*S*)-**L2**-OBn).

In the ^{1}H NMR spectrum of (*S*)-**L2**-OBn in $CDCl_3$, at 25°C (**Figure 2.5**), the signal assigned to the benzylic protons presents a lower the chemical shift (δ=4.64 ppm) when compared with that in the mono-protected BINOL derivative (δ=5.00 ppm). This signal is now a sharp singlet instead of a coupled pair of doublets. Furthermore, the resonances of 51 aromatic protons from phenyl and binaphthyl groups in the region between 6.13 and 7.69 ppm also suffered a slight decrease in chemical shifts, relatively to the starting material. In the ^{13}C NMR spectrum, a signal at δ = 70.4 ppm was assigned to the three equivalent benzylic carbon atoms, while the 78 aromatic carbon atoms gave rise to multiple signals between 115.3-153.8 ppm (section 5.2.2).

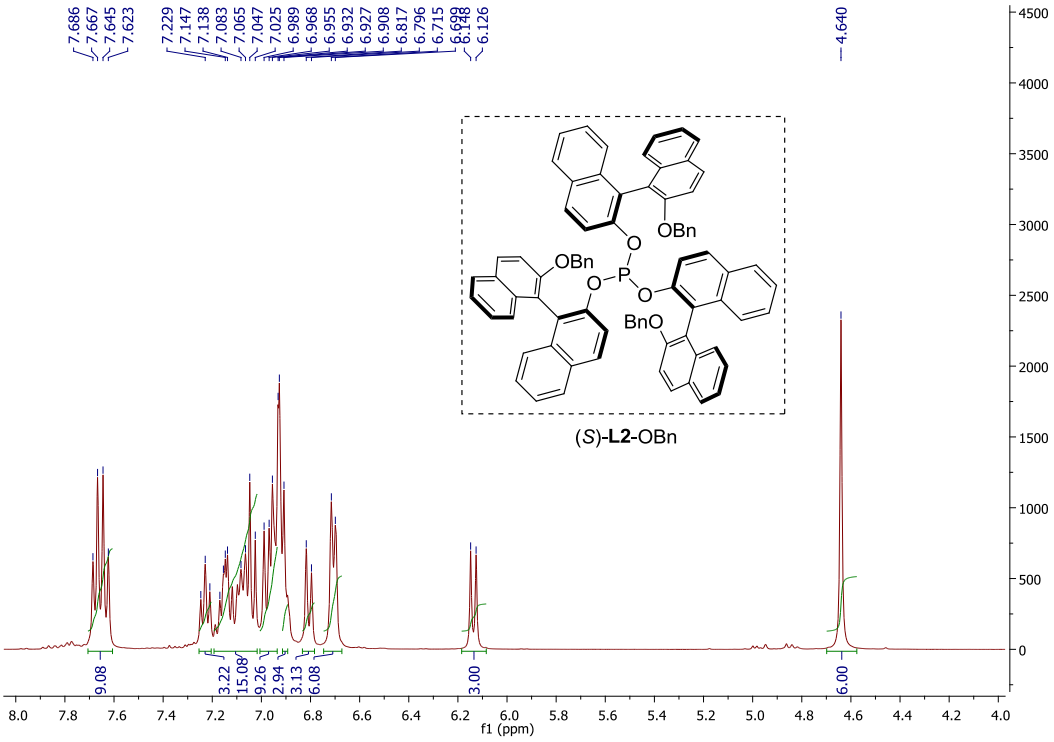


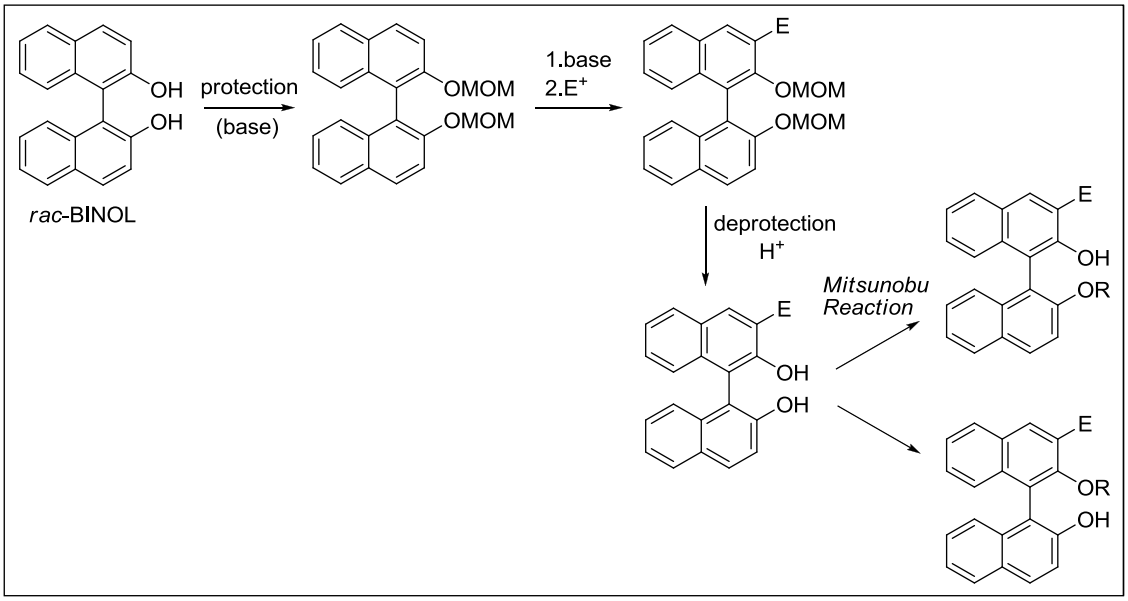
Figure 2.5 – ^{1}H NMR spectrum of tris[(*S*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl] phosphite ((*S*)-**L2**-OBn), expansion of 4.00-8.00 ppm region.

In sum, our main goal of preparing a singular family of C_3-symmetry chiral binaphthyl-based monophosphite ligands has been accomplished, in good overall yields. Furthermore, aiming the functionalization and modulation of binaphthyl ligands, studies of synthesis of 3-methyl substituted mono-protected BINOL derivatives have also been developed during the experimental work described in this thesis. The results are presented in the following section.

2.3 Synthesis of 3-methyl mono-protected BINOL derivatives

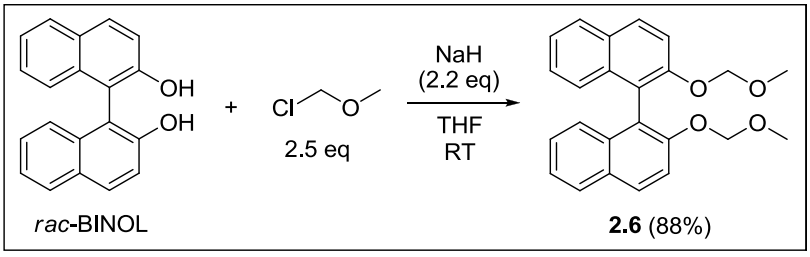
It is well established that the strategic placement of substituents into specific positions of BINOL scaffold may significantly change the steric and electronic properties of the ligands, therefore influencing the catalytic activity and selectivity.[7] Particularly, modifications at the binaphthyl 3,3'-positions have led to improved catalysts in several asymmetric catalytic reactions.[27,28,29,30,31] The synthesis of 3,3'-disubstituted BINOL's was firstly reported by Cram, in the early 1980's, *via* Mannich intermediates, and through Grignard cross-coupling reaction of 3,3'-dibromo-BINOL dimethyl ether with arylmagnesium bromides.[32] Later, Snieckus described an efficient methodology to synthesize 3- and 3,3'-substituted 1,1'-bi-2-naphthols through directed *ortho*-metalation and Suzuki *cross-coupling* reactions.[33] Other examples of 3,3'-substituted binaphthyl derivatives include the synthesis of 3,3'-diaryl-BINOL's by Suzuki cross-coupling reactions of bis(methoxy)-BINOL-3,3'-diboronic acid with aromatic bromides.[34] The synthesis of sterically hindered chiral 3,3'-bis-(trialkylsilyl)-1,1'-bi-2-naphthol derivatives was reported by Yamamoto, based on 1,3-rearrangement reactions in the presence of *tert*-butyllithium.[35] Pu described the preparation of 3,3'-aryl BINOL derivatives containing electron-withdrawing fluorine atoms in the aryl groups, by Suzuki coupling reactions with aryl bromides.[36] Ohta has developed the synthesis of a family of 3,3'-oxazolyl BINOL ligands (BINOL Box), which were applied in asymmetric Sc-catalyzed 1,3-dipolar cycloaddition reactions, providing isoxazolidine products with high diastereo- and enantioselectivity (up to 88% ee).[37] Furthermore, the preparation of BINOL derivatives containing 3,3'-(methoxyethyl) substituents was carried out by Qian's group.[38]

Our experiments were performed using the inexpensive racemic BINOL as starting material, since the main purpose was only the optimization of synthetic procedures. The adopted synthetic strategy for 3-methyl substituted mono-protected BINOL derivatives consisted of a four-step sequence, which included the treatment of a suitably protected BINOL with a basic organolithium reagent, followed by reaction with an electrophile, the deprotection of BINOL hydroxyl groups in acidic medium and finally the mono-etherification via *Mitsunobu reaction* (**Scheme 2.7**).



Scheme 2.7

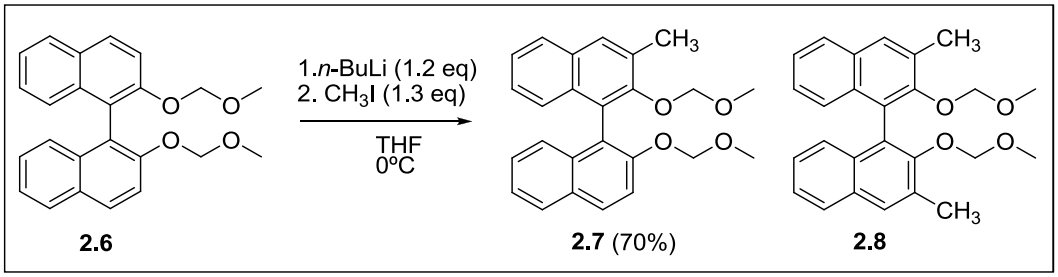
The first step, adapted from the literature,[33,39] was the synthesis of 2,2'-bis(methoxymethoxy)-1,1'-binaphthyl **2.6** (**Scheme 2.8**).



Scheme 2.8

In a standard experiment, BINOL was added to a suspension of NaH in anhydrous THF under a nitrogen atmosphere, at 0°C. This solution was stirred for 15 min, and then methoxymethyl chloride was slowly added. The mixture was allowed to warm up to room temperature and stirred for 5 h. The reaction was quenched with distilled water, and standard work-up procedures were performed. After recrystallization from toluene/*n*-hexane, the target compound 2,2'-bis(methoxymethoxy)-1,1'-binaphthyl **2.6** was isolated in 88% yield, being its spectroscopic data in conformity with the literature.[39]

In the second step of the synthesis, *n*-BuLi was added to a solution of **2.6** in anhydrous THF under a nitrogen atmosphere, at room temperature. The mixture was stirred for 4 h, which produced a grey suspension. After the mixture was cooled to 0°C, iodomethane was added. The reaction was allowed to warm up to room temperature and stirred for 5 h (**Scheme 2.9**).



Scheme 2.9

After working-up the reaction mixture and subsequent purification by column chromatography on silica gel, using as eluent a mixture of *n*-hexane/ethyl acetate (10:1), the target compound 2,2'-bis(methoxymethoxy)-3-methyl-1,1'-binaphthyl **2.7** was obtained in 70% isolated yield. Although it was previously reported by Snieckus[33] that using 2.2 molar equiv of *t*-BuLi (THF/-78°C/1 h) was found to be the optimal condition for the preparation of 3-substituted BINOL's, the use of 1.2 molar equiv of *n*-BuLi (THF/0°C/4 h) has afforded the target compound **2.7** in similar yields to those previously reported. The generation of the binaphthyl-methoxymethyl dianion was not completely avoided and the 3,3'-dimethyl binaphthyl derivative **2.8** was also formed as side product, without being isolated.

Crystals of compound **2.7** suitable for X-ray diffraction were obtained by slow evaporation of the solvents (*n*-hexane/ethyl acetate (10:1)), leaving the purified chromatography fractions open to air. The respective crystal structure is shown in **Figure 2.6**, and the full crystallographic data is presented in **Annex 2**.[40] The single crystal X-ray diffraction showed that the planes of the naphthalene aromatic rings are at an angle of 70.74 (3)°. Furthermore, no conventional hydrogen bonds were found binding the molecules.[40]

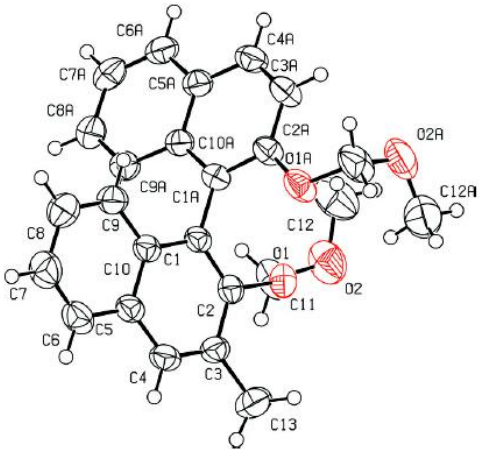
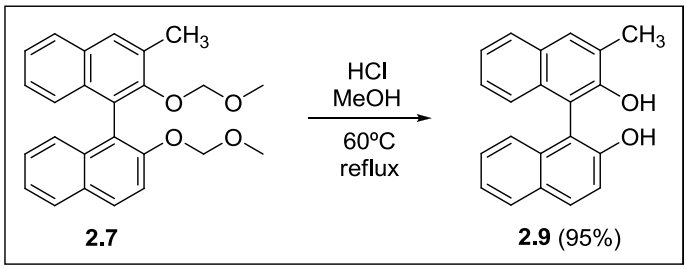


Figure 2.6 – *ORTEPII* plot of the compound **2.7**.

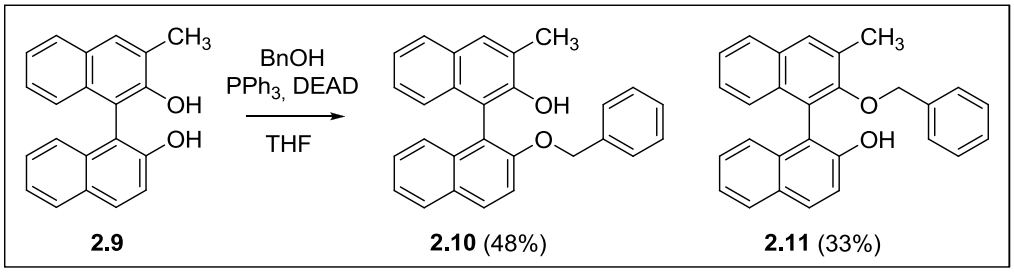
The third step of the synthesis consisted of the subsequent methoxymethyl group deprotection, performed in acidic medium (**Scheme 2.10**).



Scheme 2.10

In a standard procedure, to a solution of **2.7** in methanol, 0.25 mL HCl 37% was added and the mixture was stirred under reflux at 60°C, for 30 minutes. Then, the mixture was poured into water, extracted with ethyl acetate and after work-up, the residue was purified by column chromatography on silica gel, using as eluent a mixture of *n*-hexane/ethyl acetate (6:1), which furnished 3-methyl-1,1'-binaphthyl-2,2'-diol **2.9**, in almost quantitative 95% isolated yield. Spectroscopic data of compounds **2.7** and **2.9** were in agreement with those previously reported in the literature.[29,33,39]

Finally, the fourth step of the synthesis was the mono-etherification of 3-methyl-1,1'-binaphthyl-2,2'-diol **2.9** with benzyl alcohol, via the *Mitsunobu reaction* approach (**Scheme 2.11**), following the synthetic procedure described in section 2.2.1.



Scheme 2.11

According to the standard procedure,[25] to a solution of 3-methyl-1,1'-binaphthyl-2,2'-diol **2.9**, PPh_3 and benzyl alcohol, in dry THF, DEAD (40% in toluene) was added dropwise at 0°C and the mixture was stirred at room temperature. The reaction's progress was followed by TLC, using CH_2Cl_2/*n*-hexane (2:1) as eluent, where it was possible to observe the formation of two products, which were assumed to be the compounds **2.10** and **2.11**, as result of the formation of two possible binolate anions. The reaction was quenched with distilled water and worked-up by standard procedures. After removal of the solvents, the resulting crude mixture was immediately analyzed by ^{1}H NMR spectroscopy (**Figure 2.7**).

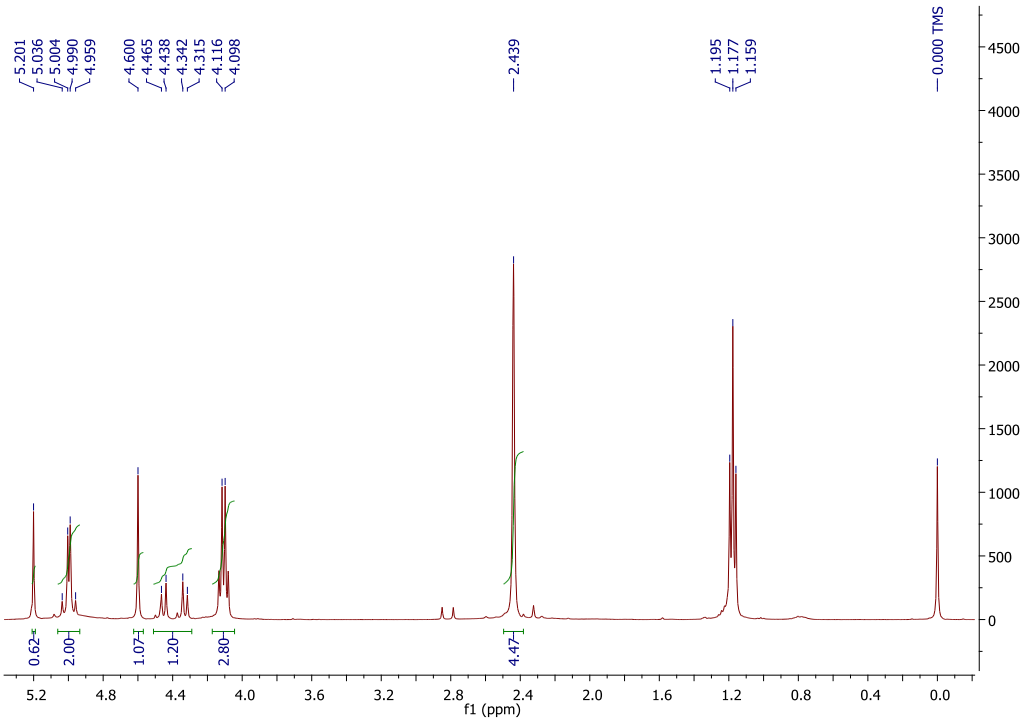


Figure 2.7 – ^{1}H NMR spectrum of the crude mixture (**Scheme 2.11**), expansion of 0.00-5.20 ppm region.

The ^{1}H NMR spectrum in $CDCl_3$, at room temperature (**Figure 2.7**), showed two singlets at δ=5.20 ppm and δ=4.60 ppm, assigned to the free hydroxyl proton of minor and major products, respectively. In addition, at δ=4.96-5.04 ppm and δ=4.32-4.47 ppm intervals, two pairs of doublets were assigned to the diastereotopic benzylic protons of each major and minor product. At δ=2.44 ppm, the superimposed signals assigned to the methyl group protons of both compounds were evidenced. Furthermore, the quartet at δ=4.11 ppm and the triplet δ=1.18 ppm were, respectively, assigned to CH_2 protons and CH_3 protons belonging to diethyl hydrazine-1,2-dicarboxylate, which is the reduced form of the reagent DEAD (species **F**, **Scheme 2.3**). Thus, the ^{1}H NMR spectrum of the reaction mixture confirmed a mixture of the expected products, in a ratio close to 3:2. However, from this analysis no unequivocal conclusions could be taken regarding the identification of each product **2.10** and **2.11**.

In order to isolate and clearly characterize both compounds, their purification was carried out by column chromatography on silica gel, using CH_2Cl_2/*n*-hexane (2:1) as eluent. The solvents were evaporated under reduced pressure, yielding two white solid compounds resulting from the both isolated fractions. After drying under vacuum, the products were analyzed by 2D NMR ^{1}H-^{1}H NOESY experiments.

The ^{1}H-^{1}H NOESY spectrum of the first compound evidenced a correlation between the benzylic and the methyl protons, which led to identification of product **2.11**, containing a CH_3 group and benzylic group in adjacent positions of the aromatic ring (**Figure 2.8**). The spectrum of second compound showed a ^{1}H-^{1}H NOESY correlation between the hydroxyl proton and the CH_3 protons, leading to the identification of product **2.10**, which contains a methyl group adjacent to the hydroxyl (**Figure 2.9**). Remarkably, in the case of **2.11** the diastereotopic benzylic protons gave rise to distinct doublets at δ=4.44 ppm and δ=4.32 ppm, as result of the restricted rotation of the 2'-benzyloxy group, close to the methyl group in the 3'-position of the binaphthyl backbone. Thus, from the ^{1}H-^{1}H NOESY spectra of both isolated products, it was concluded that this synthesis provided two products, in a combined yield of 81%, with the major product being the compound 2'-(benzyloxy)-3-methyl-1,1'-binaphthyl-2-ol (**2.10**) obtained in 48% isolated yield, while 2'-(benzyloxy)-3'-methyl-1,1'-binaphthyl-2-ol (**2.11**) was obtained in 33% isolated yield.

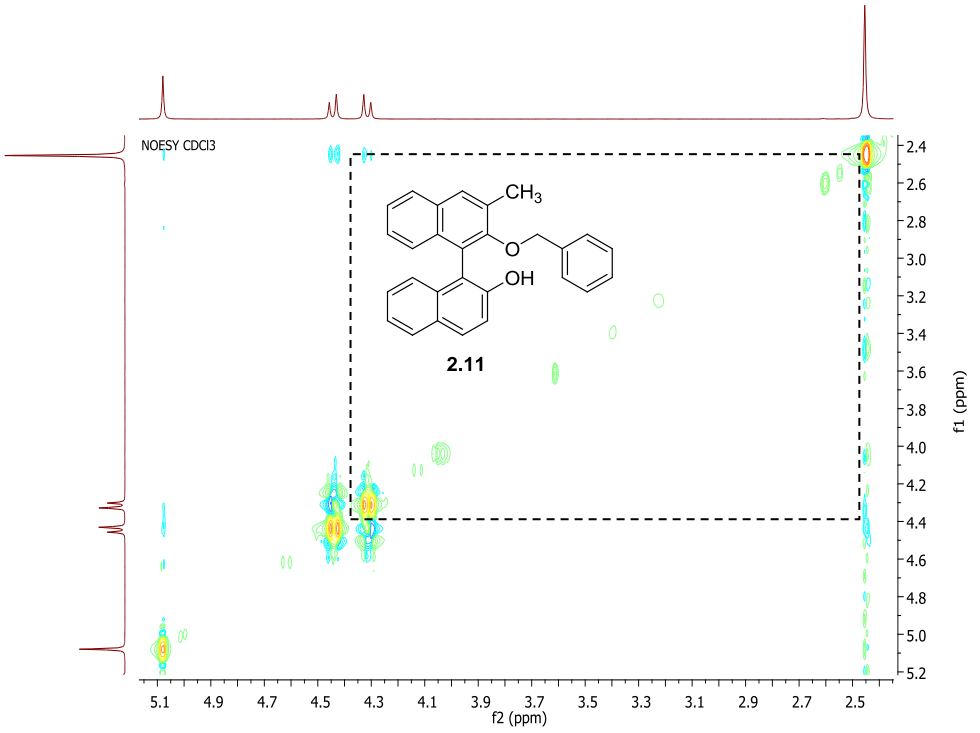


Figure 2.8 – ^{1}H-^{1}H NOESY spectrum of **2.11**.

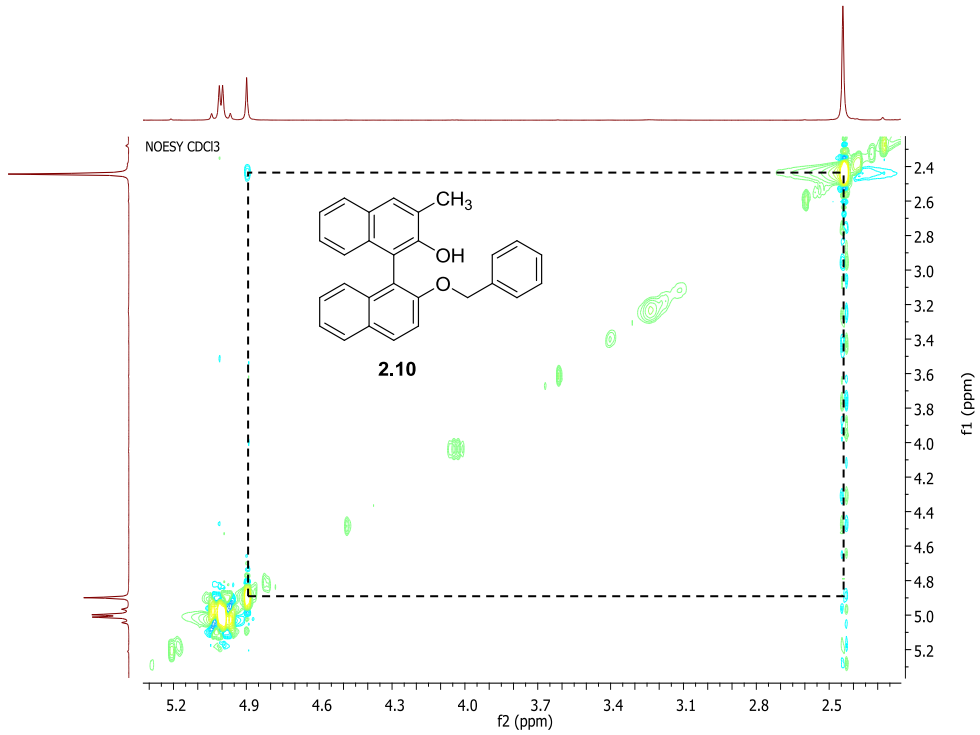


Figure 2.9 – ^{1}H-^{1}H NOESY spectrum of **2.10**.

It should be noted that, in a first attempt to perform the phosphorylation of the above mentioned 3-methyl mono-protected BINOL derivatives with PCl_3 under the previously standardized conditions, no isolable monophosphite ligands were obtained from a complex products mixture.

2.4 Conclusions

A family of C_3-symmetry monophosphite ligands, derived from enantiomerically pure (*S*)- or (*R*)-BINOL was successfully developed. Their synthesis was accomplished in good overall yields through the preparation of differently mono-protected BINOL derivatives, followed by phosphorylation with PCl_3, in basic medium. The main approach for BINOL mono-protection consisted on the etherification via *Mitsunobu reaction*, using structurally different alcohols. As expected, the steric hindrance around the alcohol hydroxyl group has strongly influenced the mono-etherification rate and yields, being higher with primary alcohols, significantly lower with secondary and more difficult using tertiary alcohols. Therefore, the desired alkyl mono-ethers **2.1**, **2.2**, **2.3** and **2.4** were obtained with 84%, 87%, 63% and 52%, respectively. A different approach based on nucleophilic addition/elimination reaction of adamantanoyl chloride with enantiopure BINOL was used to generate the corresponding chiral BINOL mono-ester **2.5** in 82% isolated yield.

The second step of the monophosphite ligands synthesis was accomplished by reaction of the previous mono-protected derivatives with phosphorus trichloride, in presence of triethylamine as base and reaction solvent, which rendered the monophosphites **L1**-OMe, **L2**-OBn, **L3**-$OCHPh_2$, **L4**-OAd and **L5**-OCOAd, in good yields (74-83%), through clean and reproducible processes, slightly dependent on the structure of the mono-protected binaphthyl derivative.

Furthermore, studies on the preparation of 3-methyl substituted mono-protected BINOL derivatives were performed through a sequential procedure, which included the protection of both hydroxyl groups of BINOL with suitable *ortho*-directing methoxymethyl substituents, and subsequent treatment with 1.2 molar equiv of *n*-BuLi, followed by an electrophilic aromatic substitution with iodomethane, and the

deprotection of BINOL hydroxyl groups in acidic medium. Subsequently, the mono-etherification of 3-methyl-1,1'-binaphthyl-2,2'-diol **2.9** via *Mitsunobu reaction* provided two different products, in a combined yield of 81%. After purification and isolation by chromatographic procedures, both compounds 2'-(benzyloxy)-3-methyl-1,1'-binaphthyl-2-ol (**2.10**) and 2'-(benzyloxy)-3'-methyl-1,1'-binaphthyl-2-ol (**2.11**) were identified by 2D NMR ^{1}H-^{1}H NOESY experiments.

All compounds have been characterized by NMR and HRMS spectroscopic techniques, described with detail in Chapter 5, section 5.2.

2.5 References

1. P. W. N. M. van Leeuwen, P. C. J. Kamer, C. Claver, O. Pàmies, M. Diéguez, *Chem. Rev.* **2011**, *111*, 2077.

2. A. Börner, *Phosphorus Ligands in Asymmetric Catalysis*, Wiley-VCH, Weinheim, **2008**.

3. P. C. J. Kamer, P. W. N. M. van Leeuwen (Eds.), *Phosphorus (III) Ligands in Homogeneous Catalysis. Design and Synthesis*, Wiley & Sons, Chichester, **2012**.

4. G. G. Rajeshwaran, M. Nandakumar, R. Sureshbabu, A. K. Mohanakrishnan, *Org. Lett.* **2011**, *13*, 1270.

5. A. K. Bhattacharya, G. Thyagarajan, *Chem. Rev.* **1981**, *81*, 415.

6. J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857.

7. Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155.

8. M. M. Pereira, M. J. F. Calvete, R. M. B. Carrilho, A. R. Abreu, *Chem. Soc. Rev.* **2013**, *42*, 6990.

9. M. M. Pereira, M. J. F. Calvete, A. R. Abreu, R. M. B. Carrilho, in *Advances in Chemistry Research, Vol. 19*, J. C. Taylor (Ed.), Nova Publishers, New York, **2013**, pp. 111-154.

10. M. T. Reetz, G. Mehler, *Angew. Chem., Int. Ed.* **2000**, *39*, 3889.

11. T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101.

12. K. N. Gavrilov, S. Lyubimov, S. V. Zheglov, E. B. Benetsky, V. A. Davankov, *J. Mol. Catal. A: Chem.* **2005**, *231*, 255.

13. O. Mitsunobu, *Synthesis* **1981**, 1.

14. M. T. Reetz, H. Guo, J.-A. Ma, R. Goddard, R. J. Mynott, *J. Am. Chem. Soc.* **2009**, *131*, 4136.

15. M. Takahashi, K. Ogasawara, *Tetrahedron: Asymmetry* **1997**, *8*, 3125.

16. (a) D. Camp, I. D. Jenkins, *J. Org. Chem.* **1989**, *54*, 3045; (b) D. Camp, I. D. Jenkins, *J. Org. Chem.* **1989**, *54*, 3049.

17. D. L. Hughes, R. A. Reamer, J. J. Bergan, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1988**, *110*, 6487;

18. E. Grochowski, B. D. Hilton, R. J. Kupper, C. J. Michejda, *J. Am. Chem. Soc.* **1982**, *104*, 6876.

19. M. Nandi, J. Jin, T. V. RajanBabu, *J. Am. Chem. Soc.* **1999**, *121,* 9899.

20. T. Jongsma, G. Challa, P. W. N. M van Leeuwen, *J. Organomet. Chem.* **1991**, *421*, 121.

21 A. van Rooy, E. N. Orij, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 34.

22. R. B. C. Jagt, P. Y. Toullec, E. P. Schudde, J. G. Vries, B. L. Feringa, A. J. Minnaard, *J. Comb. Chem.* **2007**, *9*, 407.

23. A. A. Dabbawala, H. C. Bajaj, R. V. Jasra, *J. Mol. Catal. A: Chem.* **2009**, *302*, 97.

24. R. M. B. Carrilho, *Síntese de Monofosfitos Quirais. Aplicação em Reacções Catalíticas de Hidroformilação Assimétrica*, Tese de Mestrado (Master Thesis), Universidade de Coimbra, Coimbra, **2008**.

25. R. M. B. Carrilho, A. R. Abreu, G. Petöcz, J. C. Bayón, M. J. S. M. Moreno, L. Kollár, M. M. Pereira, *Chem. Lett.* **2009**, *38*, 844.

26. R. M. B. Carrilho, A. C. B. Neves, M. A. O. Lourenço, A. R. Abreu, M. T. S. Rosado, P. E. Abreu, M. E. S. Eusébio, L. Kollár, J. C. Bayón, M. M. Pereira, *J. Organomet. Chem.* **2012**, *698*, 28.

27. H. Kitajima, Y. Aoki, K. Ito, T. Katsuki, *Chem. Lett.* **1995**, 1113.

28. (a) E. M. Vogl, S. Matsunaga, M. Kanai, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7917; (b) S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 2252.

29. B. Saha, T. V. RajanBabu, *J. Org. Chem.* **2007**, *72*, 2357.

30. B. Liu, Z.-B. Dong, C. Fang, H.-B. Song, J.-S. Li, *Chirality* **2008**, *20*, 828.

31. Q.-S. Guo, B. Liu, Y.-N. Lu, F. Y. Jiang, H.-B. Song, J.-S. Li, *Tetrahedron: Asymmetry* **2005**, *16*, 3667.

32. D. S. Lingenfelter, R. C. Helgeson, D. J. Cram, *J. Org. Chem.* **1981**, *46*, 393.

33. P. J. Cox, W. Wang, V. Snieckus, *Tetrahedron Lett.* **1992**, *33*, 2253.

34. K. B. Simonsen, K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1998**, *63*, 7536.

35. K. Maruoka, T. Itoh, Y. Araki, T. Shirasaka, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975.

36. W. Huang, L. Pu, *Tetrahedron Lett.* **2000**, *41*, 145.

37. H. Kodama, J. Ito, K. Hori, T. Ohta, I. Furukawa, *J. Organomet. Chem.* **2000**, *603*, 6.

38. C. Qian, C. Zhu, T. Huang, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2131.

39. M. Shi, C.-J. Wang, *Tetrahedron: Asymmetry* **2002**, *13*, 2161.

40. R. M. B. Carrilho, A. R. Abreu, M. M. Pereira, V. H. Rodrigues, *Acta Crystallogr. E* **2011**, *67*, o2370.

CHAPTER 3

EVALUATION OF MONOPHOSPHITE LIGANDS IN ASYMMETRIC CATALYSIS

3.1 Introduction

The requirement for chiral compounds as single enantiomers has sharply increased in recent years, as a result of the demands of pharmaceutical industry and also by several other applications, including agrochemicals, flavors, fragrances and materials.[1,2,3] This widespread demand for enantiopure molecules has then stimulated intensive research to develop improved methods for synthesizing such compounds.

In this context, asymmetric catalysis, in which each molecule of a chiral catalyst, by virtue of being continually regenerated, can yield many molecules of chiral product, has emerged as an efficient and atom economical tool with huge potential for asymmetric synthesis.[4] Important advances in this area have resulted from the convergence of a broader understanding of theory and how structure generates function, as well as from remarkable developments in the interface between organic and inorganic chemistry.[5] Therefore, the design and synthesis of chiral organometallic complexes, capable to provide and enhance asymmetric induction in catalysis, are topics with upmost relevance, from a synthetic point of view.

It is well established that a chiral organometallic complex often binds and reacts preferentially with one of the prochiral faces of the substrate, or binds the substrate and shield one of the prochiral faces, thus impeding the reaction at that face.[6] During several years, metal complexes bearing bidentate chelating *P*-donor ligands with C_2-symmetry, were considered essential for asymmetric induction.[7,8,9] However, chiral monodentate phosphorus ligands, such as phosphine,[10,11] phosphite,[12,13] phosphonite,[14] phosphoramidite[15,16] and diamidophosphite[17] ligands have recently demonstrated to be remarkably multi-talented, providing high catalytic activities and excellent enantiomeric excesses in a large number of enantioselective reactions.[18,19,20] In particular, monophosphite ligands based on the binaphthyl backbone have earned a prominent status,[21,22] shown by their efficient application in the asymmetric hydrogenation of olefins[23] and allylic substitutions.[24]

In this chapter, the catalytic evaluation of C_3-symmetry chiral monophosphite ligands (**Figure 3.1**), whose synthesis and characterization was described in Chapter 2, is performed in asymmetric catalysis. The ligands **L1**-OMe, **L2**-OBn, **L3**-OCHPh$_2$ and **L4**-OAd have been applied in rhodium-catalyzed hydroformylation of aryl olefins and a steroidal olefinic substrate (with Rh/**L2**-OBn). Furthermore, all these phosphite-ether ligands and, additionally, the adamantanoyl-derived **L5**-OCOAd have been used in the synthesis of allylpalladium complexes, which were evaluated as catalytic precursors in the asymmetric hydrovinylation of styrene.

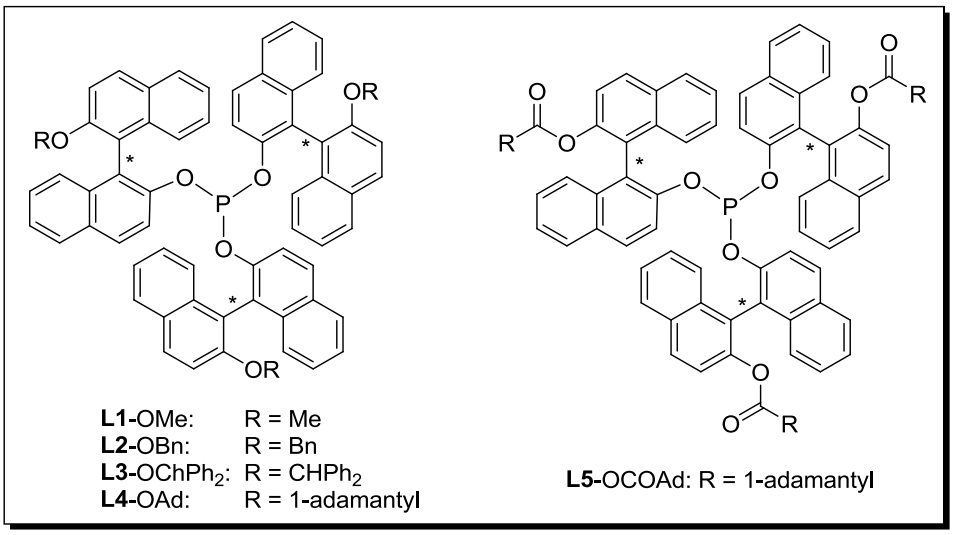


Figure 3.1 – General structure of C_3-symmetry tris-binaphthyl monophosphite ligands.

3.2 Rhodium-catalyzed asymmetric hydroformylation

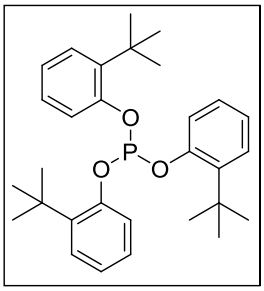
As previously mentioned in Chapter 1, the asymmetric hydroformylation of alkenes is considered as one of the most efficient tools for the preparation of enantiomerically pure aldehydes.[25,26] Several monosubstituted olefins have been systematically studied as benchmark substrates in this reaction, due to the interest in the synthesis of 2-substituted branched aldehydes.[27,28,29] For example, the hydroformylation of terminal vinylarenes has been used as a model reaction for the synthesis of 2-arylpropionaldehydes, which are intermediates in the synthesis of 2-aryl propionic acids, a well-known class of non-steroidal drugs.[30,31,32] The asymmetric hydroformylation of other monosubstituted alkenes, such as allyl cyanide and vinyl acetate, was also successfully carried out.[25] However, the hydroformylation of prochiral disubstituted olefins has received much less attention than their monosubstituted counterparts. Regarding this topic, only few examples on the asymmetric hydroformylation of 1,1- and 1,2-disubstituted alkenes have been reported so far, most of them using rhodium complexes.[33,34,35,36,37,38] Furthermore, kinetic and mechanistic studies on catalytic hydroformylation are essentially limited to model terminal or cyclic alkenes.[39,40,41]

Nowadays, despite the successful use of chiral monodentate phosphorus donor ligands in several transition metal catalyzed processes, there are only a few reports concerning their application in asymmetric hydroformylation. Although they have the advantage of higher catalytic activity when compared to bidentate chelating ligands, only moderate to good enantioselectivities were reported in asymmetric hydroformylation processes so far.[42,43,44]

3.2.1 Hydroformylation of disubstituted aryl olefins

The hydroformylation of disubstituted and internal double bounds is troublesome and usually requires harsh reaction conditions.[45] The most remarkable exceptions are rhodium(I) complexes modified with bulky aryl monophosphite ligands, such as tris(*o*-*tert*-butylphenyl)phosphite (**L6**), which have been able to hydroformylate a large number of sterically hindered olefins, under relatively mild conditions.[46,47,48,49]

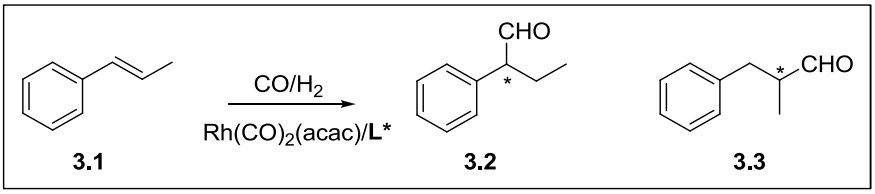
This exceptional activity results from both electronic and stereo effects: the large ligand's cone angle prevents the coordination of a second phosphite to the metal, even when used in large excess. As a consequence, the low steric hindrance around the metal, combined with the π-acidic character of the monophosphite ligand, allows a relatively fast substitution of CO by the alkene, in what is assumed to be the rate-determining step of the hydroformylation of encumbered alkenes.[25,50]



L6
(**1.26a**)

With this awareness, we formulated that the chiral hemilabile C_3-symmetry bulky tris-binaphthyl monophosphite ligands, whose synthesis and characterization were described in Chapter 2, could produce a similar effect, regarding the activity of rhodium catalysts, but additionally inducing enantioselectivity in the hydroformylation of sterically hindered alkenes.

Thus, *trans*-1-phenylpropene **3.1** was chosen as model olefinic substrate, and (*R*)-**L2**-OBn was selected as model ligand, from this family of threefold symmetry monophosphites, to perform the optimization of reaction conditions and simultaneously, to study the effects of several reaction parameters (temperature, P/Rh ratio, concentrations of substrate and catalyst and partial pressures of H_2 and CO) in the kinetics of the rhodium-catalyzed hydroformylation reaction. The hydroformylation of **3.1** can origin two possible aldehydes **3.2** and **3.3** (**Scheme 3.1**), as result of the formyl group insertion in different positions. Both products contain a stereogenic carbon atom, resulting from new C–C bonds formation, which opens the possibility for generation of two distinct pairs of enantiomers. The identification of the products was performed by appropriate NMR spectroscopic and chiral GC techniques.



Scheme 3.1

In a typical catalytic hydroformylation experiment, the autoclave was charged with the appropriate amount of monophosphite ligand, and a solution of the catalytic precursor $Rh(CO)_2(acac)$ in toluene was then introduced via *cannula*, under vacuum. The reactor was pressurized with 40 bar of an equimolar mixture of CO/H_2, and kept at 80°C for 1 hour to ensure the formation of the catalytic resting state {$Rh(H)(CO)_3$(**L**)}. After the incubation, the autoclave was slowly depressurized and set to the working temperature. Then, the substrate was introduced through the inlet *cannula* and the *syngas* pressure was set to the desired value for each catalytic experiment. Samples taken from the autoclave were analyzed by GC in order to determine conversion, chemo- and regioselectivity. For kinetic studies, samples were taken at not higher than 20% conversions of alkenes into products in order to determine the initial rates, without product interferences.

The studies were initiated with the evaluation of the effect of temperature on the activity and selectivity of the Rh/**L2**-OBn catalytic system in the hydroformylation of **3.1**. Several experiments were performed in the range 50 to 90°C, keeping constant all the other reaction parameters (Table 3.1, **Figure 3.2**).

Table 3.1 – Effect of temperature in hydroformylation of **3.1** with Rh/**L2**-OBn catalyst.[a)]

T (°C)	TOF[b)] (h^{-1})	Regio.[c)] (%)
50	40	97
60	144	95
70	176	91
80	208	89
90	232	80

[a)] **Reaction conditions**: $[Rh(CO)_2(acac)]$=0.193mM, solvent: toluene (15 mL); S/Rh=800; **3.1**/Rh=5; P=30 bar (CO/H_2); incubation: 40 bar (CO/H_2), T=80°C, 1h. [b)] Turnover frequency calculated until *ca.* 20% conversion. [c)] Regioselectivity for 2-phenylbutanal **3.2**. Chemoselectivity for aldehydes was ≥ 99% in all cases.

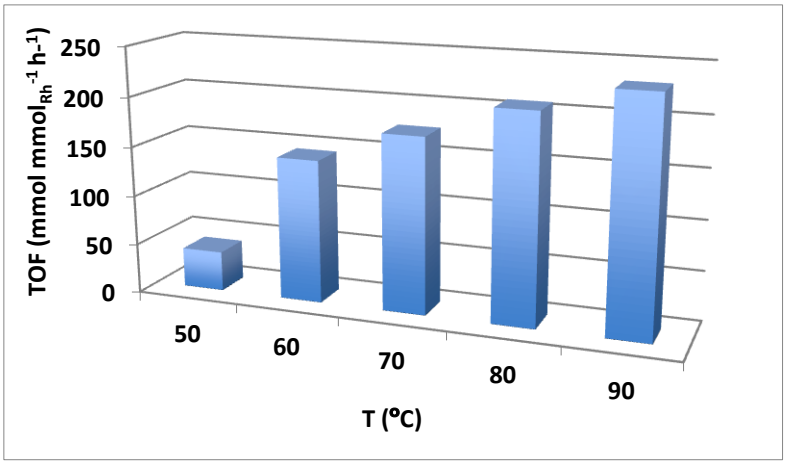
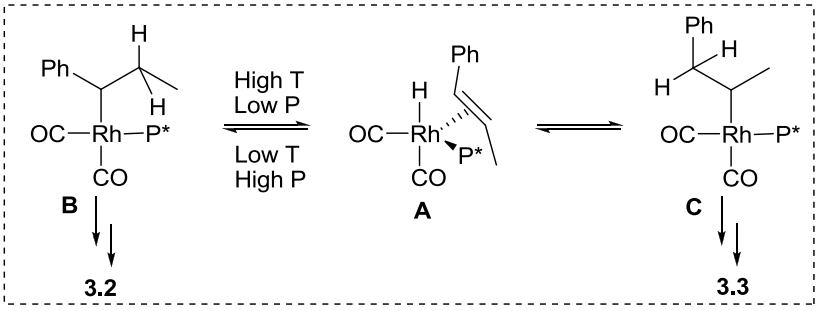


Figure 3.2 – Graphical representation of hydroformylation initial rates as a function of temperature.

The results, presented in Table 3.1 and illustrated in **Figure 3.2**, showed a sharp increase of the reaction rate (*ca.* 3.5 times) when temperature was raised from 50 to 60°C. Above 60°C, the rate steadily increased linearly with temperature, following a non-Arrhenius behavior. The low TOF value observed below 60°C can be attributed to the occurrence of a required stage for regeneration of the active catalytic species after the incubation period, or just due to low activity of Rh/**L2**-OBn toward the hydroformylation of the disubstituted olefin **3.1**, at this temperature. Furthermore, by varying the temperature from 50°C to 90°C, the regioselectivity for **3.2** decreased from 97% to 80%, possibly due to equilibrium shift toward the rhodium σ-alkyl intermediate **C**, as a result of faster occurrence of β-hydride elimination in species **B** (**Scheme 3.2**). Similar effects were previously reported by Lazzaroni *et al*. in Rh/carbonyl-catalyzed hydroformylation of styrene.[51]



Scheme 3.2

Next, the effect of the ligand/Rh molar ratio, being changed from 1 to 20, was investigated in the catalytic performance (Table 3.2, **Figure 3.3**).

Table 3.2 – Effect of **L2**-OBn/Rh molar ratio in hydroformylation of **3.1**.[a)]

L/Rh	[ligand] (mM)	TOF [b)] (h^{-1})	Regio.[c)] (%)
1	0.193	184	85
2.5	0.483	216	88
5	0.965	208	89
15	2.895	160	90
20	3.860	144	91

[a)] **Reaction conditions**: $[Rh(CO)_2(acac)]$=0.193 mM; solvent: toluene (15 mL); **3.1**/Rh=800; P=30 bar (CO/H_2); T=80°C; incubation: 40 bar (CO/H_2), T=80°C, 1h. [b)] Turnover frequency calculated until *ca.* 20% conversion. [c)] Regioselectivity for 2-phenylbutanal **3.2**. Chemoselectivity for aldehydes was ≥ 99% in all cases.

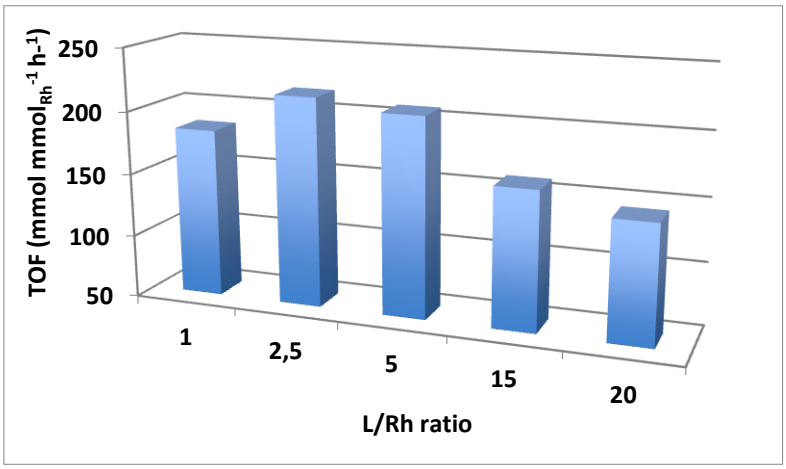
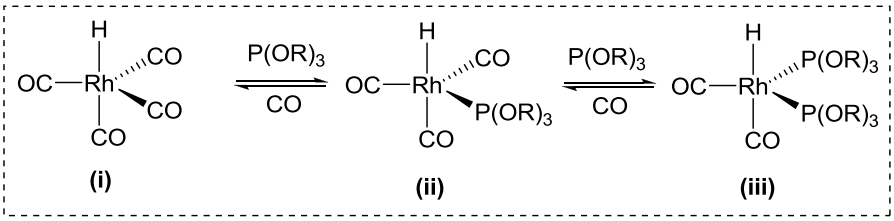


Figure 3.3 – Graphical representation of hydroformylation initial rates as a function of ligand/rhodium ratio.

The results, summarized in Table 3.2 and illustrated in **Figure 3.3**, showed that the maximum rates were achieved in the interval from 2.5 to 5 ligand/rhodium molar ratios. An equimolar Rh/phosphite ratio seems to be not enough to shift the equilibrium toward the active catalytic precursor **(ii)** (**Scheme 3.3**), indicating that its formation requires an excess of phosphite. However, further increase of the monophosphite concentration led to a drop in the rate, suggesting that a less active species containing two phosphite units **(iii)** might co-exist in equilibrium with the

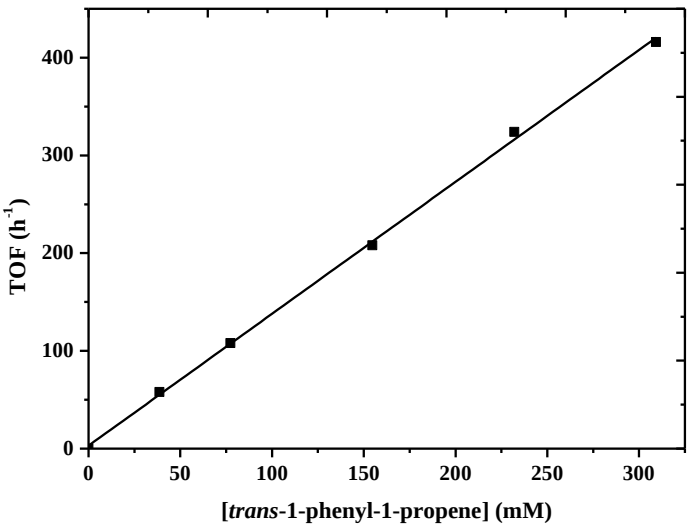
species with only one ligand coordinated **(ii)**, in a situation that resembles Rh/triphenylphosphine catalysts.[52,53,54]



Scheme 3.3

Remarkably, the regioselectivity for aldehyde **3.2** has slightly increased when the phosphite/Rh ratio was raised from 1 to 20, which indicates that the rates of formation of species **B** and **C** (**Scheme 3.2**) are also dependent from the concentration of monophosphite ligand. Similar non-linear effects of ligand/rhodium ratios in the catalytic activity and selectivity were also reported with other Rh(I) catalysts containing naphthyl and biphenyl based monodentate phosphites.[55,56]

The effect of substrate concentration on the reaction rate was then studied, by using different initial concentration of **3.1**, from 38.7 to 309.3 mM (**Figure 3.4**).



Reaction conditions: [$Rh(CO)_2(acac)$]=0.193mM, solvent: toluene (15 mL); **L2**-OBn/Rh=5; P=30 bar (CO/H_2); T=80°C.

Figure 3.4 – Turnover frequency *versus* substrate initial concentration, in hydroformylation of **3.1** with Rh/**L2**-OBn catalyst.

The plot of turnover frequencies as function of the substrate initial concentration (**Figure 3.4**) nicely fits with a straight line, indicating that the reaction is first order with respect to the substrate. This is in agreement with several reports on hydroformylation of other substituted alkenes, in which the olefin coordination and/or the hydride migration may be the reaction rate determining steps, independently from the type of catalyst used. Moreover, the chemoselectivity for aldehydes was always up to 99% and nearly constant regioselectivity (88-89%) for **3.2** was observed in all experiments.

Next, the effect of catalyst concentration on hydroformylation initial rate was analyzed (Table 3.3, **Figure 3.5**).

Table 3.3 – Effect of Rh concentration in the catalytic hydroformylation of **3.1** with Rh/**L2**-OBn.[a)]

[$Rh(CO)_2(acac)$] (mM)	Initial rate[b)] ($mmol \cdot h^{-1}$)	Regio.[c)] (%)
0.018	0.003	90
0.095	0.255	90
0.129	0.317	89
0.193	0.603	89
0.386	1.253	91
0.580	1.810	91

[a)] **Reaction conditions**: [**3.1**]=154.7mM, solvent: toluene (15 mL); **L2**-OBn/Rh=5; P=30 bar (CO/H_2); T=80°C; incubation: 40 bar (CO/H_2), T=80°C, 1h. [b)] Initial rate, expressed in mmol of substrate **3.1** converted into aldehydes per hour, until *ca.* 20% conversion. [c)] Regioselectivity for 2-phenylbutanal **3.2**. Chemoselectivity for aldehydes was ≥ 99% in all cases.

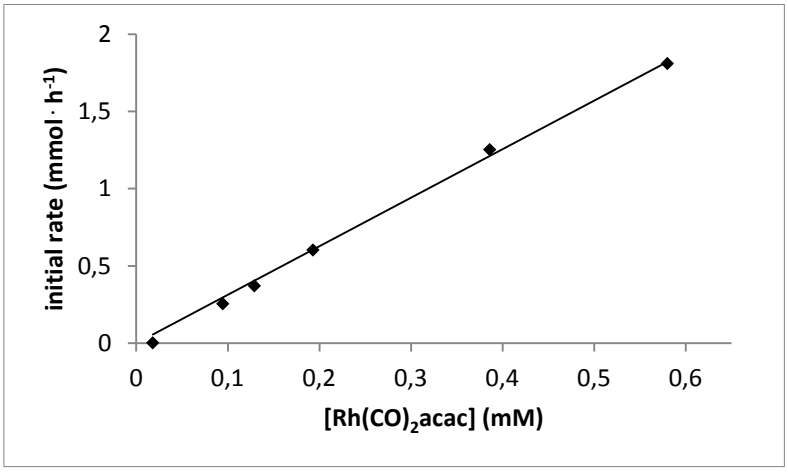


Figure 3.5 – Initial rates *versus* Rh concentration, in hydroformylation of **3.1** with Rh/**L2**-OBn catalyst.

From the results, collected in Table 3.3 and illustrated in **Figure 3.5**, it becomes evident that the formation of products is linearly proportional to the rhodium precursor concentration, which means that, as expected, the reaction is also first order with respect to the catalyst. Furthermore, no significant changes were observed in regioselectivity with variation of initial rhodium concentration, while the chemoselectivity for aldehydes was always above 99%.

Finally, the effects of CO and H_2 partial pressures were appraised in the reaction initial rate and regioselectivity, with the results being summarized in Table 3.4 and graphically represented in **Figure 3.6** and **Figure 3.7**.

Table 3.4 – Effects of H_2 and CO partial pressures on the hydroformylation of **3.1**, with Rh/**L2**-OBn catalyst.[a)]

Entry	P(CO) (bar)	P(H_2) (bar)	TOF [b)] (h^{-1})	Regio.[c)] (%)
1	10	5	102	84
2	10	10	200	85
3	10	20	376	88
4	10	30	552	88
5	20	2	66	82
6	20	5	112	88
7	20	10	176	88
8	20	20	360	90
9	5	10	277	81
10	25	10	156	95
11	2	20	313	81
12	5	20	340	86

[a)] **Reaction conditions**: [$Rh(CO)_2(acac)$]=0.193mM, solvent: toluene (15 mL) toluene; **3.1**/Rh=800, **L2**-OBn/Rh=5; T=80°C; incubation: 40 bar (CO/H_2), T=80°C, 1h. [b)]Turnover frequency calculated until *ca.* 20% conversion. [c)] Regioselectivity for 2-phenylpropanal **3.2**. Chemoselectivity for aldehydes was $\geq$ 99% in all cases.

As illustrated in **Figure 3.6**, a linear dependence was found between the reaction rate and the partial pressure of H_2, for constant partial pressures of CO, at both 10 bar (Table 3.4, entries 1-4) and 20 bar (Table 3.4, entries 5-8). Furthermore, when a CO partial pressure of 10 bar was used (Table 3.4, entries 1-4), the regioselectivity for aldehyde **3.2** did not show any dependence on p(H_2). However, at a p(CO) of 20 bar, the increase of p(H_2) from 2 to 20 bar led to a moderate improvement in the regioselectivity for **3.2** from 82 to 90% (Table 3.4, entries 5-8). These results suggest

that although the rate of aldehydes formation is first order dependent from $p(H_2)$, the rates of formation of the different regioisomers **3.2** and **3.3** are only influenced by H_2 partial pressure, when a higher CO partial pressure is used.

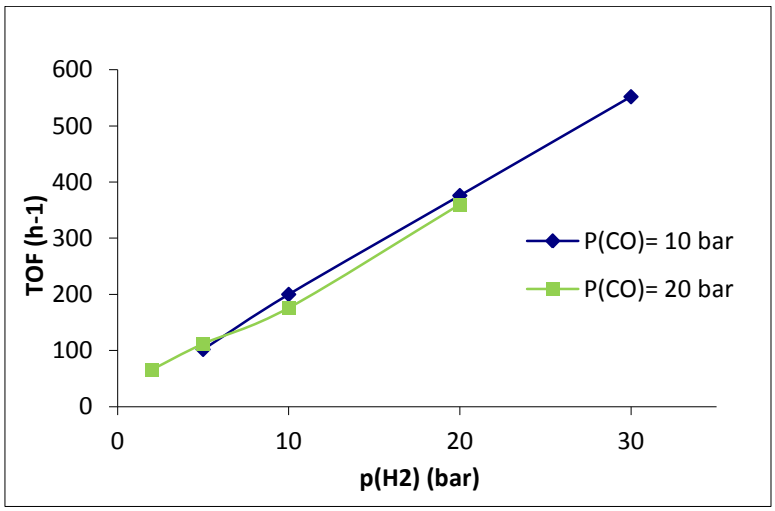


Figure 3.6 – Turnover frequency *versus* H_2 partial pressure, in hydroformylation of **3.1** with Rh/**L2**-OBn catalyst.

Regarding the influence of CO partial pressure on the reaction rate, more complex effects have been observed (**Figure 3.7**).

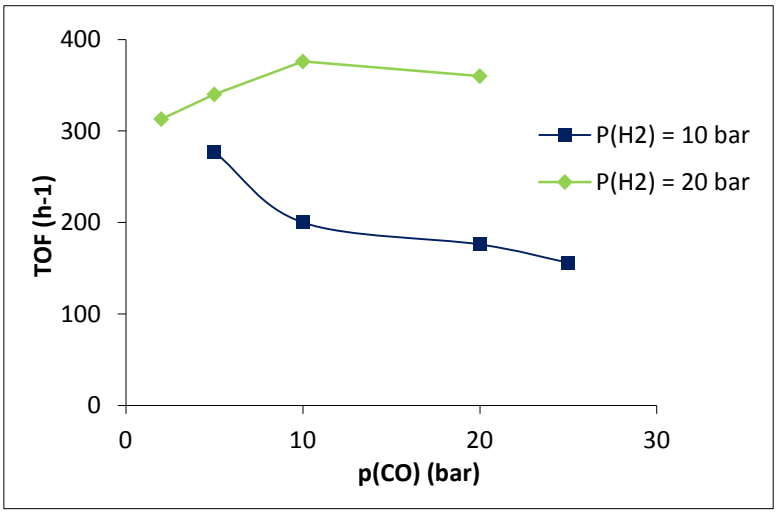


Figure 3.7 – Turnover frequency *versus* CO partial pressure, in hydroformylation of **3.1** with Rh/**L2**-OBn catalyst.

Using a constant H_2 partial pressure of 10 bar, the increase of p(CO) from 5 to 25 bar produced a considerable decrease in the reaction rates (Table 3.4, entries 2,7,9-10). On the other hand, at H_2 partial pressure of 20 bar, an increase in reaction rates was observed by varying the p(CO) from 2-10 bar (Table 3.4, entries 3,11-12), while an opposite tendency was observed by the raise of CO partial pressure from 10 to 20 bar, which has originated a slight rate decrease (Table 3.4, entries 3 and 8). Moreover, a significant increase in the regioselectivity for aldehyde **3.2** was observed when p(CO) was raised, for both H_2 partial pressures of 10 bar (Table 3.4, entries 2,7,9-10) and 20 bar (Table 3.4, entries 3,8,11-12). Therefore, the complex results depicted in **Figure 3.6** and **Figure 3.7** can be explained by the fact that the rates of formation of each isomeric aldehydes **3.2** and **3.3** have different dependences from H_2 and CO partial pressures, leading to noteworthy effects in the reaction rate and regioselectivity.

Based on the previous results, the mechanism for the hydroformylation of *trans*-1-phenylpropene (**3.1**), using the Rh/**L2**-OBn catalyst is proposed in **Figure 3.8**. Contrarily to that observed with the Rh/tris-(*o*-*tert*-butylphenyl)phosphite catalytic systems, the formation of a rhodium complex containing two coordinated monophosphite ligands **(iii)** is possible, however, this species seems to be not catalytically active. The overall steric hindrance around the rhodium center in species **(ii)** is low because it contains a single phosphite ligand and three small carbonyl ligands. In addition, the metal is electron poor, since the phosphite is a weak electron donor ligand, while the three carbonyl ligands are strong electron withdrawing groups. These conditions allow the easy dissociation of CO, with formation of species **H**, and consequently the alkene addition to the rhodium complex gives rise to species **A**. The subsequent hydride migration can result in the formation of both rhodium alkyl complexes **B** and **C**. Depending on the reaction conditions, the species **B** and **C** can undergo CO insertion, forming the complexes **D** and **E**, respectively, with subsequent CO migration resulting in rhodium acyl complexes, or give β-hydride elimination (as focused in **Scheme 3.2**). Subsequently, each rhodium acyl intermediate can suffer oxidative addition by reaction with H_2, while reductive elimination leads to the aldehydes **3.2** and **3.3**, regenerating the active catalytic species **H**.

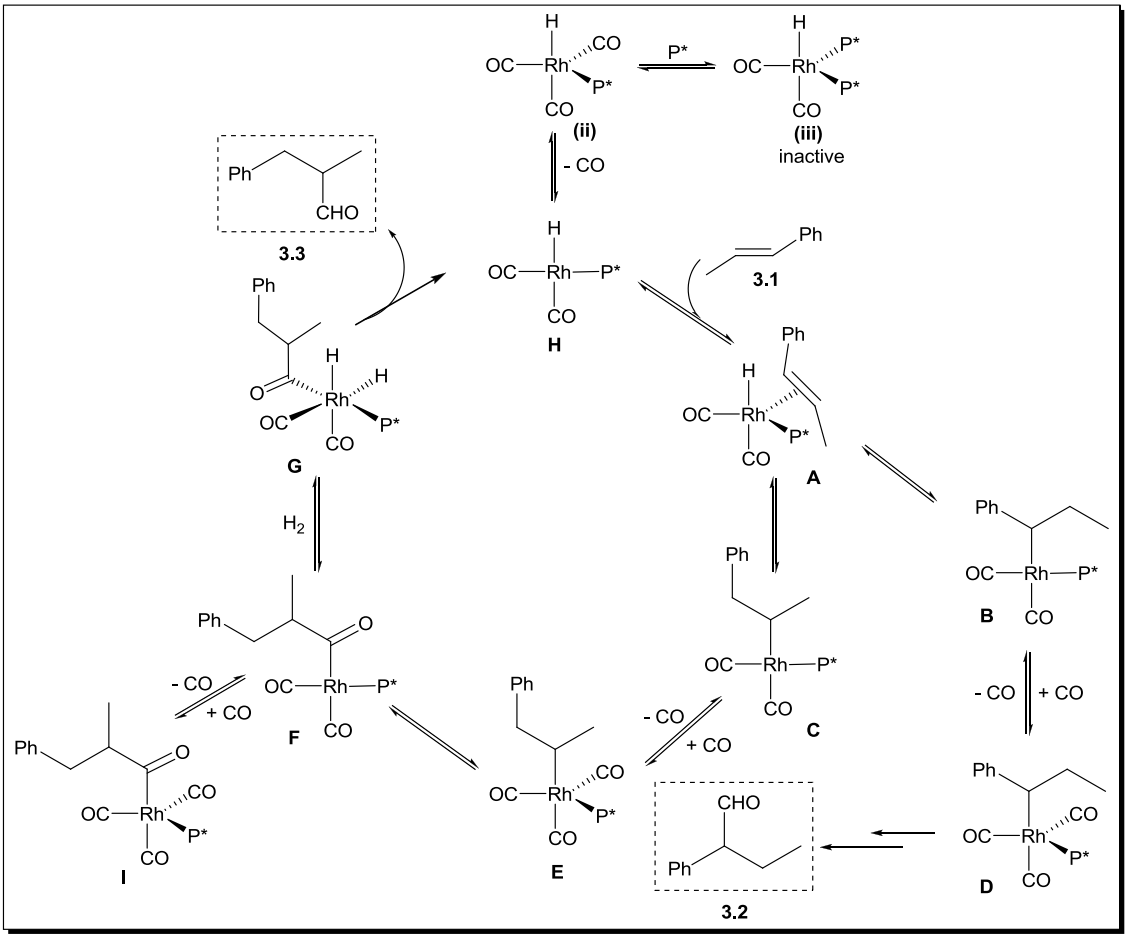


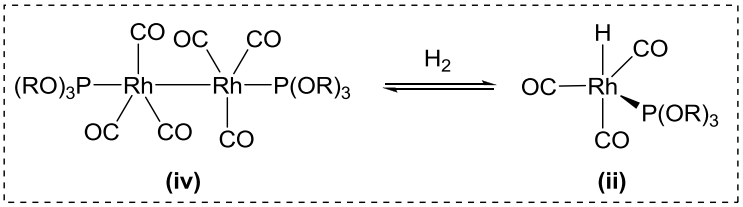
Figure 3.8 – Simplified catalytic cycle of rhodium/monophosphite catalyzed hydroformylation of **3.1**.

It is well established that the kinetics of hydroformylation reactions usually fall in one of the following two models: in the first one, often observed in presence of catalysts containing P-donor ligands with small to medium cone angles, or when sterically hindered olefins are used as substrates, using all type of rhodium catalysts, the alkene coordination and/or the hydride migration can be the rate determining steps.[25] In these cases, the reaction is first order with respect to the substrate, but it does not depend from the hydrogen pressure, while it is assumed that the resting state of the catalyst is a hydrido species, *i.e.* the species $\{RhH(CO)_xL_{(4-x)}\}$ (**ii**). In the second model, usually observed when catalysts containing bulky phosphites are used in the hydroformylation of 1-alkenes, the oxidative addition of H_2 to the acyl intermediate of type **F** is the rate determining step. Consistently, the reaction is first order with respect to H_2 partial pressure, and zero order for the substrate

concentration. Furthermore, since the resting state of the catalyst is the 18 electrons intermediate {Rh(COR)$(CO)_xL_{(4-x)}$} of type **I** (**Figure 3.8**) that must dissociate a CO ligand before the oxidative addition takes place, the reaction shows an inverse dependence with respect to the CO partial pressure.

In our case, and considering specifically the parameter intervals, [Rh]= 0.02-0.60 mM, phosphite/Rh ≥ 5, [**3.1**]= 30-300 mM, and CO and H_2 partial pressures ≥ 10 bar, the following effects were observed: i) first order with Rh concentration; ii) negative order with ligand concentration; iii) first order with the olefin concentration; iv) first order with H_2 partial pressure; v) negative order with CO partial pressure. The partially negative orders for the CO pressure and ligand, combined with a positive order with respect to the substrate are reminiscent of the expressions found for the hydroformylation of 1-alkenes with Rh/PPh_3 catalysts.[52,53,54,57,58] However, the most remarkable result on the kinetics of hydroformylation of *trans*-1-phenylpropene **3.1** with the Rh/**L2**-OBn catalyst is the positive order for both substrate and H_2 partial pressure, suggesting that either the olefin coordination/insertion or the oxidative addition of H_2 to the Rh/acyl intermediate may be the rate determining steps. This ambiguous behavior, also observed with Rh(I) catalysts modified with tris-naphthyl ligands,[55] may be attributed to an intermediate situation, in which there is not a clear rate limiting step, since two of more steps proceed at similar rate.

A second explanation that accounts for great part of similar cases, described in the literature, is the presence of a dinuclear species **(iv)** as resting state, whose fast equilibrium with the Rh-hydrido catalytic precursor **(ii)**, depends on H_2 partial pressure (**Scheme 3.4**). Thus, although the alkene coordination might be assumed as the rate limiting step, the reaction shows a positive order to p(H_2), together with a linear dependence on the substrate.



Scheme 3.4

Although in these studies, the presence of species of type **(iv)** (**Scheme 3.4**) was not proved by experimental evidences, several related dinuclear rhodium/phosphine species, whose specific formulas depend on the CO pressure, phosphine concentration and steric demand, have been spectroscopically observed or characterized in solid state.[59] Furthermore, a solid state structure of this type has also been reported by Claver *et al.* with tris-(*o-tert*-butylphenyl)phosphite,[60] in which one of the rhodium atoms is bearing only two CO ligands.

Considering the successful experiments regarding the use of Rh/**L2**-OBn catalyst in the hydroformylation of the 1,2-disubstituted alkene **3.1**, with high levels of activity, chemo- and regioselectivity, the ligands screening was subsequently carried out, to evaluate the effects of the OR substituents at 2-binaphthyl position of the monophosphite ligands, in the activity and selectivity of the respective rhodium complexes. The kinetic studies previously performed, allowed us to select the optimal reaction conditions, considering both activity and regioselectivity features.

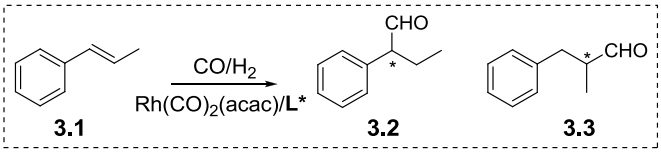
Thus, the hydroformylation of **3.1** (**Scheme 3.1**) was carried out, in the presence of Rh catalysts formed *in situ* by addition of $Rh(CO)_2(acac)$ to 5 molar equiv of each ligand **L1**-OMe, **L2**-OBn, **L3**-$OCHPh_2$ and **L4**-OAd, using a temperature of 80°C, a *syngas* pressure of 30 bar (CO/H_2 1:1), and a substrate/Rh ratio = 800. It should be noted that, prior to each reaction, incubation was carried out by reaction of the rhodium precursor, $Rh(CO)_2(acac)$ with the ligand, at 40 bar of CO/H_2 and 80°C for 1 h, to ensure the formation of the catalytic resting state. The experimental procedure was, in all cases, similar to that described for hydroformylation of **3.1** with **L2**-OBn.

As previously described, samples taken from the autoclave were analyzed by GC in order to determine conversion, chemo- and regioselectivity. Furthermore, in order to determine enantioselectivities, the resulting aldehydes, which are known to be very susceptible toward racemization as result of keto-enol tautomerism, were immediately oxidized to the corresponding carboxylic acids. In a typical oxidation procedure,[61] the aldehydes were added to a $KMnO_4$ solution in acetone and the mixture was stirred at room temperature, for 15-30 minutes. Then, the solvent was evaporated and the residue was dissolved in H_2O, at 70°C. The solution was washed with dichloromethane to remove unreacted alkenes and non-oxidized aldehydes, and the aqueous phase was

then acidified with 10% HCl solution (until pH=1) to ensure the protonation of carboxylates. The extraction of carboxylic acids was performed with dichloromethane. After drying and filtering, the solvent was removed under vacuum, and the resulting product was dissolved in CH_2Cl_2, and analyzed by GC, using a chiral column.

The comparative results of the hydroformylation of **3.1**, with the different Rh/monophosphite catalysts are presented in Table 3.5.

Table 3.5 – Ligands' evaluation in Rh-catalyzed hydroformylation of *trans*-1-phenylpropene **3.1**.[a)]



Entry	Ligand (**L***)	Conv.[b)] (%)	TOF[c)] (h^{-1})	Regio.[d)] (%)	ee (%)[e)]
1	no ligand	25	67	62	-
2	(*R*)-**L1**-OMe	81	216	84	16 (*R*)
3	(*R*)-**L2**-OBn	72	192	88	20 (*R*)
4	(*S*)-**L2**-OBn	74	197	89	20 (*S*)
5	(*R*)-**L3**-$OCHPh_2$	33	88	89	11 (*R*)
6	(*R*)-**L4**-OAd	97	259	84	12 (*R*)

[a)] **Reaction conditions**: [$Rh(CO)_2(acac)$]=0.193 mM, solvent: toluene (15 mL); **3.1**/Rh=800, **L**/Rh=5; T=80°C; P(CO/H_2)=30 bar; t=3 h; incubation: 40 bar (CO/H_2), T=80°C, 1h (except in entry 1). [b)] % of substrate converted at the indicated time. [c)] Turnover frequency expressed in mol of substrate converted per mol of Rh per hour. [d)] Regioselectivity: % of **3.2** with respect to the total amount of aldehydes. [e)] % Enantiomeric excess measured for **3.2**, after derivatization to the corresponding carboxylic acids. Chemoselectivity for aldehydes was ≥ 99% in all cases.

From analysis of Table 3.5, it is possible to observe the effects of the different ether OR substituents at the ligand in the catalytic activity and selectivity, under the studied reaction conditions. It is worth mentioning that the rhodium complex modified with ligand (*R*)-**L4**-OAd, provided the most active catalytic system, with practically full conversion (97%) in 3 h, achieving a TOF = 259 h^{-1} (Table 3.5, entry 6). The Rh/(*R*)-**L1**-OMe catalyst provided also a remarkable activity with 81% conversion in 3h, with a TOF = 216 h^{-1} (Table 3.5, entry 2). The Rh/(*R*)-**L2**-OBn catalytic system presented slightly lower activity (Table 3.5, entry 3), while the catalyst with ligand (*R*)-**L3**-$OCHPh_2$ showed the lowest activity, with only 33% of conversion in 3h (Table 3.5, entry 5).

These tendencies become more evident in **Figure 3.9**, which shows the reaction's evolution along the time.

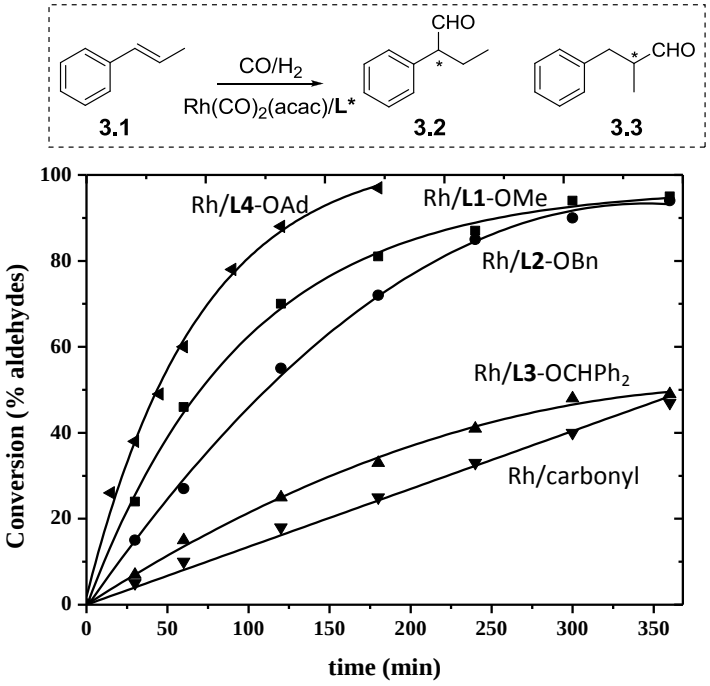


Figure 3.9 – Comparative plot of conversion *versus* time, in hydroformylation of **3.1**, catalyzed by different Rh(I) catalysts.

The most remarkable feature of the *in situ* catalytic systems, formed from $Rh(CO)_2(acac)$ and the monophosphite ligands, is the higher activity compared to the parent Rh/carbonyl catalyst. The catalytic system Rh/**L4**-OAd is clearly the most active, as can be seen by the high initial rate. Regarding the catalysts Rh/**L1**-OMe and Rh/**L2**-OBn, although presenting a fairly different behavior along the time, both achieved 90% conversion in 5h. Finally, the system Rh/**L3**-$OCHPh_2$ produced a considerably inferior performance, achieving similar conversion to that obtained with the Rh/carbonyl catalyst. The high rates obtained with the use of **L4**-OAd, **L1**-OMe and **L2**-OBn might be related with the *P*-monodentate coordination to rhodium, which is probably dominating. Furthermore, π-interactions between the phenyl moieties in **L2**-OBn or **L3**-$OCHPh_2$ with that of the substrate might be operative regarding both catalytic activity and regioselectivity (see discussion below regarding regioselectivity).

Concerning the reaction regioselectivity, the catalytic systems Rh/**L2**-OBn and Rh/**L3**-$OCHPh_2$ provided a preferential formation of *ca*. 90% for 2-phenylbutanal **3.2** (Table 3.5, entries 3-5), while the most active systems Rh/**L1**-OMe and Rh/**L4**-OAd gave slightly lower regioselectivities (84%) for **3.2** (Table 3.5, entries 2 and 6). Although the ligand **L3**-$OCHPh_2$ provided the less active catalytic system, with the reaction rate in the same magnitude of the unmodified Rh/carbonyl catalyst, the regioselectivity (90%) obtained for aldehyde **3.2** is considerably higher than that of 67% achieved in the absence of ligand. This observation suggests that **L3**-$OCHPh_2$ is able to coordinate with Rh(I), however the resulting Rh(I)/monophosphite complex presents low activity, probably as a result of the high steric hindrance exerted by the diphenylmethoxy groups (**Figure 3.10**), which may enclose the metal, preventing the olefin insertion.

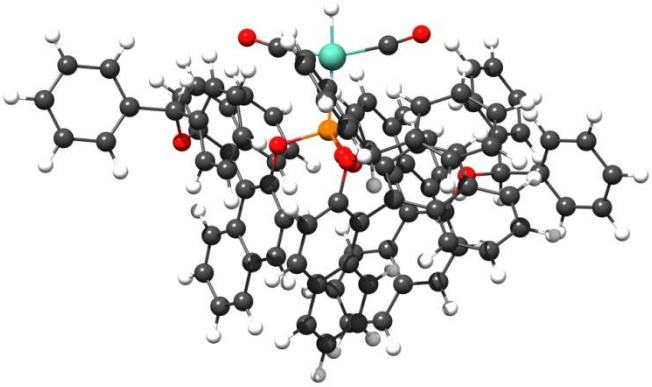
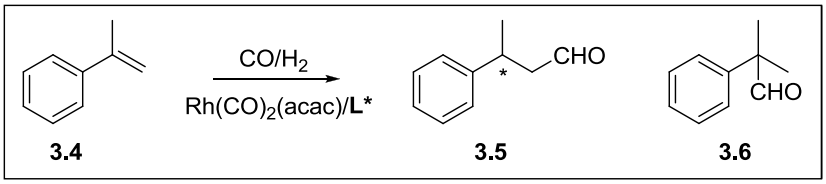


Figure 3.10 – Minimized energy structure of the coordinatively unsaturated complex *trans*-[$RhH(CO)_2$(**L3**-$OCHPh_2$)], at the ONIOM (BP86/SDD:UFF) level.

Low enantioselectivities were achieved with all the catalytic systems (11-20% ee), with the highest enantiomeric excess being achieved with Rh/**L2**-OBn catalyst. As expected, the stereo configuration of the binaphthyl backbone at the monophosphite ligand did not affect either catalytic activity or selectivity, with (*S*)-**L2**-OBn as ligand in the hydroformylation of **3.1**, produced similar results to those obtained with its (*R*) analogue, however with inverse absolute configuration of the products (Table 3.5, entries 3-4). After evaluation of the monophosphite ligands in the asymmetric Rh-catalyzed hydroformylation of *trans*-1-phenylpropene (**3.1**), the studies were extended to the 1,1-disubstitued olefin, 2-phenylpropene (**3.4**).

The hydroformylation of **3.4** can eventually origin the two aldehydes **3.5** and **3.6** (**Scheme 3.5**). However, the exclusive formation of regiosomer **3.5**, in which the stereogenic center at the more substituted carbon atom results from a new C–H bond formation, is generally observed. Thus, the asymmetric hydroformylation of 1,1-disubstituted alkene **3.4** differs from the asymmetric hydroformylation of 1,2-disubstituted alkene **3.1**, since the desired chiral product is the linear aldehyde.



Scheme 3.5

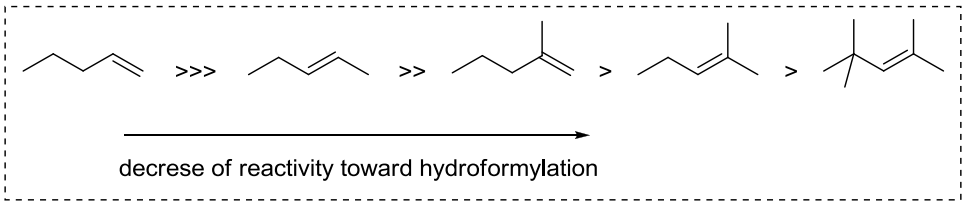
The experimental procedure and the reaction conditions were exactly the same of those used in hydroformylation of **3.1**. However, in the hydroformylation of **3.4**, a reaction time of 18 h was necessary to achieve effective conversions, as a result of the low reactivity of the 1,1-disubstituted double bond, under the previous standard conditions. The identification of the products was performed by appropriate NMR spectroscopic and chiral GC techniques. The results of the hydroformylation of **3.4**, with the different Rh/monophosphite catalysts are presented in Table 3.6.

Table 3.6 – Ligand's evaluation in Rh-catalyzed hydroformylation of 2-phenylpropene **3.4**.[a)]

Entry	Ligand (**L***)	Conv.[b)] (%)	TOF[c)] (h^{-1})	Regio.[d)] (%)	ee (%)[e)]
1	no ligand	41	18	98	-
2	(*R*)-**L1**-OMe	78	35	99	10 (*R*)
3	(*R*)-**L2**-OBn	71	32	100	15 (*R*)
4	(*R*)-**L3**-$OCHPh_2$	47	21	100	8 (*R*)
5	(*R*)-**L4**-OAd	94	42	99	10 (*R*)

[a)] **Reaction conditions**: $[Rh(CO)_2(acac)]$=0.193mM, solvent: toluene (15 mL); **3.4**/Rh=800, **L**/Rh=5; T=80°C; P (CO/H_2)=30 bar; t = 18h; incubation: 40 bar (CO/H_2), T=80°C, 1h (except in entry 1). [b)] % of substrate converted at the indicated time. [c)] Turnover frequency expressed in mol of substrate converted per mol of Rh per hour. [d)] Regioselectivity: % of **3.5** with respect to the total amount of aldehydes. [e)] % Enantiomeric excess measured for **3.5**, after derivatization to the corresponding carboxylic acids. Chemoselectivity for aldehydes was ≥ 99% in all cases.

As expected, the 1,1-disubstituted olefin **3.4** reacted significantly slower than the 1,2-disubstituted olefin **3.1**, in agreement with the previously established relative reactivity of alkenes toward hydroformylation (**Scheme 3.6**).[62,63]



Scheme 3.6

In the hydroformylation of 2-phenylpropene **3.4**, at 80°C and 30 bar of *syngas*, the *in situ* catalysts Rh/(*R*)-**L1**-OMe, Rh/(*R*)-**L2**-OBn, Rh/(*R*)-**L3**-$OCHPh_2$ and Rh/(*R*)-**L4**-OAd have reached conversions of 78, 71, 47 and 94% in 18 h, respectively (Table 3.6, entries 2-5), while a conversion of 41% was obtained without addition of ligand (Table 3.6, entry 1). Therefore, the OR substituents at the ligand have produced again a significant effect on the hydroformylation reaction rates, following the same trend observed for the substrate **3.1** (*i.e.* **L4**-OAd >> **L1**-OMe > **L2**-OBn >> **L3**-$OCHPh_2$).

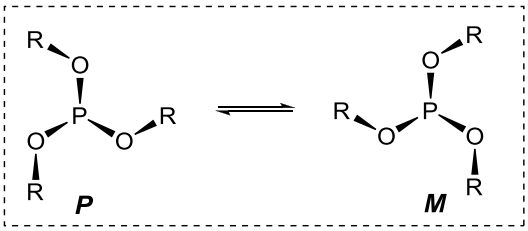
It is worth mentioning that complete chemoselectivity for aldehydes was reached with all catalytic systems, together with a substrate controlled regioselectivity (≥ 98% to the linear aldehyde **3.5**). The preferential insertion of the aldehyde functionality into the less substituted carbon atom of the double bond, follows the Keulemans' rule,[64,65] which states that the formyl group is usually added in order to avoid the formation of a quaternary carbon centre.

All the rhodium/monophosphite catalytic systems led, once more, to low enantioselectivities, being the highest enantioselectivity achieved with Rh/(*R*)-**L2**-OBn (15% ee (*R*)), while all the other systems gave enantiomeric excesses below that value. These results are fairly distant from those obtained in the hydroformylation of **3.4** with rhodium catalysts modified with a binaphthyl derived diphosphite,[66] which albeit being moderate (48% ee) are the highest so far reported for this substrate.[26]

In sum, the ligand structure affected significantly the activity of the Rh/monophosphite catalysts in hydroformylation of both 1,1- and 1,2-disubstituted

aryl olefins, with highest activities being achieved by the use monophosphite ligand containing a bulky and rigid adamantyloxy group (**L4**-OAd). The results suggest that might be a resemblance between this system and the remarkably active Rh systems modified with the bulky tris(*o*-*tert*-butylphenyl)phosphite **L6**. By their turn, the catalytic systems Rh/**L1**-OMe and Rh/**L2**-OBn provided also considerable activities, although not so high as Rh/**L4**-OAd, probably due to the possible coordination of two phosphite ligands to the metal, providing less active catalytic rhodium species (as observed for effect of **L2**-OBn/Rh ratio in hydroformylation of **3.1**). The system containing the monophosphite ligand **L3**-$OCHPh_2$ presented low catalytic activity for both substrates **3.1** and **3.2**, possibly due to steric hindrance of the rhodium complex that might prevent the olefin approach.

Although the potentially hemilabile ether groups at the ligands were intended to provide secondary interactions with the metal, providing hetero-bidentate chelates, the results suggested that under hydroformylation conditions, the monophosphite ligands coordinate to rhodium by a *P*-monodentate mode, which can hardly allow good enantiodiscrimination in this reaction. Another possible reason for the low enantioselectivity might be the formation of different diastereomeric catalytically active species, as a result of the rapid interconversion in solution between the helical *P* and *M* conformers of the monophosphite ligands, which may occur by free rotation of the substituents at the phosphorus atom (**Scheme 3.7**).[67]

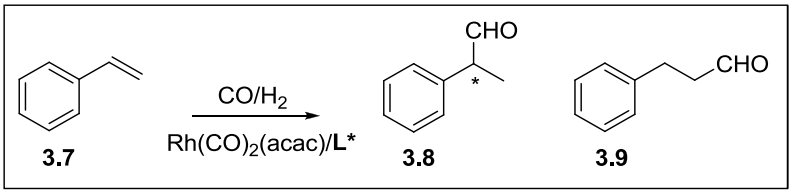


Scheme 3.7

Despite the remarkable activities, chemo- and regioselectivities obtained with the new catalytic systems in the hydroformylation of disubstituted aryl olefins, the achievement of high enantioselectivies with rhodium complexes of the tris-binaphthyl monophosphites remained a fairly distant overcome.

3.2.2 Hydroformylation of styrene

In order to perform the catalytic evaluation of the monophosphite ligands in the asymmetric hydroformylation of a typical terminal aryl olefin, styrene **3.7** was selected as substrate (**Scheme 3.8**).



Scheme 3.8

In a typical experiment, the autoclave was charged with the appropriate amount of phosphite and a solution of $Rh(CO)_2(acac)$ in toluene was then introduced. The reactor was pressurized with 40 bar of an equimolar mixture of CO/H_2, and kept at 80°C for 1 hour. After incubation, the autoclave was slowly depressurized and set to the working temperature. Then, styrene (dissolved in toluene) was introduced through the inlet *cannula* and the autoclave was pressurized with 25 bar of an equimolar mixture of CO/H_2. Samples taken from the autoclave were analyzed by GC, in order to determine conversion, chemo- and regioselectivity. After derivatization of the aldehydes into the corresponding carboxylic acids, by oxidation with $KMnO_4/MgSO_4$, the products were analyzed by chiral GC, in order to determine the enantioselectivity. The results are presented in Table 3.7.

The effects of several reaction parameters were studied, using (*R*)-**L2**-OBn as model ligand. At a temperature of 40°C and *syngas* pressure of 25 bar, the increase of **L2**-OBn/Rh ratio from 2.5 to 10 has caused a significant increment in the catalytic activity (Table 3.7, entries 2-4). The maximum rate was achieved with a tenfold excess ratio, which provided practically full conversion (97%) in 3 hours (Table 3.7, entry 4). Thus, contrarily to that observed with the 1,2-disubstituted olefin **3.1**, the hydroformylation of styrene **3.7** showed a positive order with respect to the ligand concentration. The high regioselectivity for the branched aldehyde 2-phenylpropanal **3.8** was not affected, remaining practically constant (94-96%).

Table 3.7 – Optimization of reaction conditions and ligand evaluation in hydroformylation of styrene **3.7**, with Rh/monophosphite catalysts.[a)]

Entry	Ligand	T (°C)	L/Rh	t (h)	Conv.[b)] (%)	TOF[c)] (h^{-1})	Regio.[d)] (%)	ee (%)
1	no ligand	40	-	3	0	-	-	-
2	(*R*)-**L2**-OBn	40	2.5	3	74	197	94	-
3		40	5	3	91	243	94	-
4		40	10	3	97	259	96	20 (*R*)
5		80	10	0.42	99	1900	74	12 (*R*)
6		50	10	1	94	752	94	16 (*R*)
7		40	10	1	45	360	96	-
8		30	10	3	75	200	97	20 (*R*)
9		15	10	3	10	27	99	-
10		15	10	24	51	17	99	20 (*R*)
11	(*R*)-**L1**-OMe	40	10	3	96	256	96	18 (*R*)
12	(*R*)-**L3**-$OCHPh_2$	40	10	3	91	243	96	15 (*R*)

[a)] **Reaction conditions**: $[Rh(CO)_2(acac)]$=0.2mM, solvent: toluene (7 mL); **3.7**/Rh=800; P (CO/H_2)= 25 bar; incubation: 40 bar (CO/H_2), T=80°C, 1h (except in entry 1). [b)] % of substrate converted at the indicated time. [c)] Turnover frequency expressed in mol of substrate converted per mol of Rh per hour. [d)] Regioselectivity: % of **3.8** with respect to the total amount of aldehydes. Chemoselectivity for aldehydes was ≥ 99% in all cases.

Regarding the effect of the temperature, a remarkable catalytic activity was observed for the Rh/**L2**-OBn catalytic system at 80°C, achieving complete conversion after 25 minutes, with a TOF of 1900 h^{-1} (Table 3.7, entry 5), which is within the order of magnitude of the most active catalytic systems reported so far.[46] The reactions, carried out at 50°C and 40°C were accompanied by an obvious rate decrease and a significant increase of the regioselectivity for **3.8** (Table 3.7, entries 6-7), as result of preferential formation of a branched rhodium-alkyl intermediate,[25,51] under high *syngas* pressure and low temperatures. The catalytic system Rh/**L2**-OBn was operative at 30°C, with 75% conversion in 3h and 97% of regioselectivity, while enantioselectivity achieved a maximum of 20% ee (*R*) (Table 3.7, entry 8). Remarkably, at 15°C, the same catalytic system still demonstrated to be active, providing a noteworthy 10% conversion in 3 hours (Table 3.7, entry 9) and 51% conversion after 24 h (Table 3.7, entry 10), with concomitant 99% of regioselectivity for the branched aldehyde. However, by decreasing the reaction temperature, no improvements were achieved regarding the enantioselectivity.

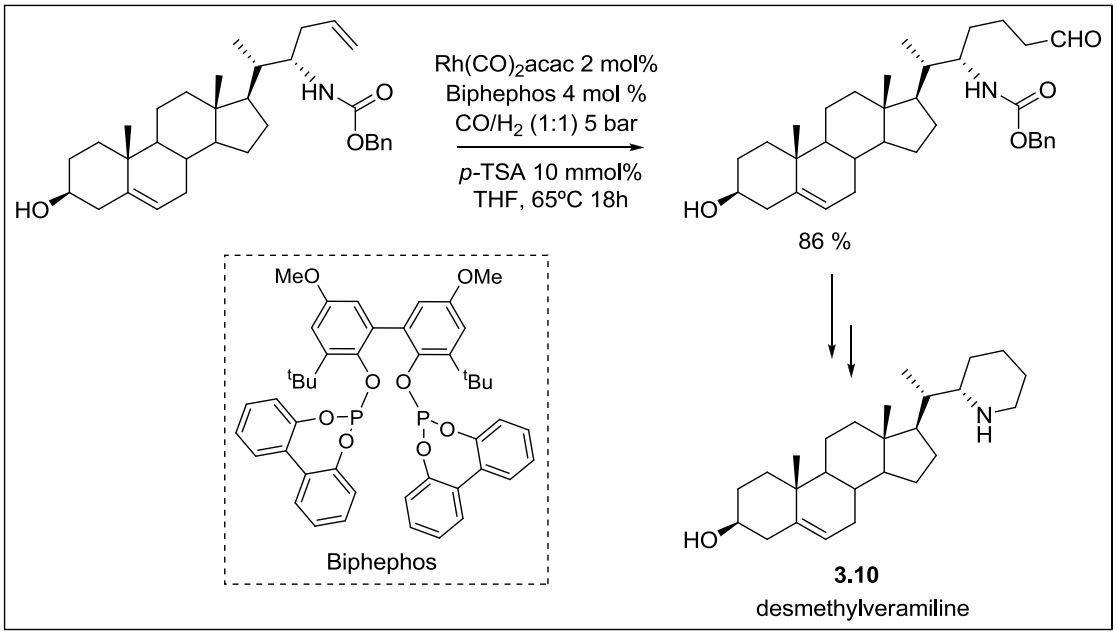
The catalytic evaluation was extended to **L1**-OMe and **L3**-$OCHPh_2$, selected for being, respectively, the less and the most bulky ligands among this C_3-symmetry monophosphites. It is worth mentioning that the catalytic activities of Rh/**L1**-OMe and Rh/**L3**-$OCHPh_2$ were similar to that achieved with Rh/**L2**-OBn, under the same reaction conditions (T = 40°C , P_{syngas} = 25 bar), both providing conversions above 90% in 3h reaction, with TOF's in the order of 250 h^{-1} (Table 3.7, entries 11-12). Furthermore, it should be also noted that, using all catalytic systems, full chemoselectivity for aldehydes, 96% of regioselectivity for the branched aldehyde and enantioselectivity equal or below 20% ee were obtained (Table 3.7, entries 4, 11 and 12). Therefore, contrarily to that observed in the hydroformylation of disubstituted aryl olefins, the OR substituent at the ligand did not affect the catalytic activity or selectivity in hydroformylation of a terminal aryl olefin.

3.2.3 Diastereoselective hydroformylation of 17β-acetoxyandrost-4-ene

Hydroformylation is now a well-established process for the direct introduction of formyl groups onto external or internal double bonds, so its use as a potential method for organic synthetic applications has been steadily growing.[30,68] Particularly, the hydroformylation of C-C double bonds in specific positions of steroidal substrates allows the modulation of their properties and may lead to the preparation of high valuable formyl steroid derivatives, with potential biological activity.[69,70]

The introduction of formyl groups onto the internal double bond of the steroid nucleus was firstly reported in the 1950's by Pike *et al.* via non-modified cobalt-catalyzed hydroformylation.[71] The hydroformylation and hydroalkoxycarbonylation of less hindered $\Delta^{16,17}$-unsaturated steroid substrates were later developed by Tőrös, using Rh/phosphine[72] and Pd-phosphine[73,74] catalysts. The same author provided the first example of androstene and pregnene derivatives functionalization, through sequential hydroformylation-amidocarbonylation reactions, using Rh/PPh_3 or binary Rh/Co catalysts.[75] Bayón and Pereira reported the diastereoselective hydroformylation of Δ^4-unsaturated steroids of androstene, cholestene and pregnene series, with the Rh(I)/tris(*o-tert*-butylphenyl)phosphite catalytic system, which allowed the one-step synthesis of new 4β-formyl-derivatives.[76,77]

More recently, Wuts have described an approach to the synthesis of a steroid molecule marketed for the treatment of hypertension – *eplerenone* – which involved a combination of microbiological and metal-catalyzed carbonylation reactions.[78] Another recent example of catalytic carbonylation reactions applied in the preparation of biologically active steroids is the work of Mann, who reported the synthesis of desmethylveramiline **3.10** (an aza steroidal derivative with remarkable enzyme inhibitor properties), through a seven steps procedure, which included the Rh/Biphephos catalyzed hydroformylation of a terminal olefin, as the key step for the construction of a piperidine appendage (**Scheme 3.9**).[79]

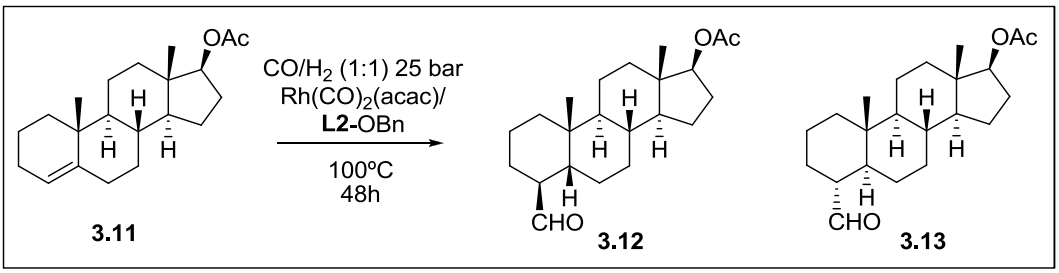


Scheme 3.9

Therefore, encouraged by the challenge of promoting the hydroformylation of carbon-carbon double bonds in steroidal nuclei, and taking advantage from the high activities and regioselectivities achieved with the new rhodium/monophosphite catalysts in the hydroformylation of disubstituted aryl olefins, the studies were extended to the hydroformylation of a steroidal alkene.

The Δ^4-unsaturated steroid 17β-acetoxyandrost-4-ene **3.11**[80] was selected as substrate, and **L2**-OBn was used as model ligand to study the applicability of the Rh/tris-binaphthyl monophosphite catalytic systems to this particular reaction.

Two possible aldehydes **3.12** and **3.13** can be formed, as result of the *cis* addition of an H atom and a formyl group to both diastereotopic faces of the steroidal olefin (**Scheme 3.10**).



Scheme 3.10

In a typical procedure procedure,[76,77] the autoclave was charged with the rhodium precursor $Rh(CO)_2(acac)$ and the ligand **L2**-OBn and (L:Rh ratio = 5), and toluene was then added under vacuum. After incubation, at 40 bar *syngas* and 80°C temperature during 1h, the steroid substrate **3.11**, dissolved in toluene was introduced via *cannula* (substrate:Rh ratio = 50), the autoclave was pressurized with 25 bar of an equimolar mixture of CO/H_2, and the reaction was conducted at 100°C, for 48h. After the reaction was finished, the autoclave was cooled, slowly depressurized, and toluene was removed under reduced pressure. The identification of products was performed by NMR and MS spectroscopic techniques. The chemo-, regio- and diastereoselectivity were determined by GC analysis and ^{1}H and ^{13}C NMR spectroscopy, based on the previously performed assignments.[76]

The results are presented in Table 3.8, in a comparative study with literature values, obtained with Rh(I)/tris(*o*-*tert*-butylphenyl)phosphite catalysts.[76] The Rh/(*R*)-**L2**-OBn catalytic system demonstrated to be active in the hydroformylation of 17β-acetoxyandrost-4-ene **3.11**, achieving 95% of conversion in 48 h, with 86% of chemoselectivity for aldehydes and 70% of diastereoselectivity for 4β-formyl-17β-acetoxy-5β-androstrane **3.12** (Table 3.8, entry 2). Nevertheless, the Rh/(*S*)-**L2**-OBn catalyst showed significantly lower activity, with the same conditions, achieving only 62% of conversion in 48 h, a similar chemoselectivity of 84% for aldehydes and a lower diastereoselectivity (61%) for the 4β-formyl derivative (Table 3.8, entry 3).

Table 3.8 – Diastereoselective hydroformylation of 17β-acetoxyandrost-4-ene **3.11**.

Entry	Ligand	P (bar)	**3.11**/Rh ratio	**L**/Rh ratio	Conv.[a] (%)	TOF[b] (h^{-1})	Chemo.[c] (%)	β-Diast.[d] (%)
1	no ligand	25	50	-	0	0	-	-
2[e]	(*R*)-**L2**-OBn	25	50	5	95	1	86	70
3[e]	(*S*)-**L2**-OBn	25	50	5	62	0.7	84	61
4[f]	**L6** $P(O\text{-}o\text{-}^tBuC_6H_4)_3$	20	50	2.5	60	0.6	78	60[76]
5[f]		20	10	2.5	89	0.2	85	61[76]
6[f]		20	10	10	89	0.2	85	61[76]
7[f]		40	10	2.5	89	0.2	77	68[76]

[a] Percentage of substrate converted; b) Turnover frequency, expressed in mmol of converted substrate per mmol Rh per hour [c] Chemoselectivity calculated as percentage of aldehydes in the total amount of products; [d] Diastereoselectivity calculated as percentage of β-isomer **3.12**, in the total amount of 4-formyl derivatives. Regioselectivity for 4-formyl-17β-acetoxy-5β-androstrane was 100% in all cases.
[e] **Reaction conditions**: 0.019 mmol of $Rh(CO)_2(acac)$, 0.057 mmol of **L2**-OBn and 0.948 mmol of substrate, solvent: toluene (6 mL); T = 100°C, t = 48 h.
[f] **Reaction conditions**: 0.025 mmol of $Rh_2(\mu\text{-}OMe)_2(cod)_2$, solvent: toluene (6 mL); T = 100°C, t = 48 h.

In general, the results are consistent with those obtained with tris(*o*-*tert*-butylphenyl)phosphite (**L6**), although these have been achieved with a different rhodium precursor, and slightly different reaction conditions. For instance, when the classic rhodium/bulky phosphite catalyst was used in a substrate/Rh molar ratio of 50 (and ligand:Rh ratio = 2.5), the TOF and β-diastereoselectivity were similar to those achieved with Rh/(*S*)-**L2**-OBn (Table 3.8, entries 3 and 4). On the other hand, using a substrate/Rh molar ratio of 10, and a *syngas* pressure of 40 bar, the β-diastereoselectivity close to 70% was similar to that obtained with Rh/(*R*)-**L2**-OBn, although with the latter being *ca.* five times for active (Table 3.8, entries 2 and 7).

As previously observed, the exclusive formation of 4-formyl derivatives occurs as result of the insertion of the aldehyde functionality into the less substituted carbon atom, avoiding the formation of a quaternary carbon centre, according to the Keulemans' rule.[64,65] Furthermore, the 100% of regioselectivity suggests also that the reaction takes place by direct hydroformylation of Δ^4 double bond and not through previous isomerization of the substrate, for which a more complicated mixture of products would be expected. The stereochemistry of the reaction can be rationalized by considering the existence of a steroidal stable conformation with a partially folded structure along the A and B rings-fusion.[81] The Δ^4-double bond is further away from the steric influence of the β-methyl substituent on C-10. Thus, the aldehyde **3.12** is the

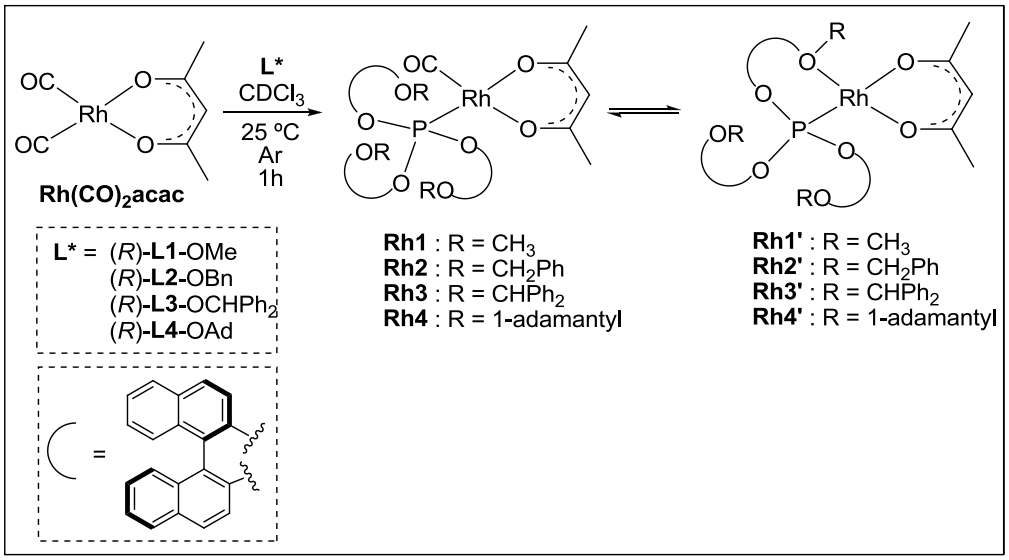
major diastereoisomer formed, as result of the preferential attack of the catalyst to the β-face of the steroidal skeleton double bond. These observations contrast with those reported for the hydroformylation of Δ^5-unsaturated steroids, which afforded preferentially α-addition products.[71,82]

In conclusion, the Rh/**L2**-OBn catalysts were able to hydroformylate a trisubstituted Δ^4-double bond of a steroidal substrate, with similar activities to those previously achieved with tris(*o-tert*-butylphenyl)phosphite. Remarkably, the (*R*)-binaphthyl derived monophosphite ligand (*R*)-**L2**-OBn led to a more active and stereoselective catalytic system than the (*S*)-binaphthyl counterpart (*S*)-**L2**-OBn, which indicates that, in the case of the diastereoselective hydroformylation of 17β-acetoxyandrost-4-ene **3.11**, there might be the existence a *matching-mismatching* effect[83] between the stereoconfiguration of the substrate and the catalysts.

3.2.4 NMR studies of Rh(I)/monophosphite complexes in solution

Rhodium catalysts are typically prepared by mixing a ligand **L** with a rhodium precursor. The resulting complexes, in presence of synthesis gas, can be further converted into a rhodium hydrido complex of type $\{RhH(CO)_xL_{(4-x)}\}$, which is generally the resting state of the catalytic active species. The rate of formation of these complexes depends not only on the reaction parameters (such as temperature, pressure and the solvent) but also on the type of ligand used. Therefore, NMR studies in solution of complexation reactions may provide important information regarding the probable structure of catalytic active species. In order to acquire some information about the coordination mode of the monophosphite ligands to rhodium (regarding the occurrence or not of secondary interactions between the metal and the oxygen atom of the ether substituent at the ligands), ^{31}P NMR studies in solution were performed.

In a typical experiment, the monophosphite ligand and the rhodium precursor $Rh(CO)_2(acac)$, in equimolar amounts, were dissolved in $CDCl_3$, under an argon inert atmosphere, at 25°C, and stirred for 1 h (**Scheme 3.11**). After this time, the ^{31}P NMR spectra of the resulting solutions were registered. After the addition of an extra molar equiv of ligand, the ^{31}P NMR spectra of the resulting solutions were registered again. The results are presented in Table 3.9.



Scheme 3.11

In all ^{31}P NMR spectra, the presence of one major species was evidenced by a ^{31}P NMR doublet in the range 120-125 ppm, with $^{1}J(^{103}Rh\text{-}^{31}P)$ = 289-292 Hz, and also a minor component (≤ 16%), presenting a doublet in the range δ=131-134 ppm with $^{1}J(^{103}Rh\text{-}^{31}P)$ within 260-265 Hz (Table 3.9). Thus, these $^{1}J(^{103}Rh, ^{31}P)$ coupling constants of diagnostic value have proved the direct rhodium-phosphorus bond in all complexes.[84]

Table 3.9 – ^{31}P NMR chemical shifts and $^{1}J(^{103}Rh\text{-}^{31}P)$ of Rh(I)/phosphite complexes.

Complex	^{31}P NMR	
	δ [ppm]	^{1}J (^{103}Rh,^{31}P) [Hz]
Rh1	120.5 (85%)	291
Rh1'	131.0 (15%)	260
Rh2	121.9 (97%)	290
Rh2'	131.2 (3%)	262
Rh3	122.3 (84%)	292
Rh3'	133.3 (16%)	265
Rh4	124.7 (90%)	289
Rh4'	132.3 (10%)	265

Conditions: $CDCl_3$ (under Ar or N_2 atmosphere, at 25°C.

When a twofold excess of ligand was added to the solution, the ^{31}P NMR spectra of the complexes remained unchanged, and only the typical signal of the non-

coordinated phosphite ligand, as a singlet in the range 131-134 ppm, was observed, as illustrated in **Figure 3.11**, for the case of rhodium complexes with (*R*)-**L1**-OMe. Thus, the exclusive formation of rhodium species bearing a single phosphite ligand coordinated to the metal was disclosed.

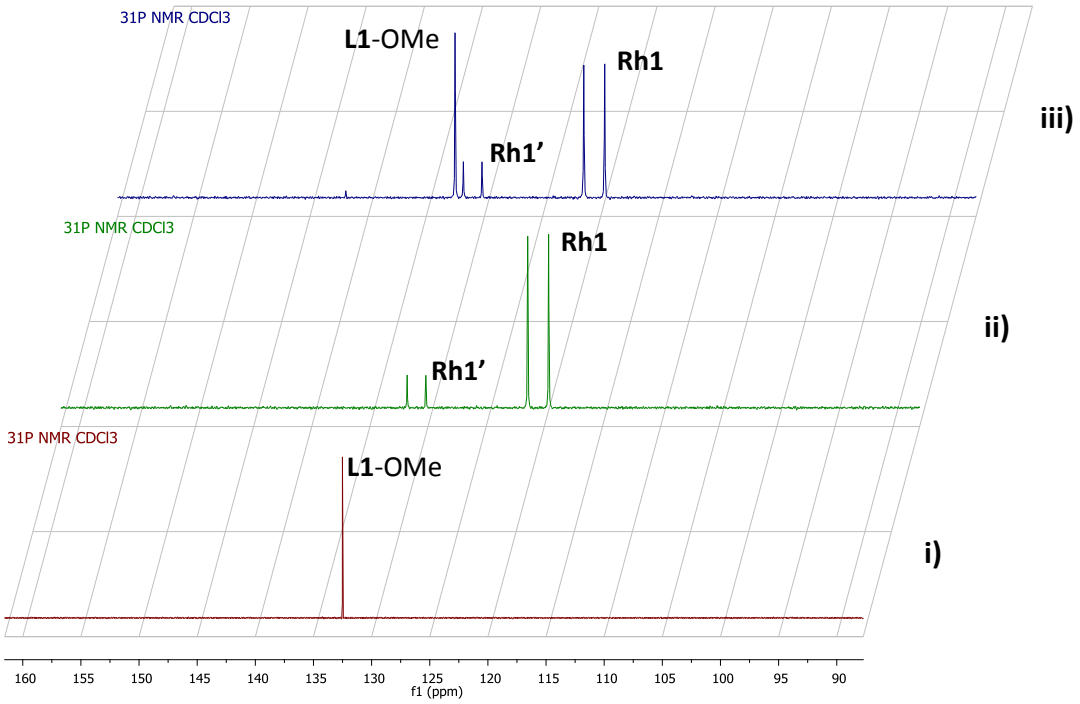
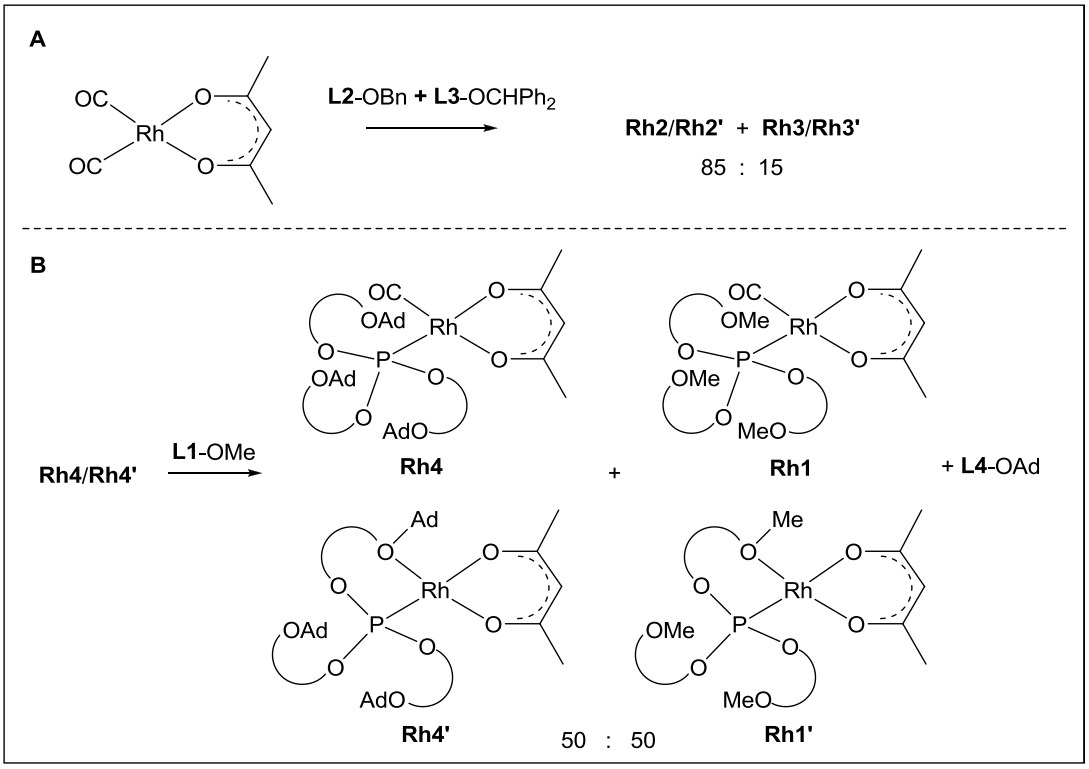


Figure 3.11 – ^{31}P NMR spectrum of: i) (*R*)-**L1**-OMe; ii) P/Rh molar ratio = 1:1; iii) P/Rh molar ratio = 2:1 (in $CDCl_3$, at 25°C, 90-160 ppm).

The IR spectra of each complex revealed a single wave-number of 2005 ± 2 cm^{-1}, which refers to the presence of one terminal carbonyl ligand. Since no further signals were observed in the this region, we could assign the major species to *P*-monodentate coordinated rhodium/phosphite complexes **Rh1**, **Rh2**, **Rh3** and **Rh4**, and the minor species to *P*,*O*-heterobidentate complexes **Rh1'**, **Rh2'**, **Rh3'** and **Rh4'**, which might coexist in equilibrium (**Scheme 3.11**). These results were consistent with those obtained with the related complex Rh(acac)(CO)($P(OPh)_3$) (δ = 122.1 ppm; $^{1}J(^{103}Rh, ^{31}P)$ = 293 Hz; IR(CO) = 2006 cm^{-1}).[85] The HRMS spectra of **Rh1** and **Rh2** isolated complexes indicated the presence of the molecular ions containing one carbonyl group and a single phosphite ligand ($[M\text{-acac}]^+$ = 1059.1914 (**Rh1**); $[M\text{-acac}]^+$ = 1287.2882 (**Rh2**)).

In order to assess the relative reactivity of the monophosphite ligands toward complexation with Rh(I), several competitive reactions were carried out. For example, the complex formation with (*R*)-**L2**-OBn was complete in *ca*. 5 min., considerably faster than that with the sterically hindered monophosphite (*R*)-**L3**-$OCHPh_2$ (*ca*. 1 hour). Furthermore, when a 1/1 mixture of the two ligands (*R*)-**L2**-OBn and (*R*)-**L3**-$OCHPh_2$ was reacted with $Rh(CO)_2(acac)$, a mixture of complexes **Rh2**/**Rh2'** and **Rh3**/**Rh3'** was formed in a 85/15 ratio, after 1h (**Scheme 3.12 A**).



Scheme 3.12

On the other hand, when the ligand (*R*)-**L1**-OMe was added to a solution of **Rh4**/**Rh4'**, a remarkable ligand exchange has occurred after 72 hours, leading to a *ca.* 1/1 mixture of **Rh4**/**RhL4'** and **Rh1**/**Rh1'** (**Scheme 3.12 B**, **Figure 3.12**).

These relevant differences observed in complex formation indicate that the rate of substitution of the coordinated CO ligands by the phosphites decreases with the steric hindrance of the R group, while the thermodynamic stability of the complexes is also affected. Moreover, no evidence has been found for the existence of [Rh(phosphite)$_2$] species containing either the same or different phosphite ligands.

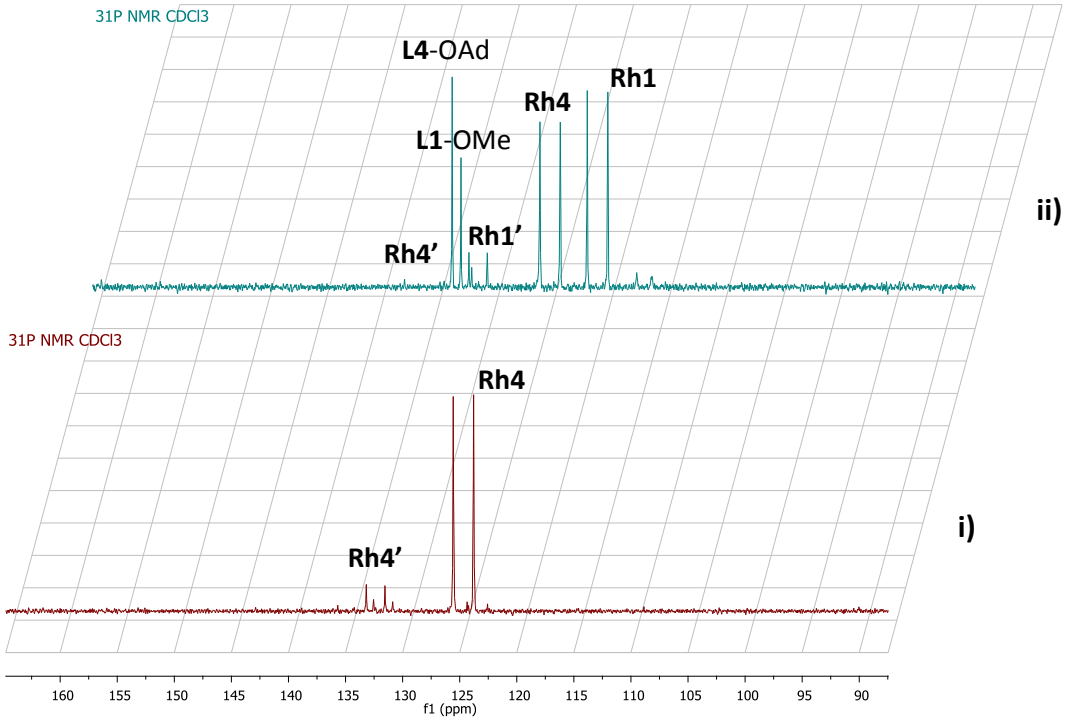


Figure 3.12 – ^{31}P NMR spectrum of: i) **Rh4**/**Rh4'**; ii) mixture after addition of (*R*)-**L1**-OMe (in $CDCl_3$, at 25°C, 90-160 ppm).

In sum, the *in situ* NMR studies described above provided some important information on the coordination modes of monophosphite ligands possessing ether oxygen as additional donor atoms. Although the coordination of only one phosphite ligand to Rh(I) in either monodentate or heterobidentate coordination manner has been proved by ^{31}P NMR at ambient conditions, the presence of Rh-P_2 species cannot be excluded under hydroformylation conditions. (Note that the negative order effect with respect to **L2**-OBn in the Rh-catalyzed hydroformylation of **3.1** might refer to the formation of a less active catalytic species bearing two phosphite ligands, as shown in **Figure 3.3** and **Scheme 3.3**).

Since the catalytic intermediates bearing phosphites with both monodentate and heterobidentate coordination manners might be operative, the large number of Rh-phosphite stereoisomeric species does not favor a well-defined stereostructure necessary to achieve high enantiodiscrimination.

3.2.5 Conclusions

In summary, the results presented in this section showed that this family of bulky tris-substituted BINOL-based monophosphite ligands formed highly stable, active and selective rhodium complexes for hydroformylation of disubstituted and internal double bonds.

In the hydroformylation of the 1,2-disubstituted olefin, *trans*-1-phenylpropene **3.1**, all catalytic systems provided full chemoselectivity for aldehydes and high selectivity (*ca.* 90%) for the regioisomer with the formyl group in α-position. Additionally, in the hydroformylation of the 1,1-disubstituted olefin, 2-phenylpropene **3.4**, complete chemoselectivity for aldehydes was also reached with all catalytic systems, however with a substrate controlled regioselectivity to the linear aldehyde, as result of the preferential insertion of the aldehyde functionality into the less substituted carbon atom of the double bond.

The structure of the ether substituents at the ligand affected considerably the catalytic activity of Rh(I)/monophosphite catalysts in the hydroformylation of 1,1- and 1,2-disubstituted aryl olefins, showing similar tendencies for both types of substrates: **L4**-OAd >> **L1**-OMe > **L2**-OBn >> **L3**-$OCHPh_2$. The bulky and rigid adamantyloxy derived monophosphite ligand seems to parallel with the classic bulky tris-(*o-tert*-butylphenyl)phosphite, providing the highest activities. However, the low activity achieved with (*R*)-**L3**-$OCHPh_2$, may result from high steric hindrance exerted by the diphenylmethoxy groups, which prevents the olefin insertion. The low enantioselectivities (up to 20% ee) achieved with all catalytic systems can be attributed to the predominant formation of *P*-monocoordinated rhodium species, and to the presence of different diastereomeric active catalytic species that can be formed under hydroformylation conditions.

The kinetic studies performed with Rh/(*R*)-**L2**-OBn in the hydroformylation of *trans*-1-phenylpropene **3.1**, showed an ambiguous behavior of the catalytic system, since positive orders were found for both substrate and H_2 partial pressure. This indicates that there is no clear rate limiting step, or even suggests that a dinuclear rhodium/phosphite complex can be formed as resting state, whose equilibrium toward the catalytic active species is dependent from H_2 partial pressure.

The high activity of Rh/**L2**-OBn catalytic system was also demonstrated by the remarkable ability to perform the hydroformylation of styrene at temperatures below 30°C, leading to a remarkable 99% of regioselectivity for the branched aldehyde, however without achievement of a good enantioselectivity (up to 20% ee).

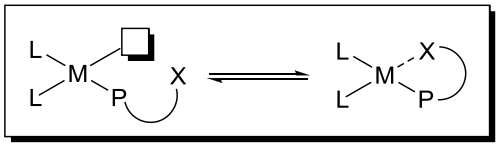
Furthermore, Rh/**L2**-OBn catalysts were still able to hydroformylate the internal C–C double bond of a steroidal olefin, 17β-acetoxyandrost-4-ene **3.11**, achieving similar activities to those obtained with Rh/tris(*o*-*tert*-butylphenyl)phosphite. Remarkably, the (*R*)-binaphthyl derived monophosphite ligand (*R*)-**L2**-OBn led to higher β-diastereoselectivity (70%) than the (*S*)-binaphthyl counterpart (*S*)-**L2**-OBn (61%), which indicates a *matching* effect between the chiral steroidal substrate with the (*R*)-binaphthyl derived catalyst.

Regardless of the low enantioselectivities obtained in the asymmetric hydroformylation of prochiral aryl olefins, the remarkable activity of the Rh/monophosphite catalysts in the hydroformylation of internal C-C double bonds of steroid molecules and the influence of the ligand stereo-configuration in the diastereoselectivity may open new perspectives, regarding the application of such complexes in the diastereoselective synthesis and/or functionalization of further natural products with biological interest.

3.3. Palladium-catalyzed asymmetric hydrovinylation

As mentioned in Chapter 1, the transition metal catalyzed hydrovinylation reaction[86,87,88,89,] comprise a great interest in enantioselective synthesis because, when applied to prochiral aryl olefins,[90,91,92] it generates a stereogenic carbon atom, providing a short route to enantiopure 3-arylbut-1-enes, possible intermediates in the preparation of 2-arylpropionic acids. Since isomerisation of 3-arylbut-1-enes to more stable 2-arylbut-2-enes may occur, as well as the formation of homodimers as side-products, the control of both chemo- and stereoselectivity represent major challenges.

Hydrovinylation constitutes a paradigmatic example of a catalytic reaction where the use of monodentate phosphorus ligands (and hemilabile ligands with electronically divergent donor atoms) was demonstrated to be crucial,[93,94,95] since those substituents capable of secondary interactions can advantageously influence catalytic activity and selectivity through a dynamic "on/off" chelating effect with the metal centre (**Scheme 3.13**).[87,93,96]



Scheme 3.13

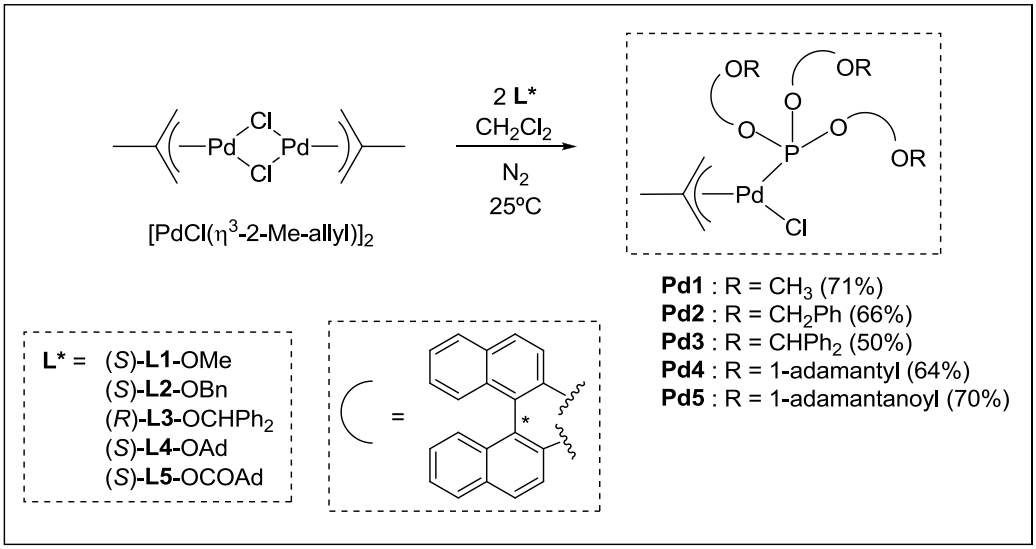
Although nickel(II) complexes[97,98,99,100,101] can be considered as the most efficient hydrovinylation catalysts, Pd(II) catalytic systems have recently attracted much attention, presenting the advantage of lower occurrence of dimerization products.[86] For instance, allyl-palladium complexes containing several types of monodentate *P*-chiral phosphines,[102,103,104] phosphinite[105] and binaphthyl-based diamidophosphite[106] have also achieved high chemoselectivities and remarkable enantioselectivities, in the hydrovinylation of several olefins.

Considering these facts, our studies proceeded with the preparation of allyl-palladium complexes, containing the C_3-symmetry tris-binaphthyl monophosphite ligands, as well as their application as pre-catalysts in the Pd-catalyzed asymmetric hydrovinylation of styrene.

3.3.1 Synthesis of allylpalladium/monophosphite complexes

The preparation of chloro-allylpalladium complexes was carried out, starting from each monophosphite and $[PdCl(\eta^3\text{-2-Me-allyl})]_2$. This palladium precursor was previously synthesized from Na_2PdCl_4 and β-methylallyl chloride, through a standard procedure[107] and kindly provided for these studies by Doctor A. Grabulosa, from the group of Professor G. Muller, in the Department of Inorganic Chemistry, University of Barcelona.

In a typical complexation reaction,[104,108,109] the 2-methylallyl chloropalladium dimer was reacted with two molar equiv. of monophosphite ligand **L1**-OMe, **L2**-OBn, **L3**-$OCHPh_2$, **L4**-OAd or **L5**-OCOAd, by stirring in anhydrous dichloromethane, at room temperature (*ca.* 25° C), under a nitrogen atmosphere, during 1 to 3 h (**Scheme 3.14**).



Scheme 3.14

The reactions' progress was performed by ^{31}P NMR spectroscopy. After complete disappearance of the signal assigned to free (non-coordinated) monophosphites, at δ in the range of 130-136 ppm, the solvent was removed *in vacuo* and the resulting pale brown foam was suspended in *n*-pentane. Finally, the solids were filtered and washed with *n*-pentane. After properly dried under vacuum, the complexes **Pd1**, **Pd2**, **Pd3**, **Pd4** and **Pd5** were obtained, in moderate to good yields, as air-stable white solids.

In general, these yields were moderately influenced by the ligand steric bulkiness, being higher with the smaller methoxy-derived **L1**-OMe (71%) and the medium size monophosphites **L2**-OBn (66%), **L4**-OAd (64%) and **L5**-OCOAd (70%) than with the high sterically hindered diphenylmethoxy derivative **L3**-$OCHPh_2$ (50%).

The chloro-allylpalladium/monophosphite complexes were then characterized by ^{31}P, ^{1}H and ^{13}C NMR spectroscopy and microanalysis. Selected spectroscopic data is presented in Table 3.10, and described below, while detailed full characterizations can be found in Chapter 5, section 5.3.3.

Table 3.10 – Selected NMR data of chloro-allylpalladium monophosphite complexes **Pd1**-**Pd5** (in $CDCl_3$, at 25°C, under N_2).

Complex (%)	^{31}P NMR δ [ppm]	^{1}H NMR δ [ppm] (multiplicity, *J* [Hz], integral)					
		H^c *anti*	allyl-CH_3	H^c *syn*	H^t *anti**	H^t *syn**	OR protons**
Pd1							
Major (80)	121.0	0.61 (s, 1H)	1.01 (s, 3H)	2.09 (s, 1H)	2.54 (d, 17.0, 1H)	3.89 (d, 9.5, 1H)	3.44 (s, 9H)
Minor (20)	121.0	1.45 (s, 1H)	1.04 (s, 3H)	2.51 (s, 1H)	3.02 (d, 16.5, 1H)	4.12 (d, 9.0, 1H)	3.58 (s, 9H)
Pd2							
Major (78)	121.9	0.48 (s, 1H)	0.65 (s, 3H)	2.13 (s, 1 H)	2.51 (d, 17.0, 1H)	3.85 (d, 10.0, 1H)	4.75 (d, 12.4, 3H) 4.79 (d, 12.4, 3H)
Minor (22)	121.6	1.19 (s, 1H)	0.94 (s, 3H)	2.31 (s, 1H)	2.82 (d, 16.4, 1H)	4.04 (d, 11.0, 1H)	4.77 (d, 12.4, 3H) 4.83 (d, 12.4, 3H)
Pd3							
Major (60)	120.2	0.51 (s, 1H)	0.99 (s, 3H)	1.87 (s, 1H)	2.45 (d, 17.0, 1H)	3.87 (d, 9.5, 1H)	6.11 (s, 3H)
Minor (40)	119.4	1.16 (s, 1H)	1.05 (s, 3H)	2.28 (s, 1H)	2.72 (d, 17.0, 1H)	4.05 (d, 10.0, 1H)	6.03 (s, 3H)
Pd4							
Major (68)	118.2	0.50 (s, 1H)	0.81-1.88 ov. (s, 3H)	0.81-1.88 ov. (s, 1H)	2.42 (d, 17.2, 1H)	3.82 (d, 12.0, 1H)	0.81-1.88 ov. (m, 45H)
Minor (32)	118.9	0.81-1.88 ov. (s, 1H)		2.13 (s, 1H)	3.00 (d, 16.4, 1H)	4.03 (d, 10.4, 1H)	
Pd5							
Major (71)	118.0	0.85 (s, 1H)	1.14 (s, 3H)	1.23-1.78 ov. (s, 1H)	1.87 (d, 16.0, 1H)	3.86 (d, 12.0, 1H)	1.23-1.78 ov. (m, 45H)
Minor (29)	118.9	1.23-1.78 ov. (s, 1H)	1.23-1.78 ov. (s, 3H)		3.13 (d, 16.0, 1H)	4.29 (d, 12.0, 1H)	

Multiplicity: s, singlet; d, doublet; m, multiplet; br s, broad signal; ov., overlapped signal.
*J_{P-H} coupling constants, given in Hz, are shown in parentheses after multiplicity.
** J_{H-H} coupling constants, given in Hz, are shown in parentheses after multiplicity.

For each complex, the ^{31}P NMR spectra showed a pair of major and minor sharp signals with close chemical shifts, in the range 118-122 ppm. This was attributed to the presence, in solution, of an unequal mixture of two isomeric Pd/phosphite complexes (R_{Pd}) and (S_{Pd}),[108,109,110] whose relative ratios varied from 1:1.5 (in case of **Pd3**) to 1:4 (in case of **Pd1**) (see Table 3.10 and section 5.3.3).

As illustrative example, the ^{31}P NMR spectrum of **Pd2** is shown in **Figure 3.13**.

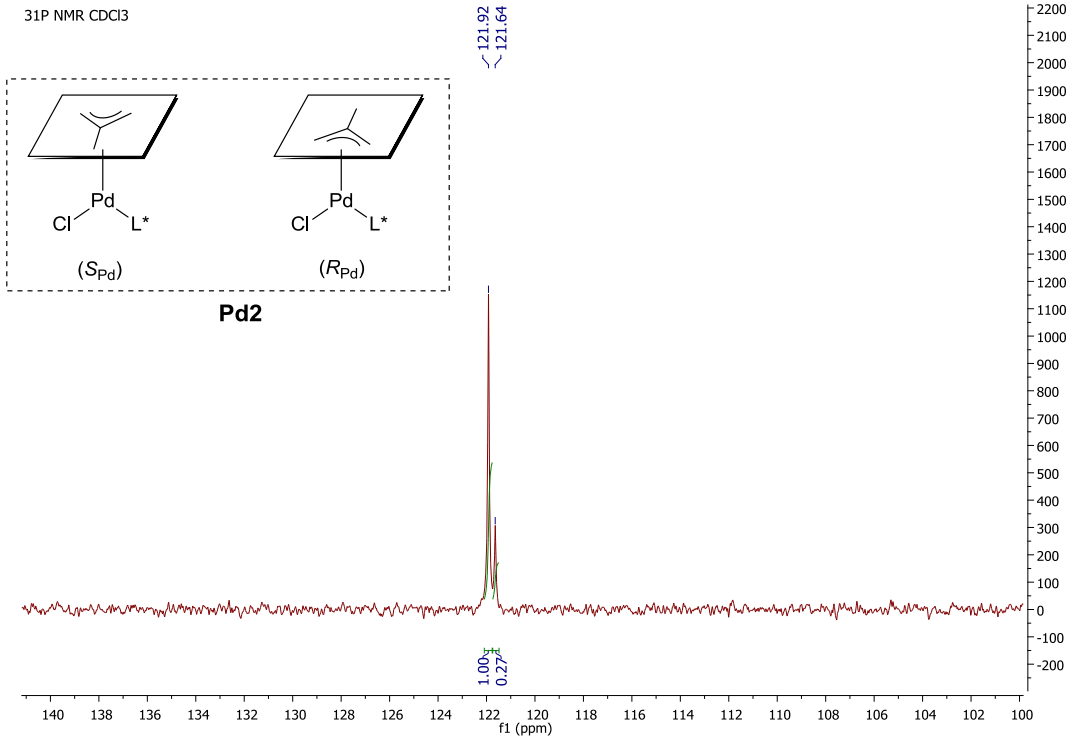
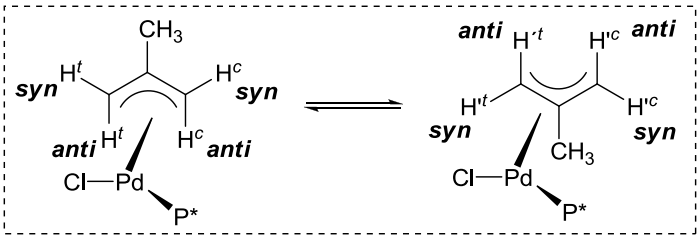


Figure 3.13 – ^{31}P NMR spectrum of **Pd2**, in $CDCl_3$, at 25°C (expansion 100-140 ppm).

Phase sensitive ^{1}H-^{1}H NOESY experiments (**Figure 3.14**) showed that, in analogy to related complexes,[102] both diastereomeric species interchange by the apparent allyl *pseudorotation* and η^3-η^1-η^3 allylic shift mechanisms (**Scheme 3.15**).[108,109]



Scheme 3.15

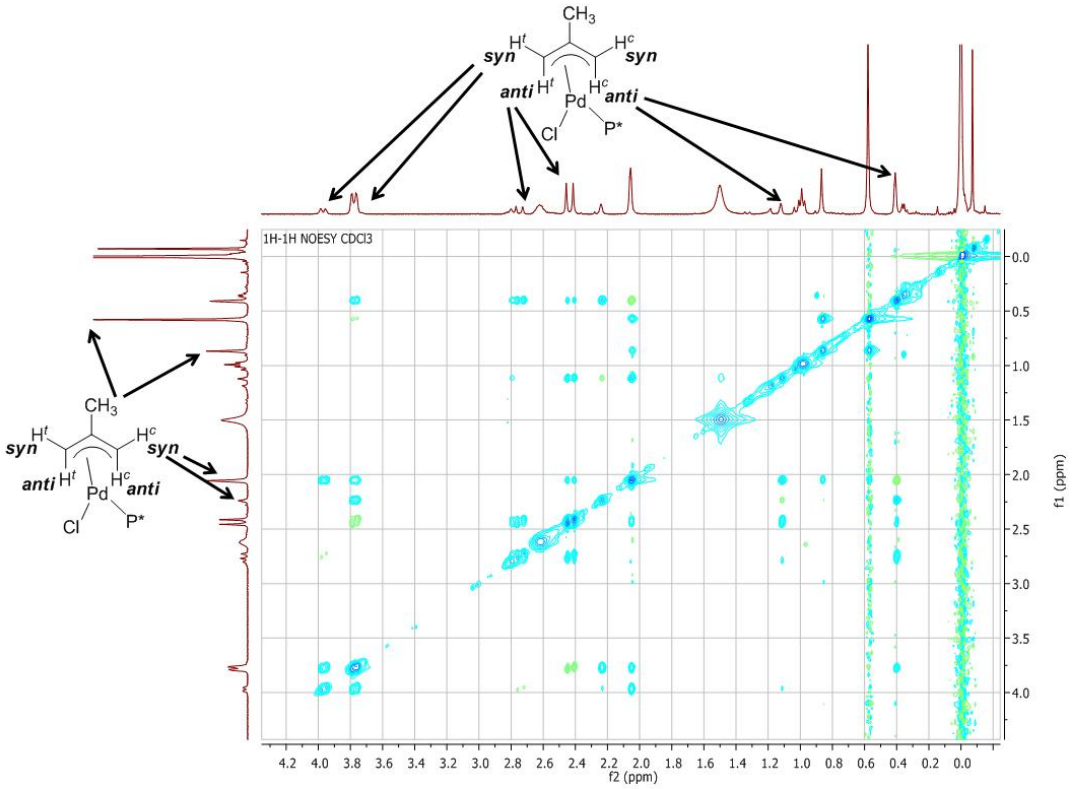


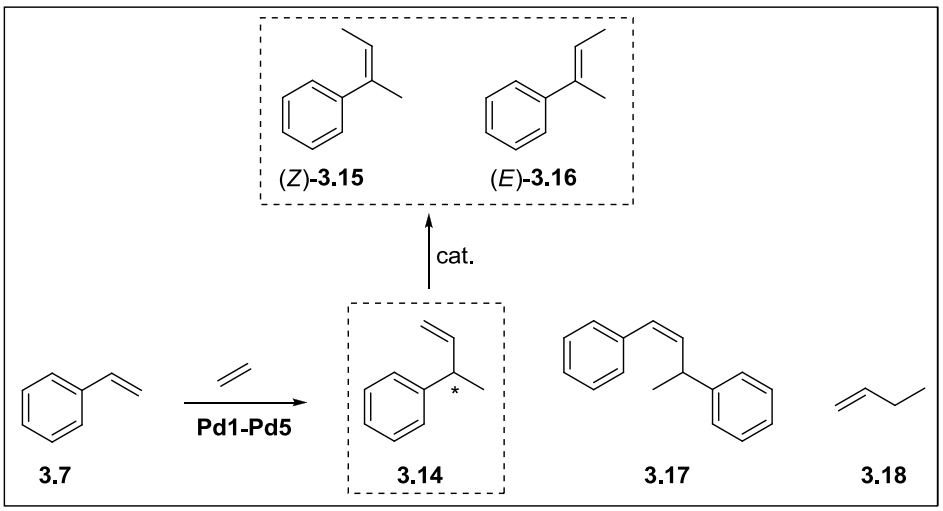
Figure 3.14 – Phase sensitive ^{1}H-^{1}H NMR NOESY spectrum of **Pd2**, in $CDCl_3$ at 25°C, with assignment of methylallyl protons (expansion 0.00-4.20 ppm).

Regarding the ^{1}H NMR spectra, the terminal allyl protons in position *trans* to the phosphorus atom H^{t}_{syn} and H^{t}_{anti} appear as doublets and present higher chemical shifts than the singlets assigned to the *cis* positions H^{c}_{syn} and H^{c}_{anti} protons. It is worth highlighting the significantly lower chemical shift value of the signals of the methyl group (δ=0.65-1.14 ppm) and *anti*-*cis*-protons (δ=0.48-1.45 ppm) of the allyl moieties (Table 3.10), when compared with similar allylpalladium complexes.[102,108,109] This fact may be due to the effect of the close aromatic rings of the phosphite ligand in a crowded environment. Furthermore, in the case of **Pd2**, the benzylic protons are diastereotopic, as evidenced by two different signals at δ = 4.73-4.84 ppm, coupled to each other with typical second order effects for each major and minor species (Table 3.10).

3.3.2 Hydrovinylation of styrene with Pd/monophosphite complexes

The diastereomeric pairs of neutral allylic complexes **Pd1-Pd5** were then evaluated as catalytic precursors in the asymmetric hydrovinylation of styrene **3.7**.

The target product of the codimerization reaction between ethylene and styrene is 3-phenylbut-1-ene **3.14**, containing a chiral center in the allylic position, as result of a new C–C bond formation. The isomerization of **3.14** to 2-phenylbut-2-enes **3.15** and **3.16** can take place as a consecutive process, in presence of a metal-hydride catalyst. In addition, depending from the catalytic system, the dimerization of styrene and ethylene may eventually occur, resulting in the homodimers *cis*-1,3-diphenylbut-1-ene **3.17** and but-1-ene **3.18**, respectively (**Scheme 3.16**).

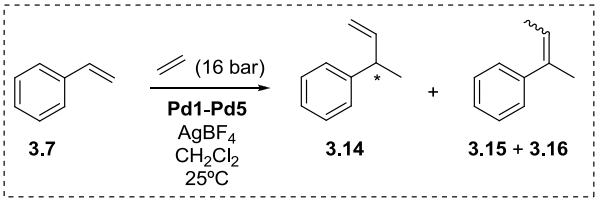


Scheme 3.16

In a typical procedure,[104,108,109] the pre-catalyst activation was carried out by chloride abstraction, through addition of 1.1 molar equiv. of $AgBF_4$ to the chloro-allylpalladium complexes **Pd1**-**Pd5**, in CH_2Cl_2, in presence of styrene (1000 molar equiv) to stabilize the cationic Pd species. After filtration of the formed AgCl, the solution was introduced into a stainless steel autoclave, previously purged by successive vacuum/nitrogen cycles and thermostated to 25°C. The autoclave was immediately pressurized with 16 bar of ethylene, and the reactions were conducted for the desired time.

After the selected time, the autoclave was slowly depressurized and 10 mL of a 10% NH_4Cl aqueous solution was added, stirring for 10 min, in order to quench the catalyst. The organic layer was then separated, dried with Na_2SO_4, filtered through a plug of silica gel and subjected to GC analysis, to determine the products distribution and ee for 3-phenylbut-1-ene **3.14**. The results are listed in Table 3.11.

Table 3.11 – Catalytic evaluation of allylpalladium/monophosphite complexes **Pd1** - **Pd5** in asymmetric hydrovinylation of styrene.[a)]



Entry	Precursor[b)]	Conversion (%)	TOF (h^{-1})	**3.14** (%)	ee (%)	**3.15**+**3.16** (%)
1[c)]	(*S*)-**Pd1**	7.5	25	97.6	39 (*R*)	2.4
2	(*S*)-**Pd1**	14.8	25	95.6	39 (*R*)	4.4
3[d)]	(*S*)-**Pd1**	57.2	24	73.0	40 (*R*)	27.0
4	(S)-**Pd2**	30.5	51	92.6	71 (*R*)	7.4
5	(*R*)-**Pd3**	14.2	24	98.6	26 (*S*)	1.4
6	(*S*)-**Pd4**	3.5	6	97.8	-	2.2
7[d)]	(*S*)-**Pd4**	13.9	6	91.1	62 (*R*)	8.9
8	(*S*)-**Pd5**	70.0	115	85.5	92 (*R*)	14.5

[a)] **Reaction conditions** (unless otherwise stated): 15 mL of CH_2Cl_2, Pd/styrene ratio = 1: 1000, 25°C, $P_{ethylene}$ =16 bar, 6h. [b)] (*R*) and (*S*) refer to the binaphthyl absolute configuration of the ligand. [c)] Pd/styrene ratio = 1:2000; [d)] 24h.

The results presented in Table 3.11, and illustrated in **Figure 3.15** clearly show that the catalytic activity and selectivity were strongly dependent on the OR substituent. The chloro-allylpalladium/monophosphite **Pd5** led to the most active catalytic system (TOF=115 h^{-1}) (Table 3.11, entry 8) and **Pd4** the less active (TOF=6 h^{-1}) (Table 3.11, entries 6 and 7). The precursor **Pd1**, led to a moderately active catalytic system (TOF=25 h^{-1}), even using a higher substrate/metal molar ratio (Table 3.11, entries 1 and 2). All catalytic systems showed high chemoselectivity (*ca.* 90%) towards 3-phenylbut-1-ene **3.14**. However, at longer reaction times the higher conversions were accompanied by isomerization to 2-phenylbut-2-enes (**3.15** and **3.16**), resulting in a decrease of the reaction's chemoselectivity (Table 3.11, entries 2-3 and 6-7).

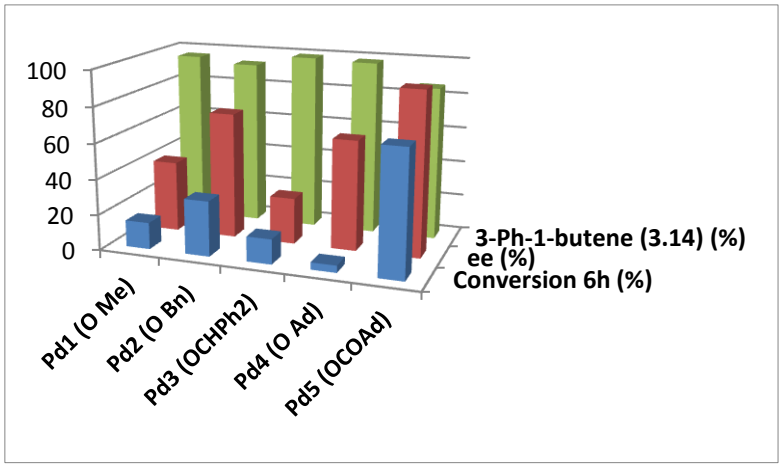
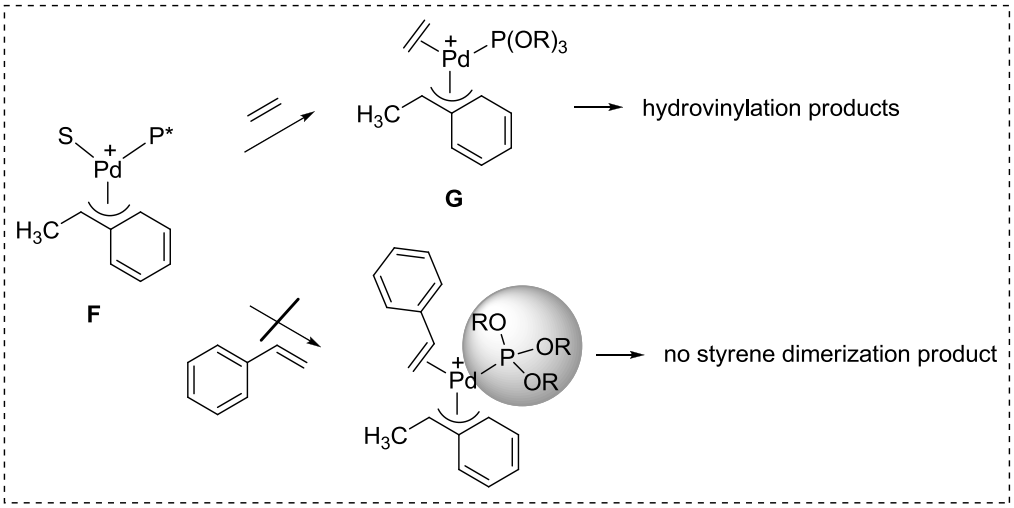


Figure 3.15 – Comparative evaluation of allylpalladium/monophosphite complexes **Pd1**-**Pd5** in the asymmetric hydrovinylation of styrene **3.7**.

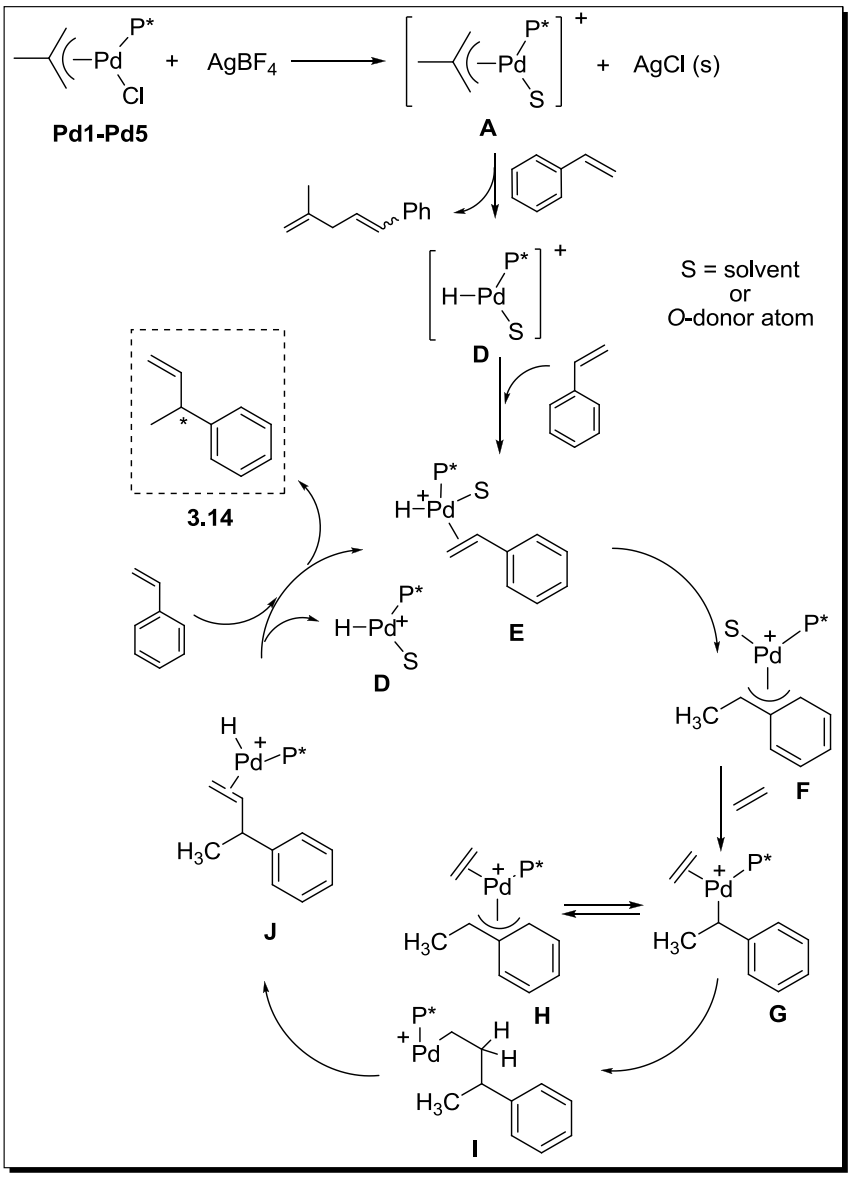
A remarkable outcome of these Pd catalysts was the lack of styrene dimerization, probably as a result of the ligands' bulkiness, which may preclude the coordination of a second styrene molecule to the Pd-η^3-styryl intermediate (**Scheme 3.17**).



Scheme 3.17

As typically achieved with vinylarenes as substrates, 100% regioselectivity toward the branched product was observed, as a result of the equilibrium between the branched intermediate **G** and the Pd-η^3-styryl intermediate **H**,[87] whose polarized C–Pd bond is strongly stabilized by resonance effects, in the presence of a phenyl group (see **Scheme 3.18**).

Regarding the reaction's enantioselectivity, the enantiomeric excesses have increased in the order **Pd3** (26%) < **Pd1** (40%) < **Pd4** (62%) < **Pd2** (71%) < **Pd5** (92%) (Table 3.11, entries 3, 4, 5, 7 and 8).

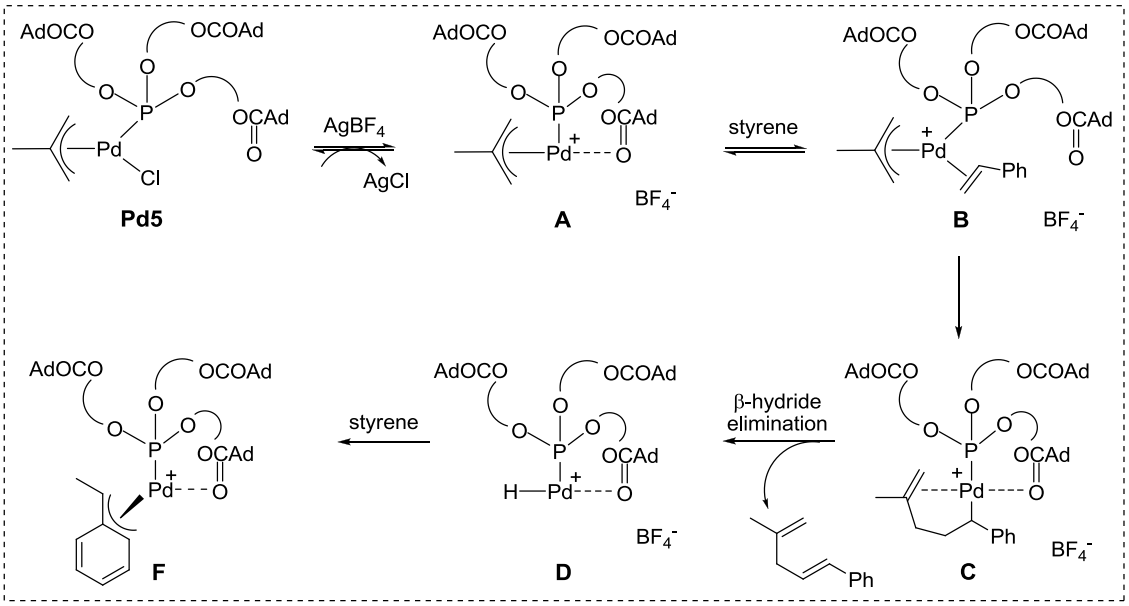


Scheme 3.18

According to the widely accepted mechanism,[93,111] the catalytic active species is the palladium hydride complex **D**, which is formed upon reaction of the catalytic precursor **Pd1**-**Pd5** with $AgBF_4$ (with formation of AgCl) and subsequent stabilization with styrene, with concomitant elimination of 1-phenyl-4-methylpenta-1,4-diene. The species **D** is able to coordinate with styrene (generating species **E**) and the subsequent

hydride migratory insertion into the vinylarene terminal carbon atom generates the η^3-species **F**. The cycle proceeds with the coordination of ethylene to **F**, producing the branched intermediate **G**, which is stabilized by the η^3-styryl intermediate **H**. The migratory insertion of ethylene results in species **I**, and β-hydride elimination generates species **J**. Finally, the target chiral olefin **3.14** is formed, and a new cycle is restarted by regeneration of the Pd-hydride complex **D** (**Scheme 3.18**).

Since it is accepted that the coordination of the catalyst to the vinylarene substrate is the step that eventually determines the reaction enantioselectivity, the excellent ee obtained with **Pd5** (92%) suggests that the adamantanoyl group at the ligand is the key feature that might supply secondary interactions with the metal, providing a Pd hydride intermediate of type **D** with high ability to discriminate one of the enantiotopic faces of styrene (**Scheme 3.19**).



Scheme 3.19

Furthermore, as previously reported by Reetz,[67] the presence of a bulky and rigid adamantanoyl substituent at the 2-binaphthyl position of the monophosphite ligand **L5**-OCOAd prevents the free rotation of the substituents at the phosphorus atom, which might increase the stability of C_3-symmetry helical structure of the monophosphite, leading to highly stereo-discriminative species.

Remarkably, despite the catalytic precursors are in fact, two interchanging isomers in solution, no correlations were found between the diastereomeric ratios and the catalytic activity/selectivity.

3.3.3 Conclusions

Neutral allylpalladium complexes stabilized by the bulky C_3-symmetry tris-binaphthyl monophosphite ligands have been synthesized in good yields, and fully characterized by NMR spectroscopy, which evidenced a dynamic equilibrium between two diastereomeric species in solution, resulting from (*R*) and (*S*) stereochemistry at the palladium atom.

Their evaluation in asymmetric hydrovinylation of styrene showed a significant dependence of activity and selectivity on the OR substituents at the ligand's 2'-binaphthyl position. All catalytic systems provided high chemoselectivity toward 3-phenylbut-1-ene **3.14** (above 85%), without occurrence of homodimerization and low formation of isomerisation products. While the palladium complexes bearing monophosphite ligands with methoxy (**Pd1**), benzyloxy (**Pd2**) and 1-adamantyloxy (**Pd4**) substituents led to moderate enantioselectivities (40-71% ee), the complex **Pd5** containing a 1-adamantanoyl derived monophosphite produced a remarkable enantiomeric excess of 92% toward (*R*)-3-phenylbut-1-ene, which constitute one of the highest enantiomeric excesses obtained so far with palladium complexes, in the catalytic hydrovinylation of styrene and, to the best of our knowledge, the best result achieved with a monophosphite ligand. This outcome suggests that the presence of bulky and rigid adamantanoyl substituents at the ligand may increase the stability of C_3-symmetry helical structures and/or might favour secondary interactions with palladium, which allows the preferential coordination of the active Pd hydride catalyst into one of the substrate prochiral faces.

3.4 Final Remarks

It is worth mentioning the fact that this type of chiral *P*,*O* monophosphite ligands demonstrated to be much more capable of enantioinduction in the asymmetric hydrovinylation than in asymmetric hydroformylation. The secondary interactions between palladium and the hard oxygen atoms in the ligands' substituents, leading to *P,O*–heterobidentate hemilabile coordination might be a crucial feature to achieve high enantioselectivities in the hydrovinylation of styrene.

Despite excellent activities and regioselectivities have been obtained with Rh/monophosphite complexes in the hydroformylation of disubstituted aryl olefins, the *P*,*O*-hemilabile ligands proved to be ineffective for asymmetric induction, which corroborates the fact that achieving high enantioselectivities in hydroformylation is strictly dependent from a stable *P*,*P*–rhodium bidentate chelate. However, the remarkable activity and diastereoselectivity obtained with Rh/monophosphite complexes in the hydroformylation of sterically hindered double bonds in steroid molecules are encouraging results for further studies regarding the application of these active systems to the hydroformylation of hardly reactive natural products.

3.5 References

1. H.-U. Blaser, E. Schmidt (Eds.), *Asymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, **2004**.

2. E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Verlag Berlin Heidelberg, **1999**.

3. K. Mikami, M. Lautens (Eds.), *New Frontiers in Asymmetric Catalysis*, Wiley & Sons, New Jersey, **2007**.

4. I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*, Wiley, **2000**.

5. B. M. Trost, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5348.

6. P. Walsh, M. Kowzlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, Sausalito, **2008**.

7. J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581.

8. A. Pfaltz, W. J. Drury, *Proc. Natl. Acad. Sci. U.S.A* **2004**, *101*, 5723.

9. M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem., Int. Ed.* **2003**, *42*, 790.

10. T. Hayashi, *Acc. Chem. Res.* **2000**, *33*, 354.

11. G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *Coord. Chem. Rev.* **2008**, *252*, 471.

12. M. T. Reetz, G. Mehler, *Angew. Chem., Int. Ed.* **2000**, *39*, 3889.

13. M. T. Reetz, G. Mehler, A. Meiswinkel, T. Sell, *Tetrahedron Lett.* **2002**, *43*, 7941.

14. M. T. Reetz, T. Sell, *Tetrahedron Lett.* **2000**, *41*, 6333.

15. M. Van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539.

16. A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40,* 1267.

17. V. N. Tsarev, S. E. Lyubimov, A. A. Shiryaev, S. V. Zheglov, O. G. Bondarev, V. A. Davankov, A. A. Kabro, S. K. Moiseev, V. N. Kalinin, K. N. Gavrilov, *Eur. J. Org. Chem.* **2004**, 2214.

18. T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101.

19. I. V. Komarov, A. Börner, *Angew. Chem., Int. Ed.* **2001**, *40*, 1197.

20. F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315.

21. M. M. Pereira, M. J. F. Calvete, A. R. Abreu, R. M. B. Carrilho, in *Advances in Chemistry Research, Vol. 19*, J. C. Taylor (Ed.), Nova Publishers, New York, **2013**, pp. 111-154.

22. M. M. Pereira, M. J. F. Calvete, R. M. B. Carrilho, A. R. Abreu, *Chem. Soc. Rev.* **2013**, *42*, 6990.

23. X.-P. Hu, D.-S. Wang, C.-B. Yu, Y.-G. Zhou, Z. Zheng, *Top. Organomet. Chem.* **2011**, *36*, 313.

24. K. N. Gavrilov, S. E. Lyubimov, S. V. Zheglov, E. B. Benetsky, V. A. Davankov, *J. Mol. Catal. A: Chem.* **2005**, *231*, 255.

25. C. Claver, P. W. N. M. van Leeuwen (Eds.), *Rhodium Catalyzed Hydroformylation*, Kluwer Academic Publishers, Dordrecht, **2000**.

26. A. Gual, C. Godard, S. Castillón, C. Claver, *Tetrahedron: Asymmetry* **2010**, *21*, 1135.

27. J. Klosin, C. R. Landis, *Acc. Chem. Res.* **2007**, *40*, 1251.

28. B. Breit, *Top. Curr. Chem.* **2007**, *279*, 139.

29. F. Ungvári, *Coord. Chem. Rev.* **2007**, *251*, 2087.

30. R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675.

31. D. Neibecker, R. Reau, S. Lecolier, *J. Org. Chem.* **1989**, *54*, 5208.

32. C. Giordano, M. Villa, S. Panossian, in *Chirality in Industry*, A. N. Collins, G. N. Sheldrake, J. Crosby (Eds.), Wiley, Chichester, **1992**, pp 303−312.

33. L. Kollár, E. Farkas, J. Bâtiu, *J. Mol. Catal. A: Chem.* **1997**, *115*, 283.

34. M. R. Axet, S. Castillón, C. Claver, *Inorg. Chim. Acta* **2006**, *359*, 2973.

35. F. Agbossou, J. F. Carpentier, A. Mortreux, *Chem. Rev.* **1995**, *95*, 2485.

36. A. Gual, C. Godard, S. Castillón, C. Claver, *Adv. Synth. Catal.* **2010**, *352*, 463.

37. S. H. Chikkali, R. Bellini, G. Berthon-Gelloz, J. I. Van der Vlugt, B. de Bruin, J. N. H. Reek, *Chem. Commun.* **2010**, *46*, 1244.

38. D. Sémeril, D. Matt, L. Toupet, *Chem. Eur. J.* **2008**, *14*, 7144.

39. M. Rosales, G. Chacón, A. González, I. Pacheco, P. J. Baricelli, L. G. Melean, *J. Mol.*

Catal. A: Chem. **2008**, *287*, 110.

40. V. K. Srivastava, S. K. Sharma, R. S. Shukla, N. Subrahmanyam, R. V. Jasra, *Ind. Eng. Chem. Res.* **2005**, *44*, 1764.

41. C. Bergounhou, D. Neibecker, R. Mathieu, *J. Mol. Catal. A: Chem.* **2004**, *220*, 167.

42. C. J. Cobley, J. Klosin, C. Qin, G. T. Whiteker, *Org. Lett.* **2004**, *6*, 3277.

43. C. J. Cobley, K. Gardner, J. Klosin, C. Praquin, C. Hill, G. T. Whiteker, A. Zanotti-Gerosa, *J. Org. Chem.* **2004**, *69*, 4031.

44. Z. Hua, V. C. Vassar, H. Choi, I. Ojima, *Proc. Natl. Acad. Sci. U.S.A* **2004**, *101*, 5411.

45. H. Siegel, W. Himmele, *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 178.

46. A. van Rooy, E. N. Orij, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 34.

47. K. F. Muilwijk, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Am. Oil Chem. Soc.* **1997**, *74*, 223.

48. A. F. Peixoto, D. S. Melo, T. F. Fernandes, Y. Fonseca, E. V. Gusevskaya, A. M. S. Silva, R. R. Contreras, M. Reyes, A. Usubillaga, E. N. Santos, M. M. Pereira, J. C. Bayón, *Appl. Catal. A: Gen.* **2008**, *340*, 212.

49. F. Grau, J. C. Bayón, P. A. Aguirre, T. Parella, E. Duñach, *Eur. J. Org. Chem.* **2008**, 1214.

50. P. W. N. M. van Leeuwen, *Homogeneous Catalysis. Understanding the Art*, Kluwer Academic Publishers, Dordrecht, **2004**.

51. R. Lazzaroni, A. Raffaelli, R. Settambolo, S. Bertozzi, G. Vitulli, *J. Mol. Catal.* **1989**, *50*, 1.

52. D. Y. Murzin, A. Bernas, T. Salmi, *J. Mol. Catal. A: Chem.* **2010**, *315*, 148.

53. V. S. Nair, S. P. Mathew, R. V. Chaudhari, *J. Mol. Catal. A: Chem.* **1999**, *143*, 99.

54. B. M. Bhanage, S. S. Divekar, R. M. Deshpande, R. V. Chaudhari, *J. Mol. Catal. A: Chem.* **1997**, *115*, 247.

55. A. A. Dabbawala, H. C. Bajaj, R. V. Jasra, *J. Mol. Catal. A: Chem.* **2009**, *302*, 97.

56. O. Saidi, J. Ruan, D. Vinci, X. Wu, J. Xiao, *Tetrahedron Lett.* **2008**, *49*, 3516.

57. P. C. d'Oro, L. Raimondi, G. Pagani, G. Montrasi, G. Gregorio, A. Andreetta, *Chim. Ind. (Milan)* **1980**, *62*, 572.

58. A. van Rooy, J. N.H. de Bruijn, K. F. Roobeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Organomet. Chem* **1996**, *507*, 69.

59. C. Bianchini, H. M. Lee, A. Meli, F. Vizza, *Organometallics* **2000**, *19*, 849.

60. E. Fernández, A. Ruiz, C. Claver, S. Castillón, P. A. Chaloner, P. B. Hitchcock, *Inorg. Chem Commun.* **1999**, *2*, 283.

61. L. C. Serrano, *Hidroformilación Asimétrica de Olefinas con Catalisadores de Rodio y Difosfitos Metalamacrocíclicos*, PhD Thesis, Universidad Autònoma de Barcelona, **2007**.

62. M. Haumann, H. Yildiz, H. Koch, R. Schomäcker, *Appl. Catal. A: Gen.* **2002**, *236*, 173.

63. C. Botteghi, R. Ganzerla, M. Lenarda, G. Moretti, *J. Mol. Catal.* **1987**, *40*, 129.

64. A. I. M. Keulemans, A. Kwantes, T. van Bavel, *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 298.

65. M. L. Clarke, G. J. Roff, *Chem. Eur. J.* **2006**, *12*, 7978.

66. I. Ojima, M. Takai, T. Takahashi, *WO Patent* 078766, **2004**.

67. M. T. Reetz, H. Guo, J.-A. Ma, R. Goddard, R. J. Mynott, *J. Am. Chem. Soc.* **2009**, *131*, 4136.

68. R. V. Chaudhari, *Curr. Opin. Drug Discov. Develop.* **2008**, *11*, 820.

69. R. Skoda-Földes, L. Kollár, *Chem. Rev.* **2003**, *103*, 4095.

70. M. Kotora, F. Hessler, B. Eignerová, *Eur. J. Org. Chem.* **2012**, 29.

71. P. F. Beal, M. A. Rebenstorf, J. E. Pike, *J. Am. Chem. Soc.* **1959**, *81*, 1231.

72. S. Törös, I. Gémes-Pécsi, B. Heil, S. Mahó, Z. Tuba, *J. Chem. Soc., Chem. Commun.* **1992**, 858.

73. S. Törös, B. Heil, G. Gálik, Z. Tuba, *Tetrahedron Lett.* **1992**, *33*, 3667.

74. E. Nagy, B. Heil, S. Törös, *J. Mol. Catal. A: Chem.* **1999**, *143*, 229.

75. E. Nagy, C. Benedek, B. Heil, S. Törös, *Appl. Organomet. Chem.* **2002**, *16*, 628.

76. Z. Freixa, M. M. Pereira, J. C. Bayón, A. M. S. Silva, J. A. R. Salvador, A. M. Beja, J. A. Paixão, M. Ramos, *Tetrahedron: Assymmetry* **2001**, *12*, 1083.

77. A. F. Peixoto, M. M. Pereira, A. M. S. Silva, C. M. Foca, J. C. Bayón, M. J. S. M. Moreno, A. M. Beja, J. A. Paixão, M. R. Silva, *J. Mol. Catal. A: Chem.* **2007**, *275*, 121.

78. P. G. M. Wuts, A. M. Anderson, S. W. Ashford, M. P. Goble, M. J. White, D. Beck, I. Gilbert, R. E. Hrab, *Synlett* **2008**, *3*, 418.

79. G. Guerlet, T. Spangenberg, A. Mann, H. Faure, M. Ruat, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3608.

80. J. R. Hanson, P. B. Hitchcock, M. D. Liman, S. Nagaratnam, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2183.

81. J. R. Bull, J. Floor, *J. Chem. Soc., Perkin Trans. 1* **1977**, 724.

82. A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman, I. Wender, *J. Am. Chem. Soc.* **1959**, *81*, 1228.

83. Z. Freixa, J. C. Bayón, *J. Chem. Soc., Dalton Trans.* **2001**, 2067.

84. A. van Rooy, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, N. Veldman, A. L. Spek, *Organometallics* **1996**, *15,* 835.

85. W. Simanko, K. Mereiter, R. Schmid, K. Kirchner, A. M. Trzeciak, J. J. Ziolkowski, *J. Organomet. Chem.* **2000**, *602*, 59.

86. R. M. Ceder, A. Grabulosa, G. Muller, M. Rocamora, *Catal. Sci. Technol*. **2013**, *3*, 1446.

87. T. V. RajanBabu, *Synlett* **2009**, 853.

88. G. Hilt, *Eur. J. Org. Chem.* **2012**, 4441.

89. T. V. RajanBabu, *Chem. Rev.* **2003**, *103*, 2845.

90. L. J. Goossen, *Angew. Chem., Int. Ed.* **2002**, *41*, 3775.

91. C. R. Smith, T. V. RajanBabu, *Org. Lett.* **2008**, *10*, 1657.

92. C. R. Smith, T. V. RajanBabu, *J. Org. Chem.* **2009**, *74*, 3066.

93. J. Joseph, T. V. RajanBabu, E. D. Jemmis, *Organometallics* **2009**, *28*, 3552.

94. M. Nandi, J. Jin, T. V. RajanBabu, *J. Am. Chem. Soc.* **1999**, *121*, 9899.

95. A. Zhang, T. V. RajanBabu, *Org. Lett.* **2004**, *6*, 1515.

96. S. Mecking, W. Keim, *Organometallics* **1996**, *15*, 2650.

97. W. Liu, T. V. RajanBabu, *J. Org. Chem.* **2010**, *75*, 7636.

98. M. Schmitkamp, W. Leitner, G. Franciò, *Catal. Sci. Technol.* **2013**, *3*, 589.

99. N. Lassauque, G. Franciò, W. Leitner, *Adv. Synth. Catal.* **2009**, *351*, 3133.

100. W. Liu, H. J. Lim, T. V. RajanBabu, *J. Am. Chem. Soc.* **2012**, *134*, 5496.

101. D. J. Mans, G. A. Cox ,T. V. RajanBabu, *J. Am. Chem. Soc.* **2011**, *133*, 5776.

102. L. Rodríguez, O. Rossell, M. Seco, A. Grabulosa, G. Muller, M. Rocamora, *Organometallics* **2006**, *25*, 1368.

103. L. Rodríguez, O. Rossell, M. Seco, G. Muller, *Organometallics* **2008**, *27*, 1328.

104. A. Grabulosa, A. Mannu, G. Muller, T. Calvet, M. Font-Bardia, *J. Organomet. Chem.* **2011**, *696*, 2338.

105. R. Bayersdörfer, B. Ganter, U. Englert, W. Keim, D. Vogt, *J. Organomet. Chem.* **1998**, *552*, 187.

106. I. Ayora, R. M. Ceder, M. Espinel, G. Muller, M. Rocamora, M. Serrano, *Organometallics* **2011**, *30*, 115.

107. A. Grabulosa, *Compostos Organometàl-lics de Pd i Ru ambs Lligands Quirals P-Estereogènics: Preparació i Caracterització en Catàlisi Asimètrica*, PhD Thesis, Universidad de Barcelona, **2005**.

108. A. Grabulosa, G. Muller, J. I. Ordinas, A. Mezzetti, M. A. Maestro, M. Font-Bardia, X. Solans, *Organometallics* **2005**, *24*, 4961.

109. R. M. Ceder, C. Garcia, A. Grabulosa, F. Karipcin, G. Muller, M. Rocamora, M. Font-Bardia, X. Solans, *J. Organomet. Chem.* **2007**, *692*, 4005.

110. J. W. Faller, N. Sarantopoulos, *Organometallics* **2004**, *23*, 2008.

111. T. V. Rajanbabu, N. Nomura, J. Jin, M. Nandi, H. Park, X. Sun, *J. Org. Chem.* **2003**, *68*, 8431.

CHAPTER 4

PALLADIUM-CATALYZED AMINOCARBONYLATION REACTIONS

4.1 Introduction

Palladium-catalyzed carbonylation reactions, carried out in the presence of various nucleophiles like amines and alcohols, belong to the most widely used homogeneous catalytic reactions in synthetic chemistry.[1,2] There are a number of applications concerning the synthesis of simple building blocks and the functionalization of biologically important skeletons.[3,4]

As previously mentioned in Chapter 1, aminocarbonylation plays a special role among these reactions, since some carboxamides which are difficult to prepare via the conventional carboxylic acid–carboxylic halide–carboxamide route (*e.g.*, with bulky substituents at the amide nitrogen) can be synthesized from easily available starting materials, such as aryl triflates, enol-triflates, and the corresponding haloarene and haloalkene analogues.[5] Therefore, catalytic aminocarbonylation reactions have found numerous applications in the synthesis of unsaturated carboxamides or aryl carboxamides with unprecedented structures and relevant biological applications.[6,7,8]

Encouraged by the increasing importance of the selective synthesis of amides and ketoamides, as potential building blocks for high value products, the palladium-catalyzed aminocarbonylation of model iodoaryl and iodo-alkenyl compounds was performed, using the tris-binaphthyl monophosphites as ligands. We have also investigated the possibility of extending the scope of aminocarbonylation to bromo- and iodo-conduritol compounds, in order to obtain new amidocarbasugar derivatives. Furthermore, the unprecedented use of diamines as *N*-nucleophiles was employed in this catalytic reaction aiming the preparation of dimeric carboxamides (**Figure 4.1**), including steroid derivatives with potential biological activity.

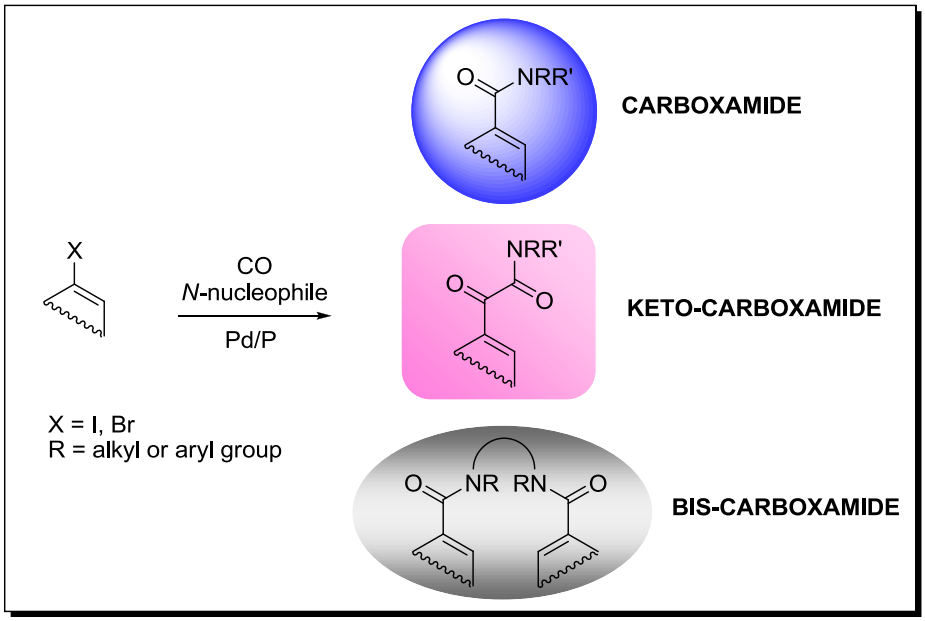


Figure 4.1 – Illustrative figure with different types of aminocarbonylated products developed in this work.

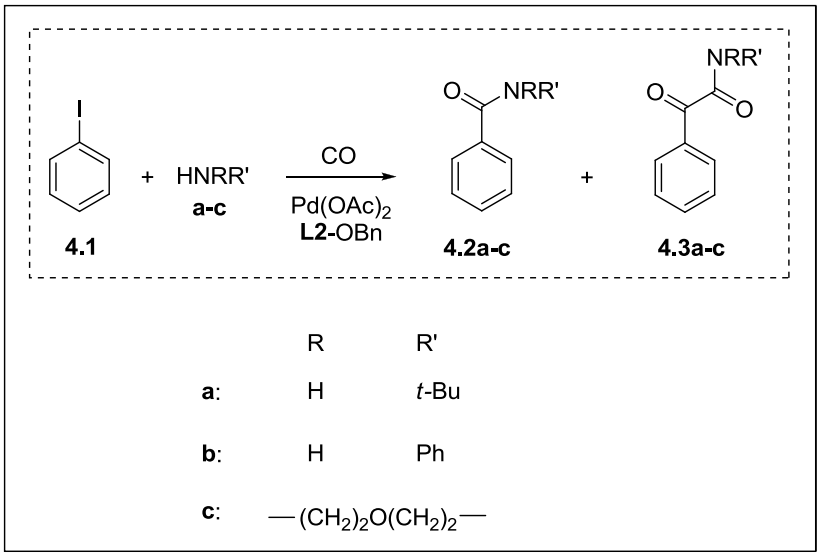
4.2 Palladium/monophosphite-catalyzed aminocarbonylation

It was our initial purpose to study the potentialities of the newly developed tris-binaphthyl monophosphites as ligands in palladium-catalyzed aminocarbonylation reactions, in order to evaluate the effects of electronic and steric properties of the ligands, although the reactions do not involve the generation of any chiral center.

4.2.1 Aminocarbonylation of iodobenzene

It is well established that aminocarbonylation of aryl halides, in presence of CO, amine nucleophiles and palladium/phosphine catalysts, generates two possible products: the carboxamide and the corresponding keto-carboxamide derivative.[8] The ratio between these two products depends on several factors, such as the structures of substrate and amine nucleophiles and the reaction conditions (namely, temperature and CO pressure) while the ligand structure is usually less significant.[9] Iodobenzene **4.1** is a typical model substrate, widely studied in this catalytic reaction, leading to carboxamides and keto-carboxamides with well-known structures.[10,11,12]

In order to find out the applicability of tris-binaphthyl monophosphites as ligands in this reaction, the aminocarbonylation of **4.1** was performed, using palladium catalysts formed *in situ* by reaction of palladium(II) acetate with tris[(*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl]phosphite, (*R*)-**L2**-OBn, which was selected as model ligand for this study. Three different amines have been used as *N*-nucleophiles: an aliphatic primary amine, *tert*-butylamine (**a**), an aromatic amine, aniline (**b**) and a secondary aliphatic heterocyclic amine, morpholine (**c**) (**Scheme 4.1**).

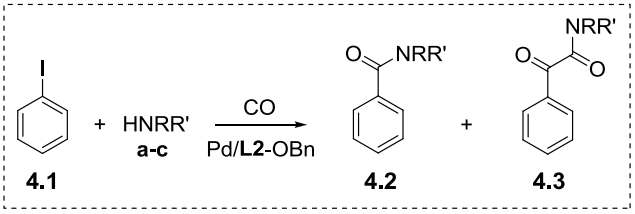


Scheme 4.1

In a typical experiment, the palladium precursor $Pd(OAc)_2$, two molar equiv. of monophosphite ligand **L2**-OBn, iodobenzene, amine nucleophile and triethylamine

were dissolved in DMF under argon in an autoclave, or a three-necked round-bottom flask (in case of 1 bar CO experiments). The autoclave was pressurized with the desired pressure of carbon monoxide and the reaction was conducted for the given time, upon stirring at 50°C. After 4h and 20h, samples taken from the autoclave were immediately analyzed by GC and GC-MS. The reaction mixtures were not subjected to work-up and purification procedures, since all the products **4.2a-c** and **4.3a-c** have been previously synthesized and characterized.[13,14] The results are summarized in Table 4.1.

Table 4.1 – Aminocarbonylation of iodobenzene **4.1**, in presence of *in situ* Pd/**L2**-OBn catalyst.[a)]



Entry	Amine	P (CO) [bar]	Conversion[b)] [%]	TOF[c)] [h^{-1}]	**4.2** : **4.3** ratio[b)]
1	**a**	1	84	8.4	40/60
2[d)]			100	> 2	53/47
3		40	42	4.2	10/90
4[d)]			75	1.5	26/74
5	**b**	1	100	> 10	100/0
6		40	30	3.0	100/0
7[d)]			67	1.3	100/0
8	**c**	1	86	8.6	15/85
9[d)]			100	> 2	16/84
10		40	46	4.6	12/88
11[d)]			77	1.5	24/76

[a)] **Reaction conditions** (unless otherwise stated): 1 mmol of substrate (**4.1**); 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of monophosphite ligand (**L2**-OBn); 3 mmol of **a**, 2 mmol of **b** or 1.5 mmol of **c**; 0.5 mL of Et_3N; solvent: DMF (10 mL); T= 50°C; time = 4h.
[b)] Determined by GC and GC-MS (naphthalene as internal standard).
[c)] Turnover frequency calculated as (mmol of **4.1** converted)×(mmol of Pd)$^{-1}$×(reaction time)$^{-1}$.
[d)] time = 20h.

Considering the effect of the amine structure in the catalytic activity, one can observe from Table 4.1 that the aminocarbonylation reaction rates, using the aliphatic primary amine (**a**) and the secondary cyclic amine (**c**) were very similar, with maximum turnover frequencies of approximately 9 h^{-1} with 1 bar of CO, and around 5 h^{-1} with 20

bar of CO (Table 4.1, entries 1-4 and 8-11). Using the aromatic amine (**b**) as *N*-nucleophile, the aminocarbonylation reaction of **4.1**, at 1 bar CO pressure has occurred faster, with complete conversion after 4 hours (Table 4.1, entry 5). Remarkably, with a CO pressure of 40 bar, the reaction rates using aniline (**b**) were significantly lower (Table 4.1, entries 6-7), when compared with the reactions using aliphatic amines (**a**) and (**c**). Although no mechanistic investigations have been carried out, the different behavior with aniline might be arisen from the lower reactivity of the corresponding palladium intermediate in activating a less nucleophilic aromatic amine.[9]

Regarding the effects of CO pressure in the catalytic activity and selectivity, the aminocarbonylation of **4.1**, carried out with *tert*-butylamine (**a**) with 1 bar of CO pressure, resulted in high conversion (84% in 4 h, 100% in 20 h) (Table 4.1, entries 1-2). However a decrease was observed when CO pressure was raised from 1 bar to 40 bar, with only 42% conversion in 4 h and 75% in 20 h (Table 4.1, entries 3-4). A significant effect of the CO pressure was also observed in the reaction chemoselectivity, with preferential formation of the keto-carboxamide product **4.3a** when a higher CO pressure is used (Table 4.1, entries 3-4). The decrease in reactivity with increasing carbon monoxide pressure can be explained by: i) the formation of Pd-dicarbonyl (or tricarbonyl) complexes with no aminocarbonylation activity or; ii) the preferred formation of the 2-ketocarboxamides due to double carbon monoxide insertion, which is generally accompanied by lower reaction rates.[1,9] Furthermore, it is worth mentioning that an increase on carboxamide/ketocarboxamide ratios was observed along the time (Table 4.1, entries 1-2, 3-4).

Similar tendencies were observed in the reaction rates when morpholine (**c**) was used as nucleophile: high conversions were achieved (86% in 4 h, 100% in 20 h) with 1 bar of CO (Table 4.1, entries 8-9) and significantly lower conversions were observed when CO pressure was raised to 40 bar (46% in 4 h and 77% in 20 h (Table 4.1, entries 10-11). However, practically no effect of CO pressure was observed in the reaction chemoselectivity, with preferential formation of the double carbonylated product **4.3c**, in both cases of 1 bar and 40 bar of CO (Table 4.1, entries 8-11).

Using aniline (**b**) as a nucleophile, the effect of CO pressure in the catalytic activity was more evident, with a decrease from 100% to 30% conversion when the

pressure was increased from 1 to 40 bar of CO. Nevertheless, the reaction was 100% chemoselective toward the carboxamide products, since no double carbon monoxide insertion has occurred, when the aromatic amine was used as nucleophile (Table 4.1, entries 5-7).

In summary, the Pd/monophosphite **L2**-OBn complexes formed *in situ* provided active catalytic systems for the aminocarbonylation of iodobenzene **4.1**, with higher conversions at lower CO pressures, while the chemoselectivity showed to be strongly dependent on the type of amine used as nucleophile, being carboxamides the only product obtained with aniline (**b**), and keto-carboxamides the major products when *tert*-butylamine (**a**) and morpholine (**c**) were employed as *N*-nucleophiles.

4.2.2 Aminocarbonylation of 1-iodo-cyclohexene

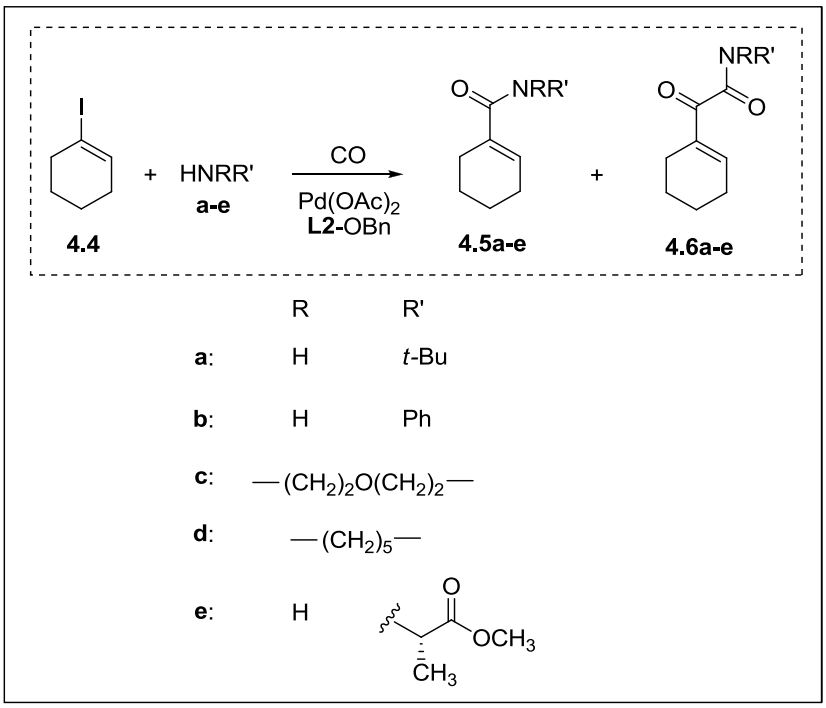
Similarly to aryl halides, iodo-alkenes can also undergo aminocarbonylations resulting in α,β-unsaturated carboxamides. However, the major difference from the corresponding aromatic substrates lies in the lack of double carbon monoxide insertion, *i.e.*, the formation of 2-ketocarboxamides is not observed under aminocarbonylation standard conditions.[1,9]

Thus, having in hand a novel family of bulky aryl monophosphite ligands with peculiar steric and electronic properties, we aimed the synthesis of new cycloalkenyl ketoamides via double carbonylation of 1-iodo-cyclohexene **4.4**.

The aminocarbonylation of **4.4** as iodoalkene substrate was performed, in the presence of palladium catalysts formed *in situ* by the reaction of $Pd(OAc)_2$ and the monophosphite (*R*)-**L2**-OBn, used as model ligand for this reaction. Five different amines, such as *tert*-butylamine (**a**), aniline (**b**), morpholine (**c**), piperidine (**d**) and (L)-alanine methyl ester (**e**), were used as *N*-nucleophiles (**Scheme 4.2**).

In a typical experiment, $Pd(OAc)_2$, 2 molar equiv. monophosphite ligand **L2**-OBn, 1-iodo-cyclohexene **4.4**, the amine nucleophile and Et_3N were dissolved in DMF under argon in the autoclave, or a three-necked round-bottom flask (in case of 1 bar CO experiments). The autoclave was pressurized with the desired CO pressure and the reaction was conducted for the given time, upon stirring at 50°C (or 30°C). The reaction evolution along the time and products identification was performed by GC and GC-MS

analysis of samples taken from the reaction mixture. The mixture was then concentrated and evaporated to dryness. After work-up procedures, the reaction mixtures were then purified by column chromatography, using silica gel as stationary phase and mixtures of EtOAc/$CHCl_3$ as eluents (exact ratios for each compound are specified in Chapter 5, section 5.4.2).



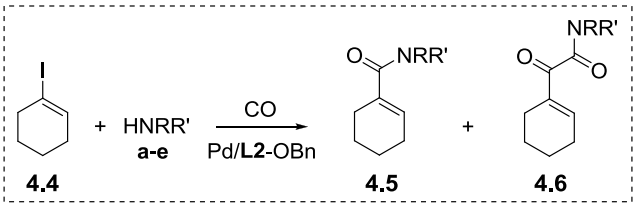
Scheme 4.2

The optimization of the reaction conditions toward the double carbonylated products using *tert*-butylamine (**a**) as *N*-nucleophile, and the subsequent screening of the several diamines was then performed. The results are presented in Table 4.2.

Under the typical conditions,[10] at 50°C and 1 bar CO, the exclusive formation of *N*-(*tert*-butyl)carboxamide derivative **4.5a** was observed (Table 4.2, entry 1). However, the target 2-keto-carboxamide **4.6a** was able to be formed in the range of 20-110 bar of CO pressure (Table 4.2, entries 2-9). At the temperature of 50°C, the increase of CO pressure from 40 bar to 60 bar had a positive influence on the formation of **4.6a** (Table 4.2, entries 2-3). Nevertheless, at a higher temperature of 80°C, the effect of the CO pressure on chemoselectivity was negligible (Table 4.2, entries 4-5). The decrease of the temperature to 30°C has remarkably favored the formation of ketoamide **4.6a**

(Table 4.2, entries 6-9). Furthermore, at this temperature, the increase in the CO pressure from 20 bar to 110 bar had a pronounced positive outcome on the formation of **4.6a**, with an almost insignificant effect on the reaction rate (Table 4.2, entries 6 and 8). Consequently, the highest chemoselectivity of 67% towards 2-ketocarboxamide **4.6a** has been obtained at 30°C and 110 bar CO pressure (Table 4.2, entry 6).

Table 4.2 – Optimization of reaction conditions and screening of amines in aminocarbonylation of 1-iodo-cyclohexene **4.4** with *in situ* Pd/**L2**-OBn catalysts.[a)]

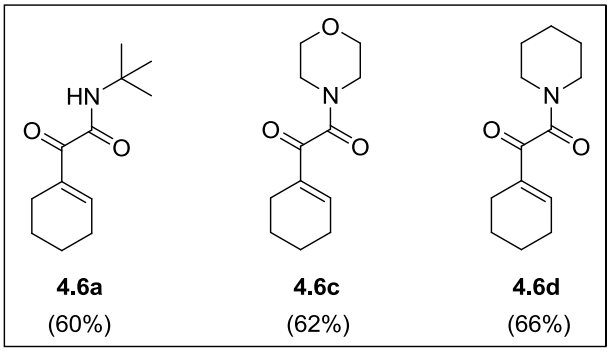


Entry	Amine	T [°C]	P(CO) [bar]	time [h]	Conversion[b)] [%]	TOF[c)] [h^{-1}]	**4.5/4.6** ratio
1	**a**	50	1	0.5	100	>80	100/0
2	**a**	50	40	3	100	>13	75/25
3	**a**	50	60	1	100	>40	66/34
4	**a**	80	40	1	100	>40	86/14
5	**a**	80	60	1	100	>40	86/14
6	**a**	30	110	2	75	15	33/67
7	**a**	30	110	6	100	>7	46/54
8	**a**	30	20	2	69	13.8	61/39
9	**a**	30	20	3	80	10.7	60/40
10	**b**	50	1	1	64	25.6	100/0
11	**b**	50	40	0.5	100	>80	100/0
12	**b**	30	110	2	100	>20	100/0
13	**c**	50	1	1	100	>40	100/0
14	**c**	30	110	2	92	18.4	34/66
15	**c**	30	110	4	100	>10	33/67
16	**d**	30	110	4	100	>10	29/71
17	**e**	50	1	1	100	>40	100/0
18	**e**	50	40	1	100	>40	97/3
19	**e**	30	110	2	87	17.4	93/7

[a)] **Reaction conditions**: 1 mmol of substrate (**4.4**); 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of monophosphite ligand (**L2**-OBn); 3 mmol of **a**, 2 mmol of **b**, 1.5 mmol of **c** and **d**, or 1.1 mmol of **e** (as a hydrochloride salt); 0.5 mL of Et_3N; solvent: DMF (10 mL).
[b)] Determined by GC and GC-MS (naphthalene as internal standard).
[c)] Turnover frequency calculated as (mmol of **4.4** converted)×(mmol of Pd)$^{-1}$×(reaction time)$^{-1}$.

Regarding the screening of the other amines, the exclusive formation of carboxamide derivatives of type **4.5** was also observed, as expected, at 1 bar CO and

50°C (Table 4.2, entries 10, 13 and 17). Under the optimized reaction conditions of 30°C and 110 bar CO, the use of secondary amines morpholine (**c**) and piperidine (**d**) as nucleophiles, resulted in chemoselectivities of 67 and 71%, respectively, toward the double carbonylated products **4.6c** and **4.6d** (Table 4.2, entries 15 and 16). After the respective purification by column chromatography in silica gel, the desired ketoamides with unprecedented structures **4.6a**, **4.6c** and **4.6d** have been isolated in 60%, 62% and 66% yields, respectively and chemically characterized by spectroscopic techniques.

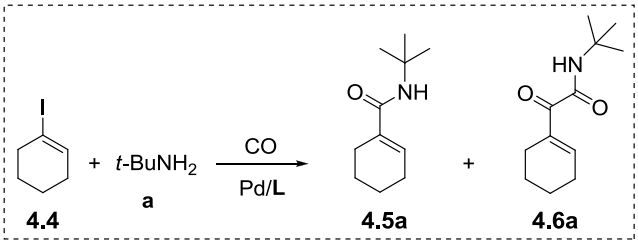


The aminocarbonylation of **4.4** with aniline (**b**) as a nucleophile did not provide double carbon monoxide insertion, although unexpectedly high activities for the formation of the corresponding carboxamide **4.5b** were observed (Table 4.2, entries 10-12). As previously observed with **4.1**, the insertion of a "second" CO unit leading to the corresponding Pd-carbamoyl intermediate {Pd(CO)NRR'} seems not to be favored in case of an aromatic moiety.

Furthermore, using methyl (L)-alaninate (**e**), a very low chemoselectivity toward the double carbonylation product **4.6e** was also observed (Table 4.2, entries 18 and 19). It should be mentioned that the carboxamides of known structure (**4.5a**,[15] **4.5c**,[16] **4.5d**[17] and **4.5e**[10] gave identical spectra to those reported in the literature, obtained by conventional synthetic methods.

Following our initial goal of evaluate the effect of the OR substituents at the monophosphite ligands in the catalytic performance, the comparative screening of ligands (*R*)-**L1**-OMe, (*R*)-**L2**-OBn, (*R*)-**L3**-$OCHPh_2$ and (*R*)-**L4**-OAd was performed in the palladium-catalyzed aminocarbonylation of 1-iodo-cyclohexene **4.4**, using *tert*-butylamine (**a**), as model *N*-nucleophile. The results are summarized in Table 4.3.

Table 4.3 – Ligand screening in *tert*-butylaminocarbonylation of 1-iodo-cyclohexene **4.4**.[a)]



Entry	Ligand (**L**)	T [°C]	P(CO) [bar]	time [h]	Conversion [b)] [%]	TOF [c)] [h^{-1}]	**4.5a**/**4.6a** ratio
1	**L1**-OMe	50	1	1	100	>40	100/0
2	**L1**-OMe	30	110	2	100	>20	39/61
3	**L2**-OBn	50	1	0.5	100	>80	100/0
4	**L2**-OBn	30	110	2	75	15	33/67
5	**L3**-$OCHPh_2$	30	110	1	59	23.6	43/57
6	**L3**-$OCHPh_2$	30	110	2	71	14.2	28/72
7	**L4**-OAd	50	1	1	100	>40	100/0
8	**L4**-OAd	30	110	2	76	15.2	33/67

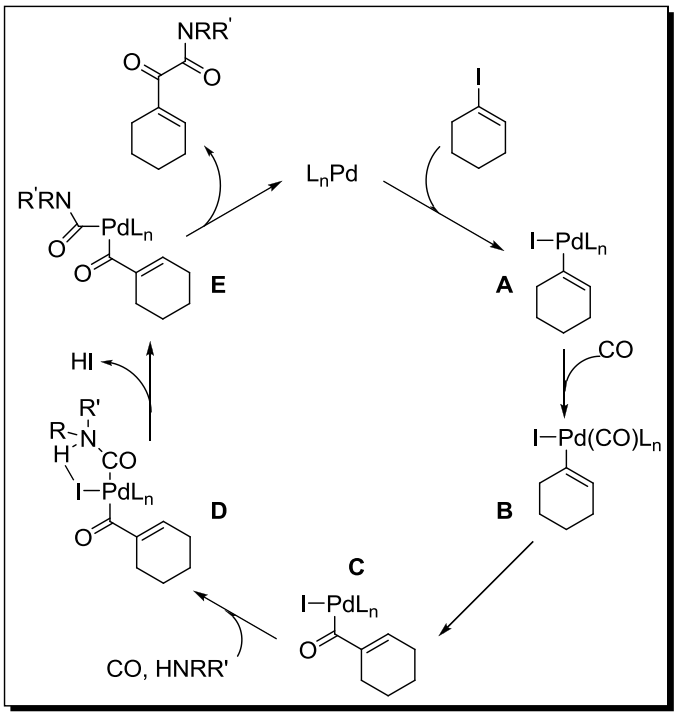
[a)] **Reaction conditions** (unless otherwise stated): 1 mmol of substrate (**4.4**); 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of ligand; 3 mmol of **a**; 0.5 mL of Et_3N; solvent: DMF (10 mL).
[b)] Determined by GC and GC-MS (naphthalene as internal standard).
[c)] Turnover frequency calculated as (mmol of **4.4** converted)×(mmol of Pd)$^{-1}$×(reaction time)$^{-1}$.

Under the optimized reaction conditions toward double carbonylation, *i.e.*, at a high CO pressure (110 bar) and low temperature (30°C), the *tert*-butylaminocarbonylation reaction of **4.4**, using the ligands **L1**-OMe, **L3**-$OCHPh_2$ and **L4**-OAd, showed similar activities and chemoselectivities to those achieved with **L2**-OBn, being the ketocarboxamide **4.6a** achieved as the major product (≈70%) in all cases (Table 4.3, entries 2, 4, 6, and 8). As expected, when the reactions were performed at 50°C and 1 bar of CO pressure the Pd/L catalytic systems (with **L1**-OMe, **L2**-OBn and **L4**-OAd as ligands) provided exclusively the monocarboxamide **4.5a** (Table 4.3, entries 1, 3, and 7). Therefore, the OR moiety at the monophosphite ligand did not significantly influence either the catalytic activity or the chemoselectivity. These results might refer to the fact that, under aminocarbonylation conditions, the monophosphites coordinate to palladium as monodentate *P*-ligands (upon the activation of the iodoalkene substrate).

Mechanistic considerations

It is worth mentioning that these *in situ* catalysts are the phosphite analogues of the widely studied palladium(0)-tertiary phosphine systems. It has been proved that palladium(II) is reduced to palladium(0) while one of the two equivalents of ligand is oxidized.[18,19] In our case, the formation of coordinatively highly unsaturated [Pd(**L**)$(S)_n$]complex (wherein S stands for solvent (DMF) and L stands for the monophosphite) is believed to occur, while the second equivalent of monophosphite ligand is oxidized to the corresponding triaryl phosphate. The action of other compounds (amine, carbon monoxide) as reducing agents cannot be excluded.

Although the formation of 2-oxo-carboxamides from haloaromatics can be explained in two ways, namely, by both the "glyoxyl-route" and the "acyl-carbamoyl-route", detailed mechanistic studies revealed that the latter is responsible for double-carbonylation.[20,21] A similar mechanism could be operative in the case of these palladium/phosphite systems containing sterically hindered *P*-heterodonor ligands. A simplified catalytic cycle describing the formation of 1-cyclohexenylglyoxylamides, from aminocarbonylation of 1-iodo-cyclohexene is then proposed in **Scheme 4.3**.



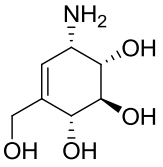
Scheme 4.3

The facile oxidative addition of *in situ* formed palladium(0) species results in an alkenyl-palladium(II) (**A**) intermediate which is able to coordinate carbon monoxide (**B**). The acyl complex (**C**), formed by carbon monoxide insertion, is ready to coordinate the "second" carbon monoxide as a terminal carbonyl, which undergoes a nucleophilic attack by the *N*-nucleophile (**D**). In this way, the bulky tris-binaphthyl ligands might favor the formation of the acyl-carbamoyl-palladium(II) intermediates (**E**), [Pd{RC(O)}{C(O)NRR′}], which readily undergo reductive elimination providing 2-ketocarboxamides. Although several further features in the catalytic cycle may promote the insertion of a second CO into the acyl-palladium complex, leading to the Pd-carbamoyl intermediate, phosphites with low electron donor character (and being strong π-acceptors) create a relatively electron-poor transition metal center, which favors the subsequent reductive elimination.

In sum, the palladium complexes formed *in situ* with the new tris-binaphthyl monophosphite ligands provided the first examples of active and selective catalytic systems toward the double carbonylated products in the aminocarbonylation of 1-iodo-cyclohexene. The resulting cyclohexenyl-glyoxylamides, which have been efficiently synthesized for the first time using this methodology, are valuable building blocks in synthetic chemistry.

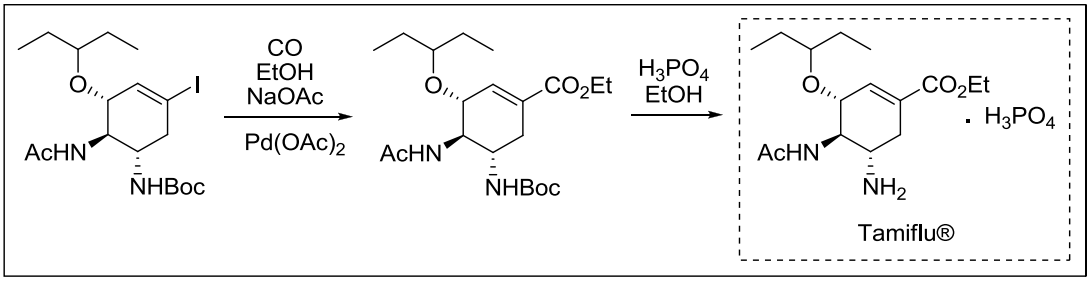
4.3 Palladium-catalyzed aminocarbonylation of halogenated conduritol derivatives

Conduritol derivatives (*i.e.*, 1,2,3,4-cyclohexenetetrols) are considered useful chiral building blocks for the asymmetric synthesis of natural products,[22,23] since their chemical constitution resemble the structure of sugars. In fact, the design and synthesis of small molecules, which can mimic complex carbohydrates involved in diverse cellular processes – *glycomimics*,[24,25] may lead to a better understanding of carbohydrate functions and can eventually culminate in potential drug candidates.[26] These *glycomimics* include carbasugars and aminocarbasugars, which usually display various biological properties as enzyme inhibitors,[27,28,29] and may be involved in relevant biological processes or biotechnological applications.[30] For example, several aminocyclitols,[31,32,33] such as valienamine **4.7** and its related analogues have demonstrated strong *glucosidase* inhibitory activity, thus showing particular importance as chemotherapeutic agents.[34]



4.7
Valienamine

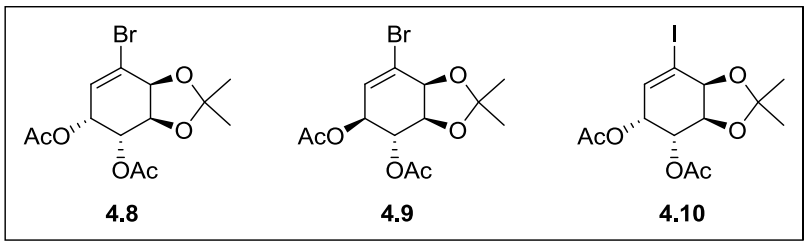
Among the several examples of biologically relevant targets prepared by palladium-catalyzed carbonylation reactions, are the syntheses of carbasugars[35,36] and the antiviral agent oseltamivir,[37] known as Tamiflu® (**Scheme 4.4**).



Scheme 4.4

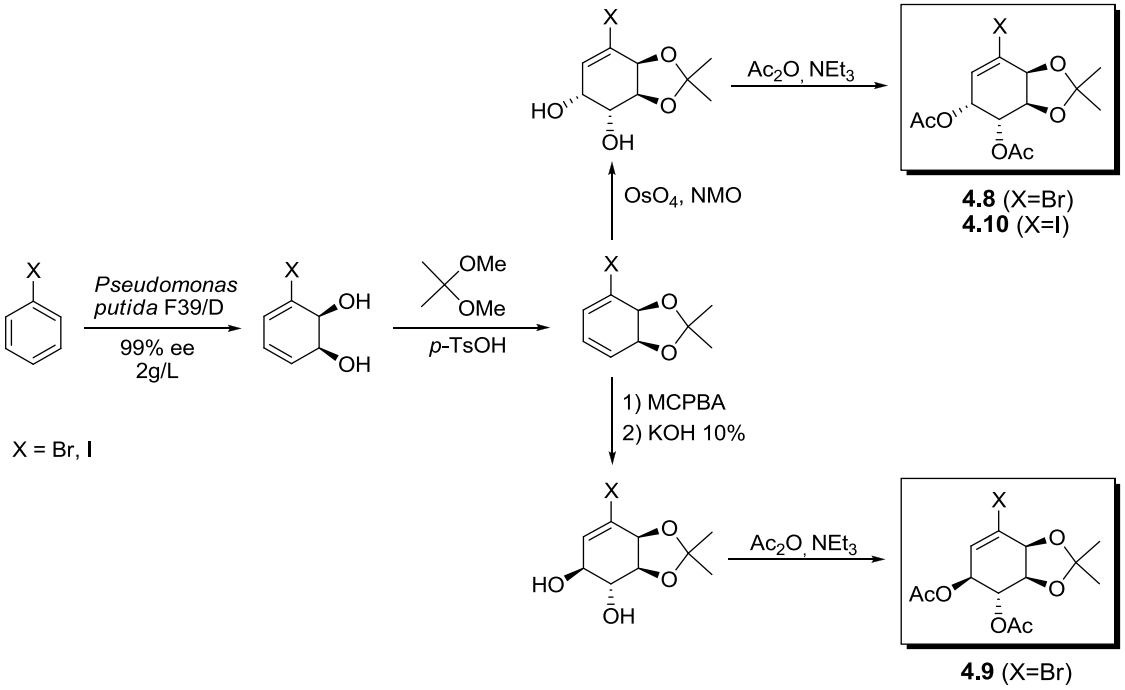
Iodoarenes and iodoalkenes are the most frequent substrates in coupling reactions, due to the presence of a more polarizable iodo leaving group that enables facile reactions, under mild reaction conditions. However, aryl and alkenyl bromides[38] present several advantages, such as higher synthetic availability, lower cost and easier manipulation when compared to the iodo-analogues. Therefore, the carbonylation of bromo-alkenes represents a great challenge, from a synthetic point of view.

In this section, the studies of palladium-catalyzed aminocarbonylation reactions were extended to bromo- and iodo-cyclohexenetetraols as substrates, aiming the synthesis of chiral conduritol-derived carboxamides. The halogenated conduritol derivatives **4.8**, **4.9** and **4.10** were prepared in the laboratory of Professor E. Pandolfi, from Universidad de La Republica (UdelaR), in Montevideo (Uruguay), and were kindly provided by Doctor V. Heguaburu and Doctor V. Schapiro, in the scope of a bilateral cooperation project.[39]



4.8 **4.9** **4.10**

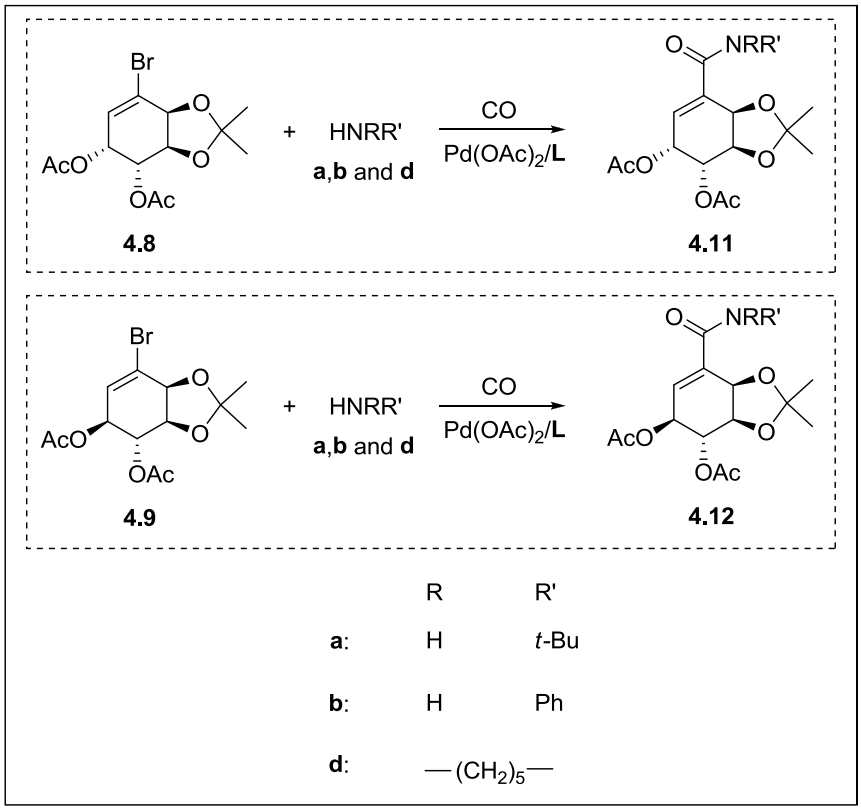
The synthesis of the substrates has followed the sequential pathway represented in **Scheme 4.5**. The first step was the biotransformation of bromobenzene in the presence of *Pseudomonas putida* F39/D.[40] The reaction with 2,2-dimethoxypropane[41] yielded the protected *cis*-cyclohexadienediol derivative, whose further oxygenation was followed by two different synthetic approaches: the dihydroxylation with OsO_4 and NMO (*N*-methylmorpholine *N*-oxide), attaining the *cis*-hydroxylated product,[42] or the *trans* dihydroxylation through reaction of the protected cyclohexadienediol with MCPBA (*meta*-chloroperoxybenzoic acid), followed by epoxide ring opening with KOH.[41] The subsequent protections of the hydroxyl groups with acetic anhydride in basic media afforded the target compounds **4.8**, **4.9** and **4.10**, which were used as substrates in palladium-catalyzed aminocarbonylation reactions.[43]



Scheme 4.5

The diastereomeric conduritol derivatives **4.8** and **4.9** were subjected to aminocarbonylation reactions with different amines: *tert*-butylamine (**a**), aniline (**b**) and piperidine (**d**), in the presence of *in situ* generated Pd(0) catalysts (**Scheme 4.6**).

In a typical experiment, the $Pd(OAc)_2$ precursor, 2 molar equiv. of phosphorus ligand and the haloconduritol derivative were placed in the autoclave. After three cycles of CO/vacuum, the desired amine and triethylamine, dissolved in DMF under N_2 atmosphere, were added via *cannula*. The autoclave was then pressurized with 30 bar of carbon monoxide and the mixture was magnetically stirred for 24 h at 100°C. It should be mentioned that the employed amine/substrate ratios were based on the volatility properties of each amine. For instance, the most volatile amine, *tert*-butylamine (**a**) was used in threefold excess, while in the case of less volatile piperidine (**d**), a ratio of 1.5 to substrate was sufficient. The reactions' progress was followed by TLC and GC analysis of aliquots taken from the reactor via *cannula*, and the final conversions were determined by GC and confirmed by ^{1}H NMR spectroscopy of the crude mixture, through integration of the olefinic protons of both the substrate and the reaction products.



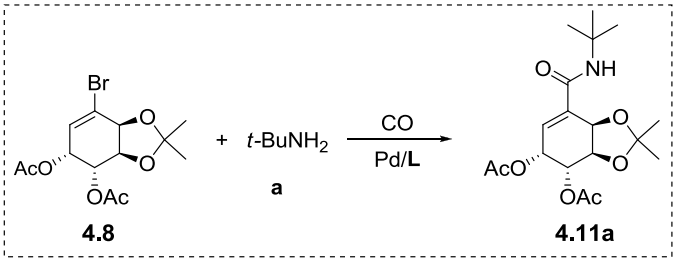
Scheme 4.6

The optimization of the reaction conditions was performed using **4.8** as model substrate and *tert*-butylamine (**a**) as model *N*-nucleophile (Table 4.4). Similarly to previous studies, in the first assessment, tris[(*S*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl]phosphite, (*S*)-**L2**-OBn was used as model ligand from the family of C_3-symmetry tris-binaphthyl monophosphites and the reaction was carried out at 30 bar of CO pressure and 100°C. However, no conversion has occurred using the *in situ* Pd/**L2**-OBn catalyst, in 24 hours (Table 4.4, entry 1). Consequently, triphenylphosphine was then selected as ligand, to study the effects of several reaction parameters.

Under a 30 bar CO pressure and 50°C temperature, the *in situ* Pd/PPh_3 catalyst was inactive in the aminocarbonylation of **4.8**, since the reaction did not proceed after 24 h (Table 4.4, entry 2). To overcome problems related to the low reactivity of the bromoalkene substrate, a temperature of 100°C was employed, keeping the CO pressure in 30 bar. Under these conditions, a conversion of 60% was achieved in 24 h (Table 4.4, entry 3). However, at longer reaction time (48 h), a complex mixture, containing hydrolyzed products (Table 4.4, entry 4) was evidenced by GC, ^{1}H NMR and

^{13}C NMR. The decrease of CO pressure to 20 bar led to a drop in the conversion (30% in 24 h) (Table 4.4, entry 5). Furthermore, by using a different solvent, butan-2-one instead of DMF, a considerably higher conversion of substrate (90%) was observed, however a significantly lower selectivity was achieved, resulting in a complex mixture of mono-, double carbonylated and hydrolyzed products (Table 4.4, entry 6).

Table 4.4 – Optimization of reaction conditions in aminocarbonylation of **4.8**, using *tert*-butylamine (**a**) as nucleophile.[a)]



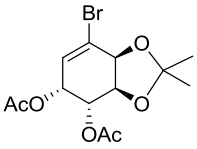
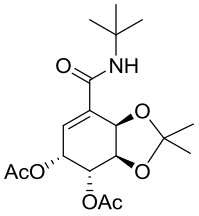
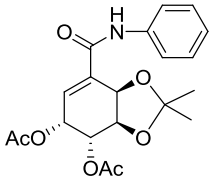
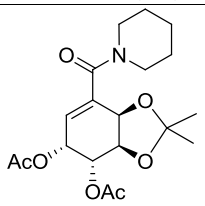
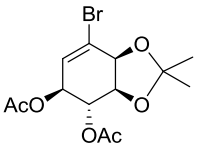
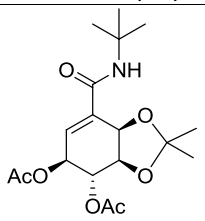
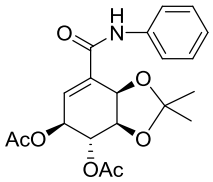
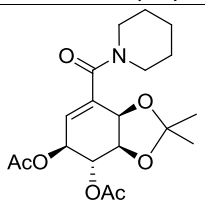
4.8 **4.11a**

Entry	Ligand (**L**)	T [°C]	P(CO) [bar]	solvent	time [h]	Conversion [b)] [%]
1	**L2**-OBn	100	30	DMF	24	-
2	PPh_3	50	30	DMF	24	-
3	PPh_3	100	30	DMF	24	60
4	PPh_3	100	30	DMF	48	100[c)]
5	PPh_3	100	20	DMF	24	30
6	PPh_3	100	30	butan-2-one	24	90[c)]

[a)] **Reaction conditions**: 0.3 mmol of substrate **4.8**; 0.015 mmol of $Pd(OAc)_2$; 0.03 mmol of ligand; 0.9 mmol of **a**; 0.25 mL Et_3N, solvent: DMF or butan-2-one (7 mL).
[b)] % of substrate converted at the indicated time, determined by GC and ^{1}H NMR.
[c)] complex product mixture.

In order to turn this reaction into a real synthetic tool for the preparation of conduritol-derived amidocarbasugars, the aminocarbonylation of **4.8** and **4.9** was then performed under the previously optimized reaction conditions (T=100°C; P(CO)=30 bar; $Pd(OAc)_2/PPh_3$ (1:2) as in situ catalyst; DMF as solvent; time=24 h), using *tert*-butylamine (**a**), aniline (**b**) and piperidine (**d**) as *N*-nucleophiles. At the end of each reaction, metallic "palladium-black" particles were filtered off, and the mixture was evaporated to dryness. After work-up, the desired products of type **4.11** and **4.12** were purified, by column chromatography in silica gel, using mixtures of chloroform/ethyl acetate or *n*-hexane/ethyl acetate as eluent (exact ratios for each compound are specified in Chapter 5, section 5.4.3). The results are summarized in Table 4.5.

Table 4.5 – Catalytic aminocarbonylation of bromoconduritol derivatives **4.8** and **4.9**.[a)]

Entry	Substrate	Amine	Product conversion[b)] [%] (isolated yield [%])
1	 **4.8**	**a**	 **4.11a** 60 (50)
2		**b**	 **4.11b** 57 (45)
3		**d**	 **4.11d** 67 (56)
4	 **4.9**	**a**	 **4.12a** 63 (52)
5		**b**	 **4.12b** 45 (27)
6		**d**	 **4.12d** 66 (53)

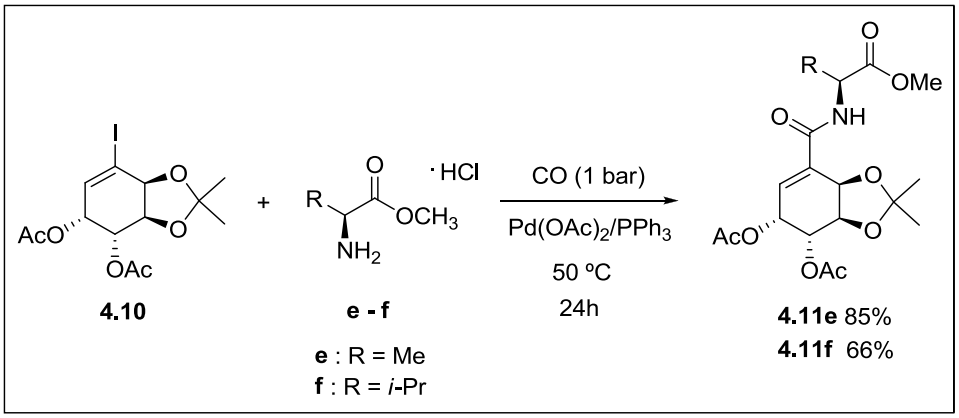
[a)] **Reaction conditions**: 0.3 mmol of substrate; 0.015 mmol of $Pd(OAc)_2$; 0.03 mmol of PPh_3; 0.9 mmol of **a**, 0.6 mmol of **b**, or 0.45 mmol of **d**; 0.25 mL of Et_3N; solvent: DMF (7 mL); T=100°C; P(CO)=30 bar.

[b)] % of substrate converted at the indicated time, determined by GC and ^1H NMR.

The overall results show that, using moderate CO pressures (30 bar) and a temperature of 100°C, total selectivity for the carboxamide products was achieved in all cases, since no double carbonylated products (2-ketocarboxamides) were formed. Furthermore, conversions did not depend on the stereo configuration of the substrate, but were basically influenced by the amine nucleophilicity, being higher with alkyl amines **a** and **d** (Table 4.4, entries 1, 3, 4 and 6) than with the aromatic amine **b** (Table 4.4, entries 2 and 5). It is worth mentioning that the sensitiveness of acetate protecting group toward hydrolysis, during the isolation/purification process resulted in significantly decreased isolated yields, comparatively to reaction conversions.

The aminocarbonylation of **4.8**, using *tert*-butylamine (**a**) as nucleophile, provided the respective carboxamide **4.11a** with an isolated yield of 50%. Likewise, using the same amine, product **4.12a** was reached from the aminocarbonylation of substrate **4.9**, in 52% isolated yield (Table 4.5, entries 1 and 4). In the same way, the reactions with the secondary amine piperidine (**d**) gave the corresponding products **4.11d** and **4.12d**, in similar isolated yields of 56% and 53%, respectively (Table 4.5, entries 3 and 6). However, using aniline (**b**) as nucleophile, lower conversions were observed, and the target carboxamides **4.11b** and **4.12b** were more susceptible to decomposition during the purification procedures, as demonstrated by the significantly lower isolated yields of with 45% and 27%, respectively (Table 4.5, entries 2 and 5).

Aiming to expand the structural motifs of these conduritol-derived carboxamides, retaining the resemblance with natural products, two amino acid derivatives were also used as *N*-nucleophiles: (*L*)-alanine methyl ester (**e**) and (*L*)-valine methyl ester (**f**). However, to overcome issues related to products decomposition under heavy reaction conditions, these Pd-catalyzed aminocarbonylation reactions were performed, using **4.10** as substrate (**Scheme 4 7**), the iodo analogue of **4.8**. This way, it was possible to use considerably milder reaction conditions (1 bar CO, 50°C) than those previously employed in reactions of bromocyclohexenetetraols. The amino acid methyl esters were used in hydrochloride form (solids), so the "free" nucleophiles were made available "*in situ*" upon the effect of triethylamine as HCl acceptor.



Scheme 4.7

The aminocarbonylations of the iodo-cyclohexenetetraol derivative **4.10** yielded the carboxamide products with high conversions (99% in the case of (*L*)-alanine and 93% with (*L*)-valine methyl ester) under mild reaction conditions. After work-up and purification by column chromatography in silica gel, using as eluent a mixture of chloroform/EtOAc (exact ratios for each compound are specified in Chapter 5, section 5.4.3), the target carboxamide compounds **4.11e** and **4.11f** were obtained in 85% and 66% isolated yields, respectively.

All products were fully characterized, using the appropriate spectroscopic techniques, namely ^{1}H NMR, ^{13}C NMR (full assignments were based on 2D NMR homonuclear (COSY and NOESY) and heteronuclear (HSQC and HMBC) experiments) and mass spectrometry (Chapter 5, section 5.4.3).

As illustrative example, the ^{1}H NMR spectrum of the *tert*-butylcarbamoyl derivative **4.12a** in $CDCl_3$ at room temperature (**Figure 4.2**), shows a doublet at δ = 6.63 ppm, with a small coupling constant of 2 Hz, which was assigned to the olefinic proton at position 6. The broad singlet at δ = 6.48 ppm was assigned to the amide N–H proton. The different cyclohexenyl protons in the close proximity of electronegative oxygen atoms gave rise to distinct signals with chemical shifts in the region between 4.28-5.51 ppm. At δ = 5.49 ppm, a doublet of doublets was assigned to the proton at position 5, as result of the couplings with the olefinic proton in position 6 (with a coupling constant of 2 Hz) and with the proton in adjacent position 4 (with a coupling constant of 9 Hz). At δ = 5.23 ppm, another doublet of doublets, with coupling

constants close to 9 Hz, was assigned to the proton in position 4, which couples with protons in both adjacent positions 5 and 3a. The sharp doublet with a coupling constant of 6 Hz, at δ = 4.82 ppm, was assigned to the proton at position 7a, as result of coupling with a single proton in the position 3a. At δ = 4.29 ppm, the proton at position 3a is evidenced by a doublet of doublets, with *J* = 6 Hz and *J* = 9 Hz, as result of the respective couplings with the protons in both adjacent positions 7a and 4. At δ = 2.10 ppm and δ = 2.09 ppm, two close singlets were assigned to the three methyl protons of each acetate groups in 3 and 4 positions. Two other singlets can be observed at δ = 1.55 ppm and δ = 1.44 ppm, which were assigned to six methyl protons of the isopropylidene group. Finally, the intense singlet at δ = 1.39 ppm was assigned to the nine protons of the *tert*-butyl group.

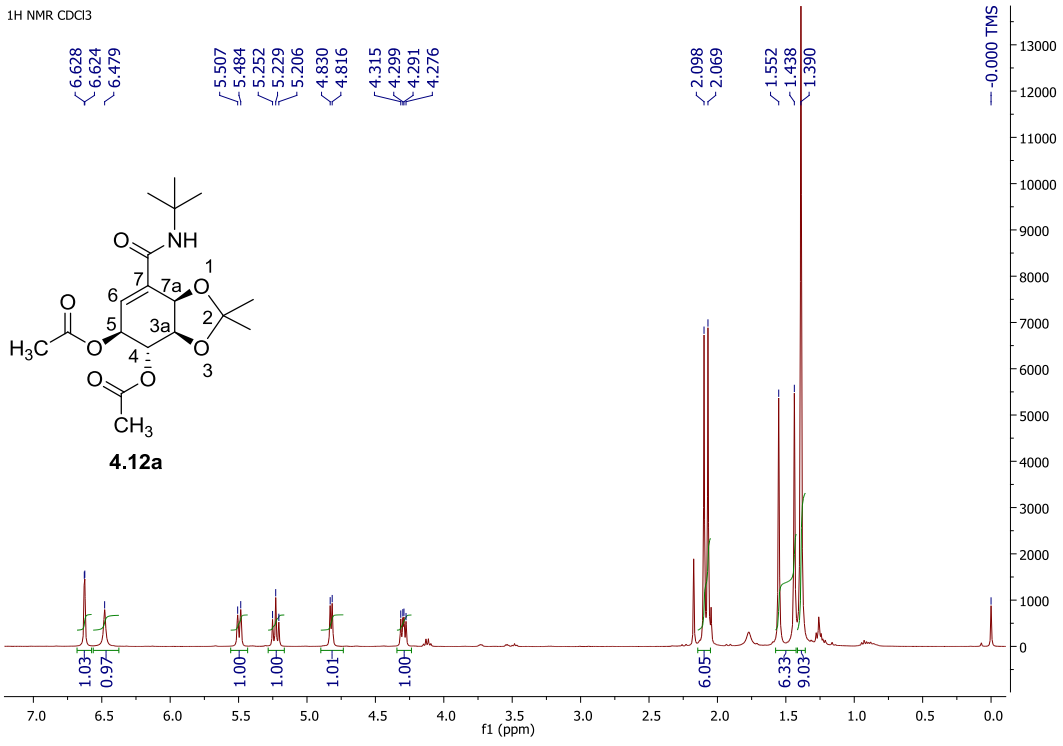


Figure 4.2 – ^{1}H NMR spectrum of (3a*R*,4*R*,5*S*,7a*R*)-7-(*tert*-butylcarbamoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate (**4.12a**).

The ^{13}C NMR spectrum of **4.12a** in $CDCl_3$ at room temperature (**Figure 4.3**), shows two signals at δ = 170.2 ppm and δ = 170.1 ppm, assigned to the carbonyl carbon atoms belonging to both acetate groups in positions 4 and 5. At δ = 163.8 ppm,

the signal was assigned to the carboxamide carbon atom. The peaks at δ = 135.0 ppm and δ = 132.1 ppm were assigned to the olefinic C6 and C7 atoms. The signal at δ = 111.9 ppm was assigned to the isopropylidene C2 atom. The four peaks at 75.6 ppm, 71.8 ppm, 71.4 ppm and 69.9 ppm were assigned to C3a, C7a, C4 and C5, respectively. The signal at δ = 51.4 ppm was assigned to the nitrogen-bounded *tert*-butyl carbon atom, while at δ = 28.6 ppm a triple intensity signal was assigned to the three equivalent methyl carbon atoms of the *tert*-butyl group. The two signals at δ = 27.8 ppm and δ = 26.4 ppm were assigned to methyl carbon atoms of the isopropylidene group. Finally, the two close peaks at δ = 20.9 ppm and δ = 20.8 ppm were assigned to the methyl carbon atoms of each acetate groups.

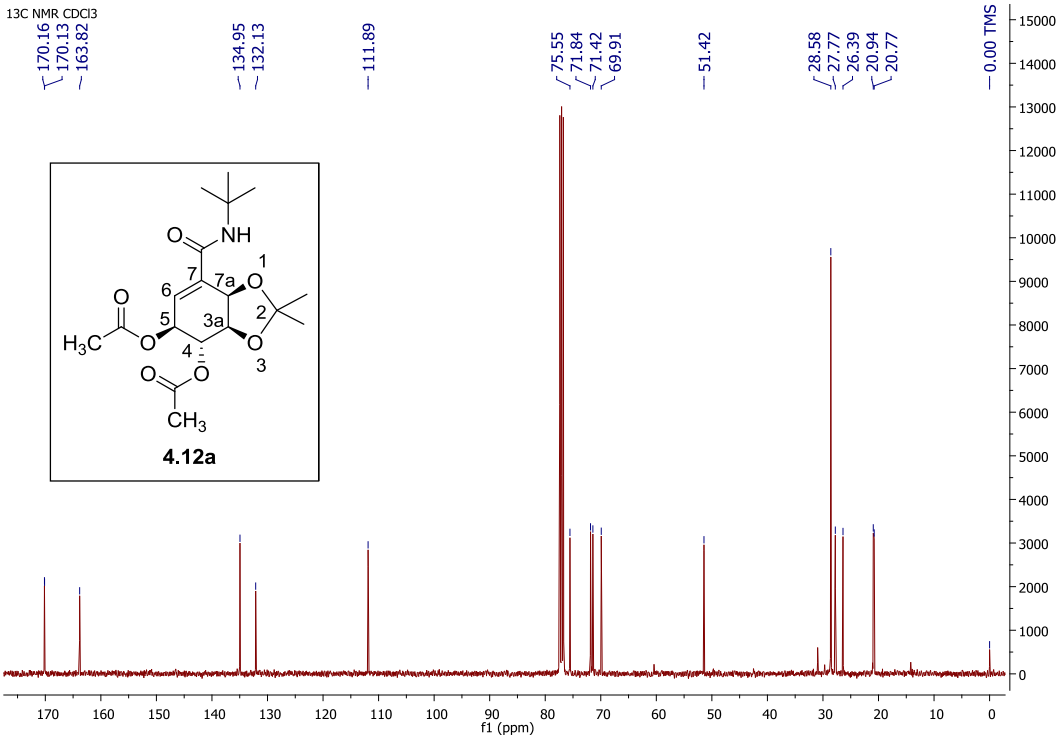


Figure 4.3 – ^{13}C NMR spectrum of (3a*R*,4*R*,5*S*,7a*R*)-7-(*tert*-butylcarbamoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate (**4.12a**).

4.4 Synthesis of dicarboxamides *via* catalytic carbonylative dimerizations

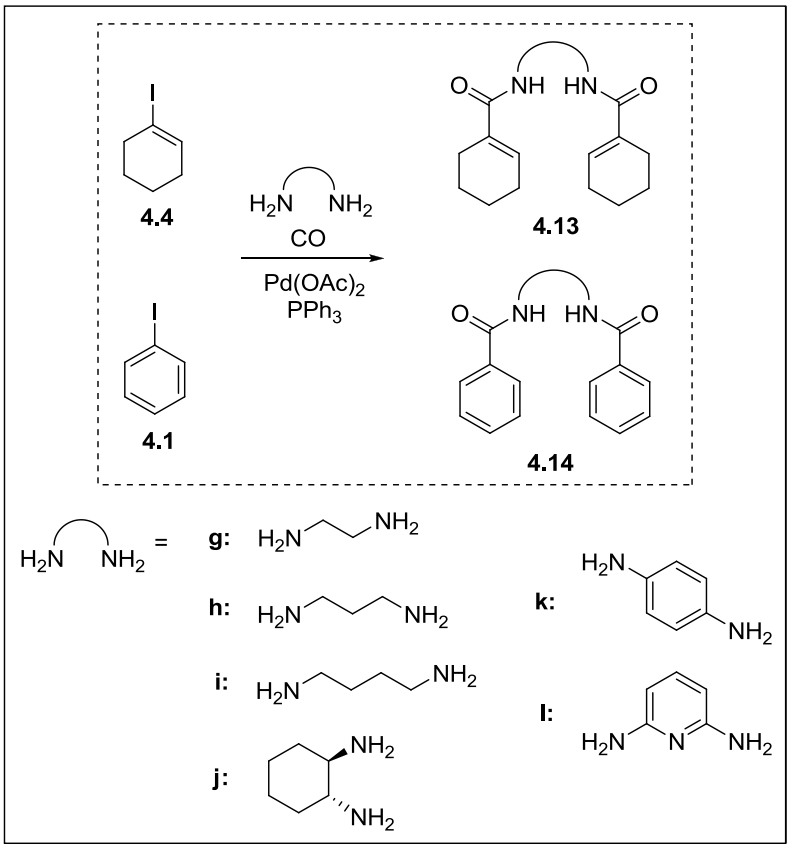
Recently, dicarboxamides have found extensive applications in several fields such as synthetic, coordination and pharmacological chemistry.[44,45,46] Particularly, heterocycles containing two carboxamide functionalities are of high synthetic relevance. For instance, pyrrolidine-2,5-dicarboxamides,[47] pyridine-2,6-dicarboxamides,[48,49] thiophene-2,5-dicarboxamides[50] and their selenophene analogues,[51] imidazole-4,5-dicarboxamides,[52,53] oxindol-1,3-dicarboxamides[54] and binaphthyl-based dicarboxamides[55] have been prepared and used as chiral synthons. *N,N,N',N'*-Tetraalkylpyridine-2,6-dicarboxamides proved to be efficient ligands in coordination chemistry.[56] Biological tests on imidazole-dicarboxamides have evidenced their antiproliferative activity against *HL-60* cells.[57] The activity of various diamides was also evaluated in vinblastine accumulation processes.[58]

In spite of its high efficiency in the synthesis of carboxamides of practical importance, palladium-catalyzed aminocarbonylation has scarcely been used for the synthesis of diamides. Regarding this subject, one paper reported the synthesis of "mixed" diamides possessing both aryl-carboxamide and alkenyl-carboxamide functionalities from the corresponding diiodo substrate.[59] Additionally, α,ω-diamino-alkanes have been carbonylated to cyclic ureas in the presence of palladium(II) iodide[60] or tungstenhexacarbonyl-iodine[61] catalytic systems.

Therefore, it was our purpose to extend the scope of palladium-catalyzed aminocarbonylation reactions to the synthesis of symmetric dicarboxamides, through the pioneering use of diamines of different structures (aliphatic, cycloaliphatic and aromatic) as *N*-nucleophiles. Iodobenzene **4.1** and 1-iodo-cyclohexene **4.4** were used as model substrates, to explore this new synthetic route for the preparation of dimeric phenyl and cyclohexenyl dicarboxamides. The methodology was subsequently applied in the synthesis of dicarboxamide-functionalized steroid dimers, whose preliminary studies of biological activity as cytotoxic agents against *A549* tumor cells are currently underway.

4.4.1 Diaminocarbonylation of model iodoalkenyl and iodoaryl compounds

1-Iodo-cyclohexene **4.4** and iodobenzene **4.1**, as model compounds, were aminocarbonylated in the presence of the desired diamine and carbon monoxide, with palladium catalysts formed *in situ* by addition of palladium(II) acetate to triphenylphosphine. Different aliphatic diamines 1,2-diaminoethane (**g**), 1,3-diaminopropane (**h**) and 1,4-diaminobutane (**i**), a chiral cycloaliphatic diamine (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (**j**) and aromatic diamines 1,4-diaminobenzene (**k**) and 2,6-diaminopyridine (**l**) were used as *N*-nucleophiles (**Scheme 4.8**).



Scheme 4.8

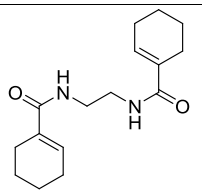
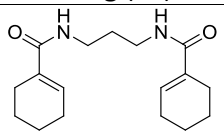
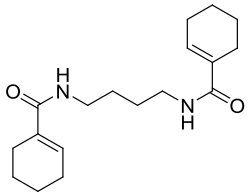
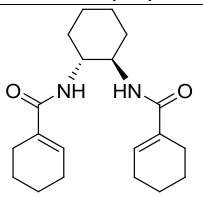
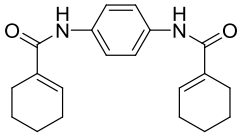
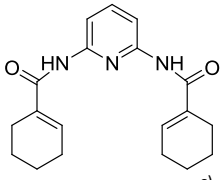
In a typical experiment,[62] $Pd(OAc)_2$, two molar equiv of PPh_3, the iodo-substrate, diamine nucleophile and triethylamine were dissolved in DMF under argon, in an autoclave. The autoclave was then pressurized to the desired pressure of carbon monoxide and the reaction was conducted for a given time, upon stirring at the selected temperature. The reactions' progress along the time was followed by TLC and,

when possible, GC analysis of aliquots taken from the reactor via *cannula*. The final conversions were determined by GC and/or by ^{1}H NMR spectroscopy of the crude mixture, through integration of the olefinic protons of both substrate and reaction products (in the case of aminocarbonylation of **4.4**). After the reactions were completed, the autoclave was slowly depressurized and metallic palladium black particles were filtered off. The mixture was then concentrated and evaporated to dryness and worked-up by standard techniques. Finally, all compounds were subjected to column chromatography in silica gel, or simply recrystallized from solvents (the exact ratios are specified for each compound in Chapter 5, section 5.4.4). The results of Pd-catalyzed aminocarbonylation of **4.4** are summarized in Table 4.6.

First, a preliminary optimization of reaction conditions for the aminocarbonylation of **4.4** was performed using 1,2-diaminoethane (**g**) as nucleophile. In spite of the high reactivity of iodoalkenes that is generally observed in aminocarbonylation with monoamines,[10] the standard conditions (1 bar CO, 50°C) proved to be ineffective when diamine **g** was used as *N*-nucleophile (Table 4.6, entry 1). Although the increase of carbon monoxide pressure resulted in a higher conversion (Table 4.6, entry 2), yields of synthetic interest towards the target dicarboxamide **4.13g** could only be obtained under at 100°C temperature (Table 4.6, entries 3 and 4). Since full conversions have been obtained either under 40 bar or 30 bar of carbon monoxide, the screening of other diamines in aminocarbonylation of **4.4** was performed at 100°C and 30 bar CO (Table 4.6, entries 5-9).

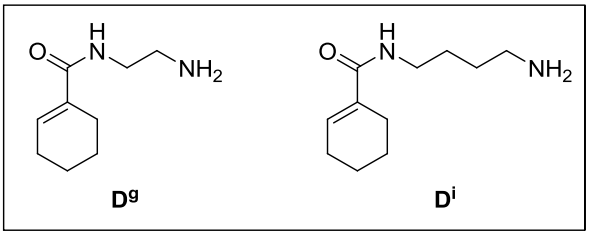
Under these optimized conditions, the catalytic aminocarbonylation of **4.4** with diamines **g**-**l** proceeded with practically complete conversions in 3h, in all cases, leading to the corresponding dicarboxamides **4.13g**-**4.13l**, with isolated yields that varied from 52% (**4.13j**) up to 69% (**4.13i**), after purification procedures. Furthermore, the use of 2,6-diaminopyridine (**l**) as *N*-nucleophile resulted in a mixture of unidentified products, which suffered decomposition after work-up (Table 4.6, entry 9). Although no significant effect of the diamine structure was observed in the reaction conversions, the noteworthy differences in isolated yields of the target diamides might be related to their chemical stability and solubility issues during the work-up and purification procedures.

Table 4.6 – Diaminocarbonylation of 1-iodo-cyclohexene **4.4** in the presence of *in situ* Pd/PPh_3 catalysts.[a)]

Entry	Diamine	P(CO) [bar]	T [^oC]	Product (isolated yield) [b)] [%]
1	**g**	1	50 (18h)	n.d. (1% conv.)
2	**g**	40	50 (18h)	n.d. (27% conv.)
3	**g**	40	100	n.d.
4	**g**	30	100	 **4.13g** (58)
5	**h**	30	100	 **4.13h** (53)
6	**i**	30	100	 **4.13i** (69)
7	**j**	30	100	 **4.13j** (52)
8	**k**	30	100	 **4.13k** (55)
9	**l**	30	100	 **4.13l** (decomp.)[c)]

[a)] **Reaction conditions** (unless otherwise stated): 1 mmol of substrate **4.4**; 0.5 mmol of diamine; 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of PPh_3; 0.5 mL of triethylamine; solvent: DMF (10 mL); time=3 h; Conversions were above 96%, except when indicated.
[b)] based on the amount of the substrate **4.4**; n.d. (not determined).
[c)] decomposition

It is worth mentioning that reactions were chemoselective regarding the transformation of the iodo-alkenyl substrate into bis(carboxamides), which means that no double carbonyl insertion, resulting in either carboxamide-ketocarboxamide or bis(ketocarboxamide) derivatives, was observed by GC-MS and NMR analysis of crude mixtures and on isolated products prior to purification. This observation is in agreement with previous finding showing that iodoalkene substrates undergo double carbon monoxide insertion only under special conditions (as those focused in section 4.2.2).[63] However, the formation of cyclic urea or linear polyurea type compounds[64] via carbonylation of the α,ω-diamines was not excluded. Furthermore, the GC-MS of samples taken from reaction mixtures suggested the presence of amino-monocarboxamide products (for example, when diamines **g** and **i** were used as nucleophiles, the molecular ions with m/z=168 and m/z=196, corresponding to species $\mathbf{D}^{g}$ and $\mathbf{D}^{i}$, were found in 10-25%).

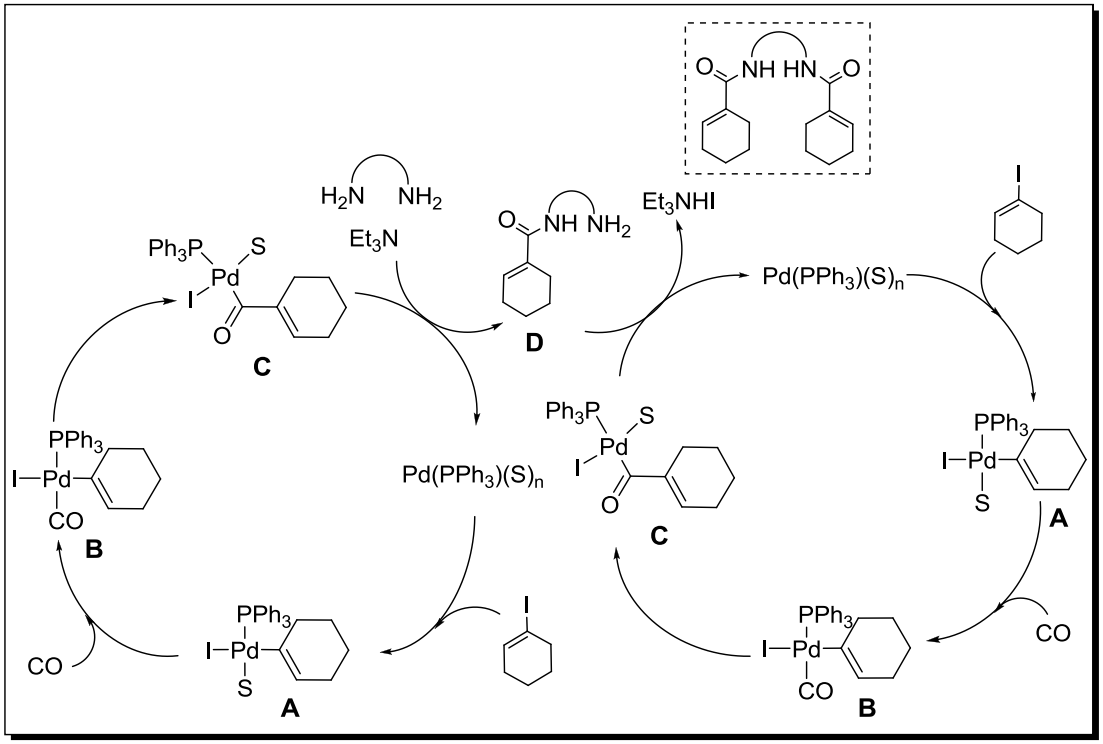


$\mathbf{D}^{g}$ $\mathbf{D}^{i}$

These findings may justify the low isolated yields of dicarboxamides in spite of the high conversions. At the same time, the presence of type **D** intermediate species was demonstrated playing a key-role in the proposed catalytic cycle (**Scheme 4.9**).

According to a widely accepted mechanism, the reduction of the palladium(II) precursor to palladium(0) is necessary for the activation of alkenyl halide via oxidative addition. It has been proved that the ligand itself could serve as reducing agent. While one of the two equivalents of ligands is oxidized phosphine-oxide, the second one coordinates to palladium(0) centre forming a highly reactive, coordinatively unsaturated species.[18,19] Under the reaction conditions used, the action of other compounds (amine, carbon monoxide) as reducing agents cannot be excluded.

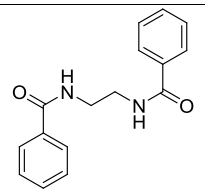
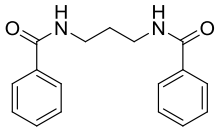
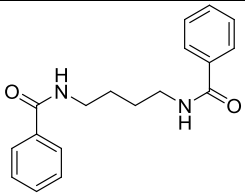
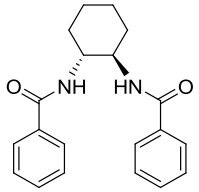
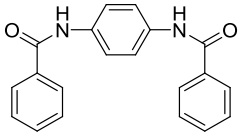
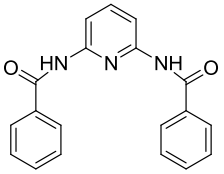
The oxidative addition of the iodoalkene to *in situ* formed palladium(0) species results in alkenyl-palladium(II) (**A**) intermediate, which is able to coordinate with carbon monoxide (**B**). The acyl complex (**C**), formed by CO migratory insertion, undergoes a nucleophilic attack by the amino-monocarboxamide (**D**), formed previously in the catalytic cycle, resulting in the formation of the dicarboxamide and regeneration of Pd(0) catalytic resting state (**Scheme 4.9**).



Scheme 4.9

Aiming the synthesis of dibenzamides, the Pd-catalyzed diaminocarbonylation of iodobenzene **4.1** was also carried out, using the diamines **g**-**l** as *N*-nucleophiles, with *in situ* Pd/PPh_3 catalytic systems (**Scheme 4.8**). Although the compounds **4.14g**, **4.14h**, **4.14i**, **4.14k** and **4.14l** have been previously synthesized via conventional acylation of diamines,[65,66,67,68,69,70] by the use of 2,2,2-trichloro-1-arylethanones as benzoylating agents[71] or aminosilane derivatives,[72] our purpose was to develop a more sustainable and atom economic route for the preparation of such dicarboxamide compounds. The results summarized in Table 4.7.

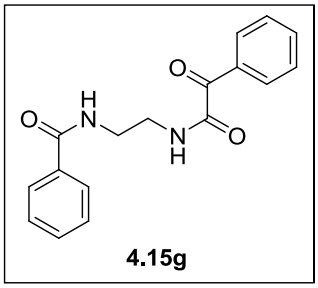
Table 4.7 – Diaminocarbonylation of iodobenzene **4.1** with *in situ* Pd/PPh_3 catalysts.[a)]

Entry	Diamine	P(CO) [bar]	Product (isolated yield)[b)] [%]
1	**g**	30	n.d.[c)]
2	**g**	10	 **4.14g** (42)
3[d)]	**g**	10	n.d. (4% conv.)
4	**h**	10	 **4.14h** (35)
5	**i**	10	 **4.14i** (44)
6	**i**	1	**4.14i** (45)
7	**j**	10	 **4.14j** (39)
8	**k**	10	 **4.14k** (65)
9	**k**	1	**4.14k** (62)
10	**l**	10	 **4.14l** (40)

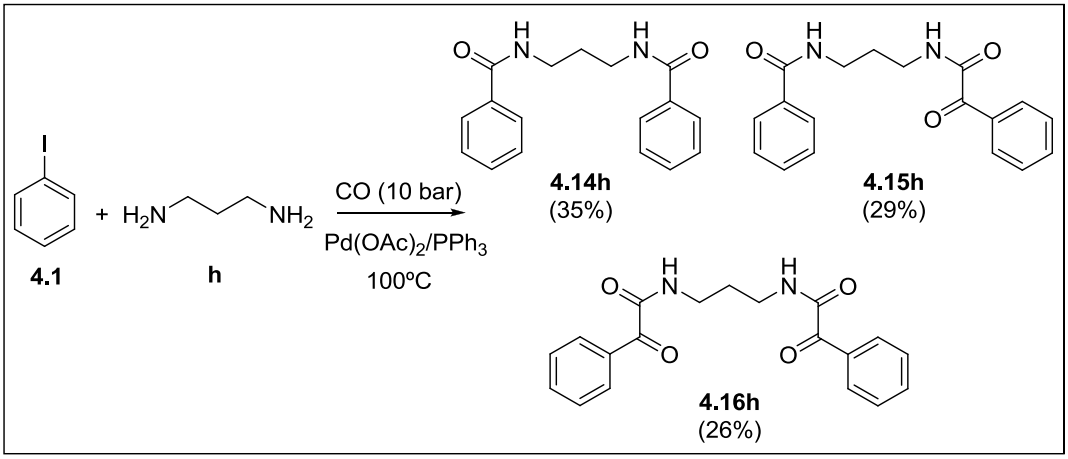
[a)] **Reaction conditions** (unless otherwise stated): 1 mmol of substrate **4.1**; 0.5 mmol of diamine; 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of PPh_3; 0.5 mL of triethylamine; solvent: DMF (10 mL); T=100°C; time=3 h; Conversions were above 96%, except when indicated.
[b)] based on the amount of the substrate **4.1**; n.d. (not determined).
[c)] mixture of carboxamide/ketocarboxamide products.
[d)] T = 50°C.

The aminocarbonylation of **4.1** using 1,2-diaminoethane (**g**) as nucleophile was initially carried out, at 100°C and 30 bar CO. However, a mixture of carboxamide/ketocarboxamide compounds was obtained under these conditions (Table 4.7, entry 1), resulting from the possibility of double insertion of carbon monoxide. Expecting to improve chemoselectivity toward the target bis(carboxamide) compound, the reaction was then performed at a lower CO pressure of 10 bar, which allowed to obtain **4.14g** in 42% isolated yield (Table 4.7, entry 2). Nevertheless, the decrease of reaction temperature to 50°C resulted in a practically ineffective catalytic system, with conversion below 5% (Table 4.7, entry 3). Consequently, the Pd-catalyzed aminocarbonylation reactions of **4.1**, using the other diamines as nucleophiles, were performed at 100°C and 10 bar CO pressure, as standard conditions.

The catalytic aminocarbonylation of **4.1** with diamines **g**-**l** proceeded with complete conversions in 3 hours, leading to the corresponding dicarboxamides **4.14g**-**4.14l** in low to moderate isolated yields, which varied from 35% (**4.14h**) up to 65% (**4.14k**) (Table 4.7, entries 2, 4-10). The decrease of CO pressure to 1 bar did not substantially affect the reaction chemoselectivity, providing isolated yields similar to those obtained under 10 bar CO pressure (Table 2, entries 6 and 9, for **4.14i** and **4.14k**, respectively). Although complete conversions in 3h were achieved under the standard conditions in all aminocarbonylation reactions, independently from the diamine used as nucleophile, the 1,4-phenylene-derived dibenzamide (**4.14k**) was obtained in significantly higher yield than all the other dicarboxamides linked by aliphatic "bridges". This fact might be due to lower tendency for formation of ketocarboxamide type products, when aromatic amines are used as nucleophiles. In the case of 2,6-pyridyl-derived dibenzamide **4.14l**, the low isolated yield can be explained by loss of the target product, during the purification by chromatography in silica gel, as a result of the occurrence of pyridine protonation. The relatively low yields obtained with linear aliphatic and cycloaliphatic diamines are probably due to the formation of carboxamide-ketocarboxamide and bis(ketocarboxamide) compounds. For instance, it should be noted that the GC-MS of the crude mixture of reaction with diamine **g** revealed the presence of a molecular ion with m/z=296, assigned to the carboxamide-ketocarboxamide compound **4.15g**.



Furthermore, in the case of aminocarbonylation of **4.1**, using 1,3-diaminopropane (**h**) as nucleophile, three products were isolated after purification by chromatography: the bis(carboxamide) **4.14h** (35%), the carboxamide-ketocarboxamide **4.15h** (29%) and the bis(ketocarboxamide) **4.16h** (26%) (**Scheme 4.10**).



Scheme 4.10

All products were fully characterized, using the appropriate spectroscopic techniques, namely ^{1}H NMR, ^{13}C NMR and mass spectroscopy (Chapter 5, section 5.4.4).

As illustrative example, the ^{1}H NMR spectrum of *N*,*N*'-(butane-1,4-diyl)dicyclohex-1-enecarboxamide **4.13i** in $CDCl_3$, at room temperature (**Figure 4.4**), shows a broad signal at δ = 6.64 ppm, which was assigned to both olefinic protons in a symmetric structure. The amide N–H protons were clearly evidenced by a broad singlet at δ = 5.91 ppm, while the N–CH_2 protons gave rise to a multiplet at δ = 3.34-3.36 ppm.

The different alkyl protons of the cyclohexenyl ring gave rise to distinct signals with chemical shifts in the region between 1.58-2.26 ppm. For instance, at higher chemical shift interval 2.21-2.26 ppm, the multiplet was assigned to the four protons in positions 7 and 7'. Then, at δ = 2.15-2.19 ppm, another multiplet was assigned to four protons in positions 4 and 4'. Finally, at δ = 1.58-1.74 ppm, typical of resonance of more shielded alkyl protons, the multiplet was assigned to the 8 protons of positions 5, 5', 6 and 6', together with four protons in positions 9 and 9' of the *n*-butyl "bridge".

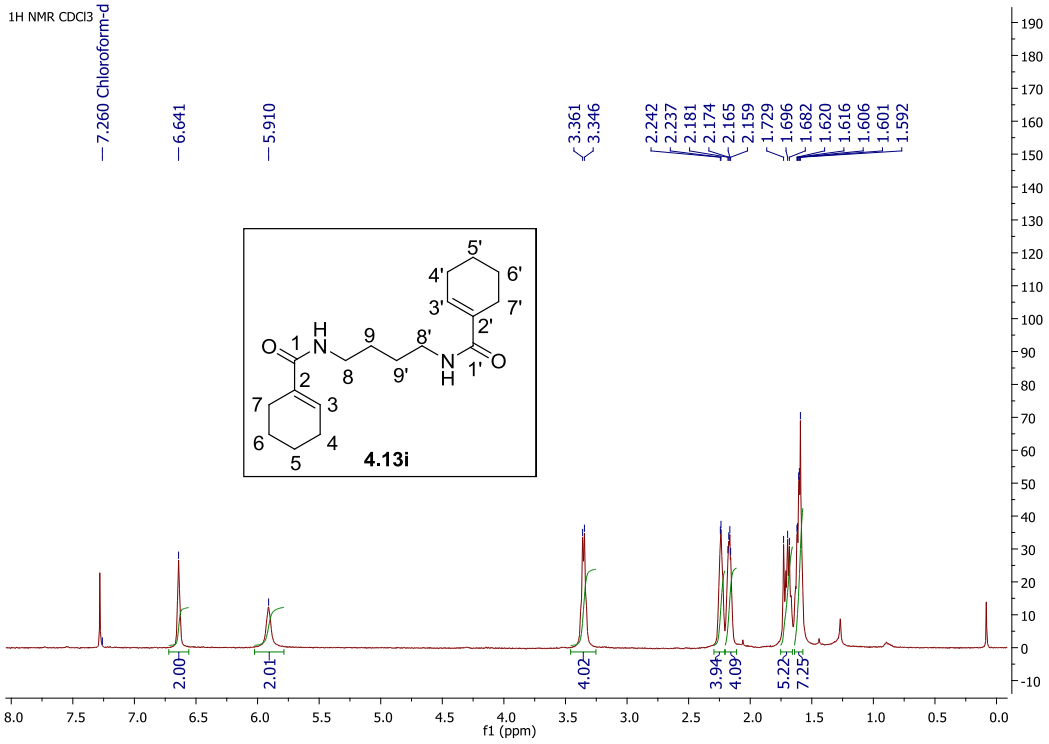


Figure 4.4 – ^{1}H NMR spectrum of *N*,*N*'-(butane-1,4-diyl)dicyclohex-1-enecarboxamide **4.13i**, in $CDCl_3$.

The ^{13}C NMR spectrum of **4.13i** in $CDCl_3$, at room temperature (**Figure 4.5**) shows a signal at δ = 169.9 ppm assigned to carboxamide carbon atoms. At δ = 133.6 ppm and δ = 133.2 ppm, two close signals have evidenced the presence of the olefinic carbon atoms. The presence of N–bounded C8 and C8' in a symmetric structure was clearly demonstrated by the signal at δ = 39.2 ppm. Finally, the five peaks in the aliphatic region, at 27.2 ppm, 25.5 ppm, 24.4 ppm, 22.3 ppm and 21.7 ppm were assigned to C9/C9', C7/C7', C4/C4', C5/C5' and C6/C6', respectively.

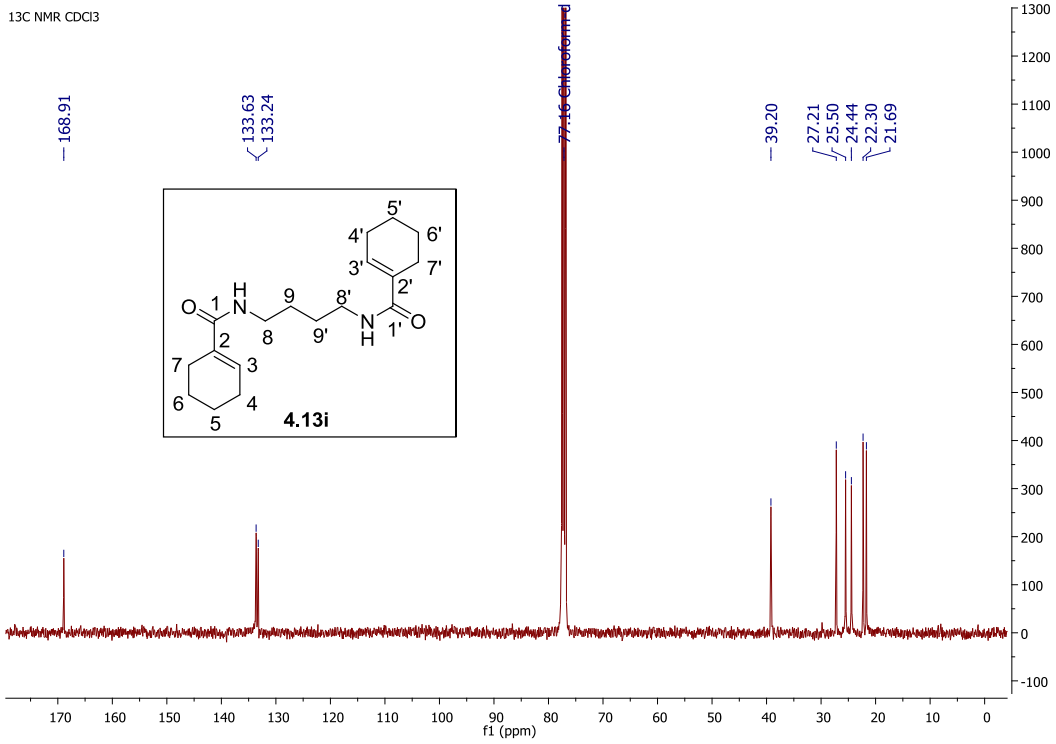
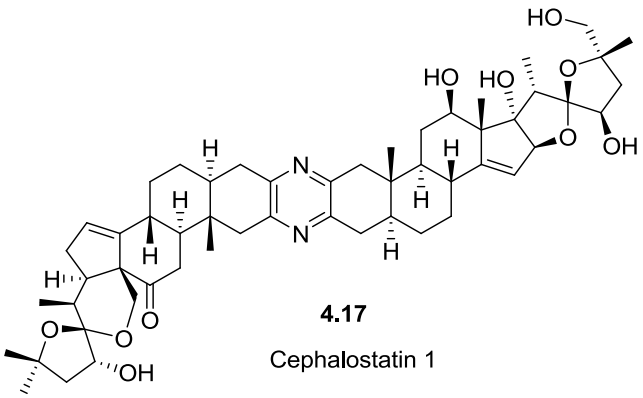


Figure 4.5 – ^{13}C NMR spectrum of *N*,*N*'-(butane-1,4-diyl)dicyclohex-1-enecarboxamide **4.13i**, in $CDCl_3$.

4.4.2 Catalytic synthesis of steroid dimers containing dicarboxamide "*bridges*"

Steroids are widely found in both plant and animal kingdoms, and play crucial roles in biological systems.[73,74] Among them, dimeric steroids constitute an important class of compounds,[75,76,77] which have recently attracted much attention due to their remarkable properties as potential cytotoxic and antimalarial agents, cholesterol lowering drugs as well as molecular umbrellas in drug delivery.[78,79] For instance, Cephalostatin 1 (**4.17**),[80] which was firstly isolated in 1988 from the marine tube worm *Cephalodiscus gilchristi* in the Indian Ocean, has demonstrated a very potent anticancer activity against several human cancer cell lines.[81]



4.17

Cephalostatin 1

In addition to their pharmacological importance, several dimeric and oligomeric steroids display micellar activity.[82] They can also act as ligands for proteins and trigger cellular processes or may promote the affinity of ligands to their binding locations by providing extra anchoring points to the active site of certain domains.[83,84] Some of them show liquid-crystal behavior[85] and play a key role in the rate enhancement from hydrophobic binding.[86] Furthermore, steroid dimers containing dicarboxamide functionalities were found to be of great importance as molecular umbrellas in drug delivery, as well as antifungal and cell anti-proliferative agents.[87,88]

The synthetic approaches reported so far, have led to preparation of cyclic and acyclic steroidal dimers by connection between two *cyclopentano-perhydrophenanthrene* skeletons (through A-A, B-B, C-C, D-D or A-D rings).[75,76,77] The steroidal moieties could be directly linked,[89,90] through spacer groups[91,92] or connection through side chains.[93] Concerning steroidal D-D ring dimers linked through

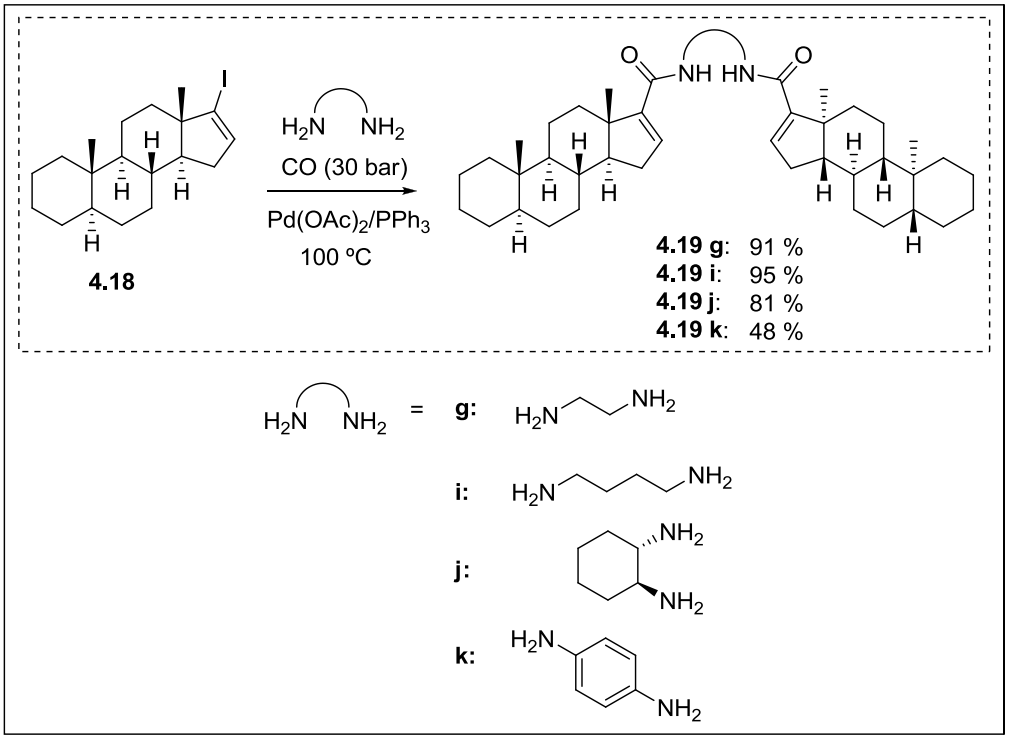
spacer groups, a number of pollutant multi-step and low-yielding synthetic approaches have been frequently used.[75] Thus, other environmentally sustainable alternatives to promote steroids dimerization still constitute a great challenge.

It is well established that transition-metal-catalyzed reactions are versatile tools to introduce different functionalities into specific positions of the steroidal framework, which can render marked changes in their biological properties.[94] In spite of several recent reports on the aminocarbonylation of steroidal alkenyl-iodides towards carboxamides,[95,96,97] there is only one example on the synthesis of dimeric steroids involving Pd-catalyzed carbonylative dimerization of alkenyl-iodide intermediates, to form 17-carboxylic anhydrides, in presence of carbon monoxide and water.[98]

Therefore, in order to investigate the scope of the above studied catalytic reaction for the synthesis of steroid dimers containing dicarboxamide "bridges", at 17,17'- or 3,3'-positions, palladium-catalyzed aminocarbonylations were carried out, using as substrates two steroidal iodoalkenes with markedly different reactivity: 17-iodo-5α-androst-16-ene (**4.18**) and 3-iodo-androst-3,5-diene-17-ketal (**4.20**). As nucleophiles, diamines of different structures were used: aliphatic, such as 1,2-diaminoethane (**g**) and 1,4-diaminobutane (**i**), a chiral cycloaliphatic (*1S*,*2S*)-(+)-1,2-diaminocyclohexane (**j**) and the aromatic 1,4-diaminobenzene (**k**). It should be noted that these steroidal substrates with iodoalkene functionality were synthesized from the corresponding steroidal 17-ketone and 3-ketone, by modified Barton's procedure,[99] and kindly provided by Professor R. Skoda-Földes (University of Veszprém, Hungary) and by Mercédesz Kiss (University of Pécs, Hungary), respectively.

In a typical experiment,[100] the iodo-steroid substrate, palladium (II) acetate, 2 molar equiv. of triphenylphosphine, the desired diamine and triethylamine were introduced into a stainless steel autoclave and dissolved in DMF, under argon. The atmosphere was pressurized to 30 bar of carbon monoxide and the reaction was conducted for 5 hours, upon stirring at 100°C. After cooling and venting the autoclave, the mixture was evaporated to dryness and worked-up by standard techniques, to a solid material or to a waxy residue, which was subjected to column chromatography in silica gel, using as eluent EtOAc/$CHCl_3$ mixtures, or simply washed with ethyl acetate (specifications for each compound are described in Chapter 5, section 5.4.4.1).

The Pd-catalyzed aminocarbonylation of 17-iodo-5α-androst-16-ene **4.18** was performed at 100°C and 30 bar CO, using the diamines **g**, **i**, **j** and **k** as nucleophiles, (**Scheme 4.11**).



Scheme 4.11

In all experiments, the initial iodoalkenyl steroid was near fully converted in 5 hours. After work-up and purification procedures, the symmetric androst-16-ene dicarboxamide dimers **4.19g**, **4.19i**, **4.19j** and **4.19k** were obtained in 91%, 95%, 81% and 48% isolated yields, respectively. From these results, it was concluded that aliphatic diamines 1,2-diaminoethane (**g**), 1,4-diaminobutane (**i**) and (*1S*,*2S*)-(+)-1,2-diaminocyclohexane (**j**) gave significantly higher yields than that obtained with the aromatic diamine 1,4-diaminobenzene (**k**).

It is worth mentioning that the use of chiral (*1S*,*2S*)-(+)-diaminocyclohexane (**j**) produced the optically pure steroidal dimer **4.19j**. However, when racemic *trans*-(±)-1,2-diaminocyclohexane was used as nucleophile, a 1:1 mixture of two diastereomeric steroidal dimers was obtained, as evidenced by duplicate signals on ^{1}H and ^{13}C NMR spectra. For instance, the expansion of the region between 75.0 ppm and 180.0 ppm

on the ^{13}C NMR spectrum (**Figure 4.6**) clearly shows 1 pair of close signals for each carboxamide carbon atom (δ = 167.1 ppm/166.8 ppm) and two pairs of signals assigned to the respective olefinic C16/C16' and C17/C17' atoms of each diastereoisomer.

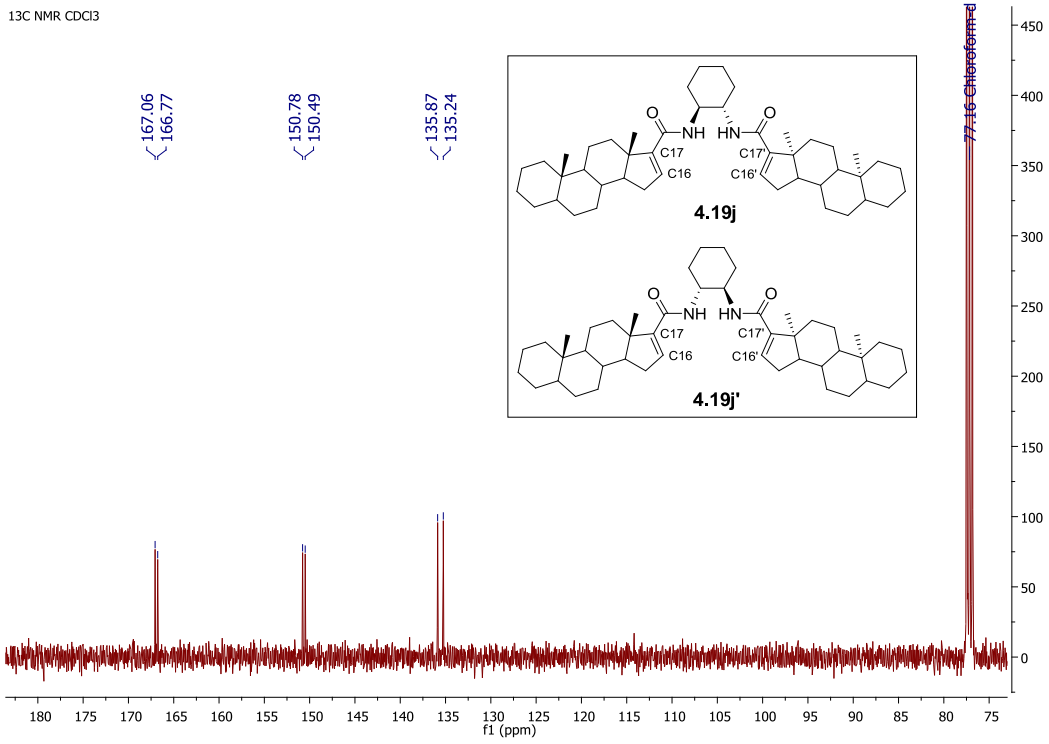


Figure 4.6 – ^{13}C NMR spectrum of diastereomeric mixture of **4.19j** and **4.19j'** in $CDCl_3$, expansion of 75-180 ppm region.

Detailed NMR and MS studies carried out on reaction mixtures and on raw products (*i.e.*, on isolated products prior to chromatography) revealed that no double carbon monoxide insertion into the Pd-alkenyl species occurred. That is, the formation of 2-ketocarboxamide-type derivatives could not be observed. Furthermore, the isolated yields were excellent, when compared with those obtained from model iodoalkene substrates.

In sum, the one-step aminocarbonylation reaction of **4.18**, performed under relatively mild conditions (30 bar CO, 100°C), led to a set of dimeric androst-16-enes, with structurally different dicarboxamide spacers at C-17.

The dimeric steroidal compounds were fully characterized, using the appropriate spectroscopic techniques, namely ^{1}H NMR, ^{13}C NMR and mass spectroscopy (Chapter 5, section 5.4.4.1).

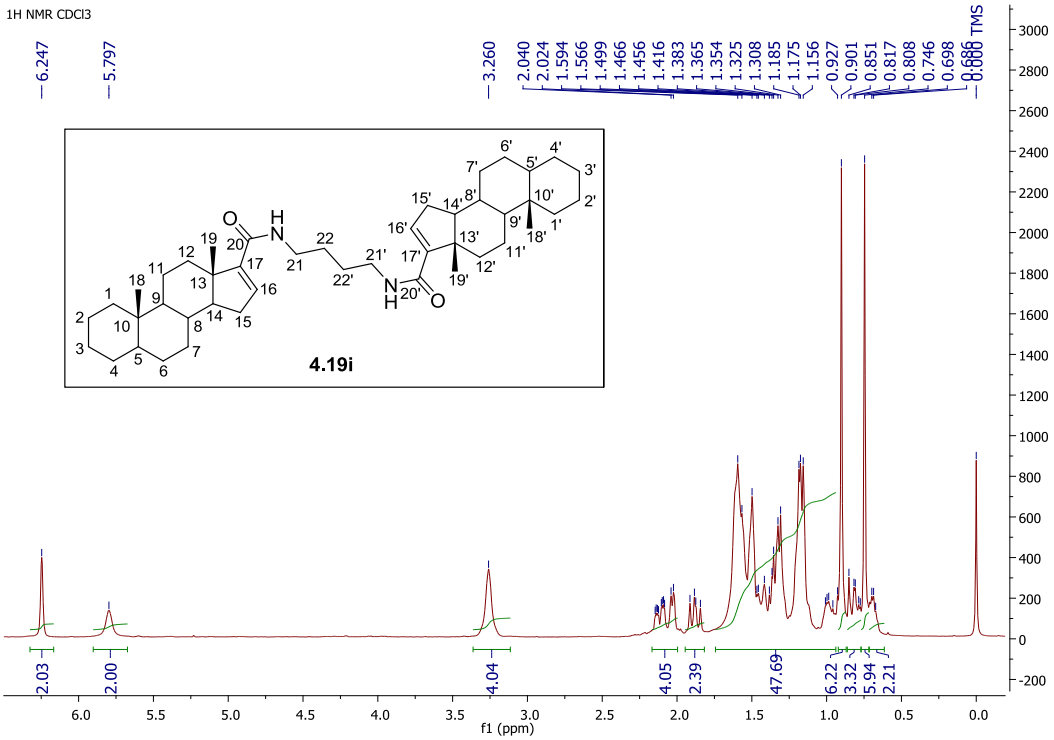


Figure 4.7 – ^{1}H NMR spectrum of *N*,*N*'-(butane-1,4-diyl)-5α-diandrost-16-ene-17-carboxamide (**4.19i**) in $CDCl_3$.

As illustrative example, the ^{1}H NMR spectrum of *N*,*N*'-(butane-1,4-diyl)-5α-diandrost-16-ene-17-carboxamide (**4.19i**), in $CDCl_3$ at room temperature (**Figure 4.7**), shows a broad singlet at δ = 6.25 ppm, assigned to both symmetric olefinic protons in positions 16 and 16'. The amide N–H protons are clearly evidenced by a very broad signal at δ = 5.80 ppm. Another broad signal, assigned to four N–CH_2 protons of positions 21 and 21', was observed at δ = 3.26 ppm. At δ = 2.02-2.15 ppm, a multiplet was assigned to the four protons at positions 15 and 15', while the two protons in positions 14 and 14' gave rise to a doublet of doublets at δ = 1.88 ppm, as result of the couplings with one proton at position 8/8' and with one proton in position 15. The other aliphatic protons of the steroid skeleton, together with the internal protons of the *n*-butyl group (positions 22 and 22') gave rise to a large group of signals, in the

typical region between 0.66-1.60 ppm. Among these, the singlets at δ = 0.90 ppm and δ = 0.75 ppm are assigned to each six methyl protons in positions 19/19' and 18/18', respectively (**Figure 4.7**).

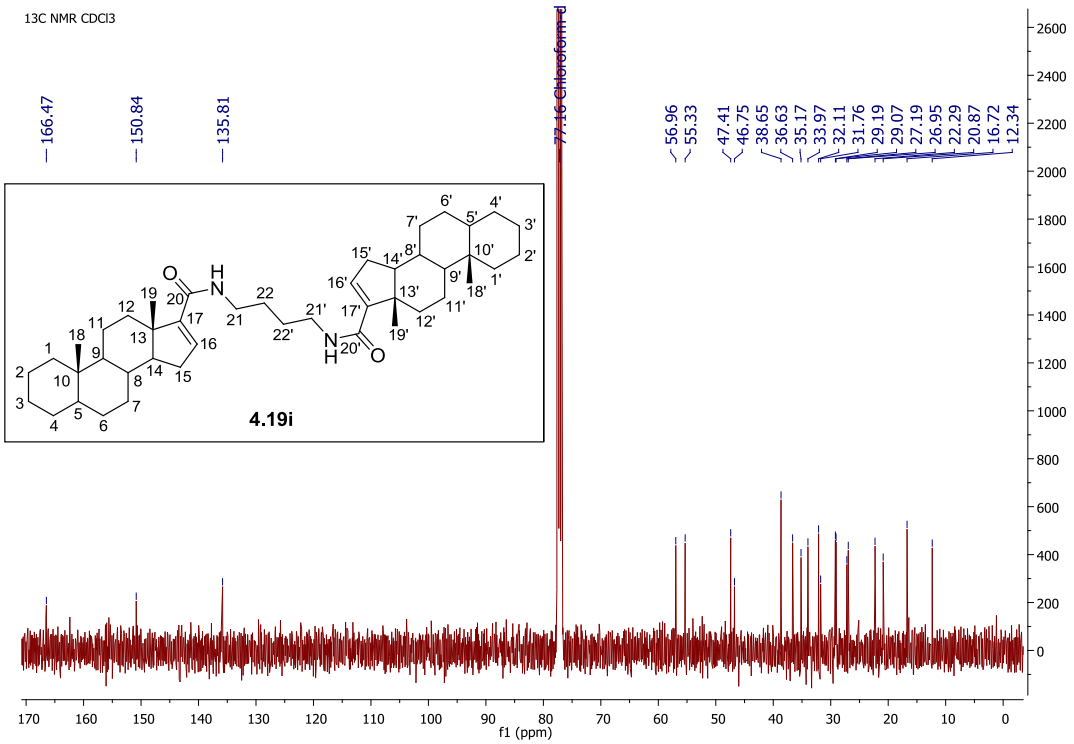
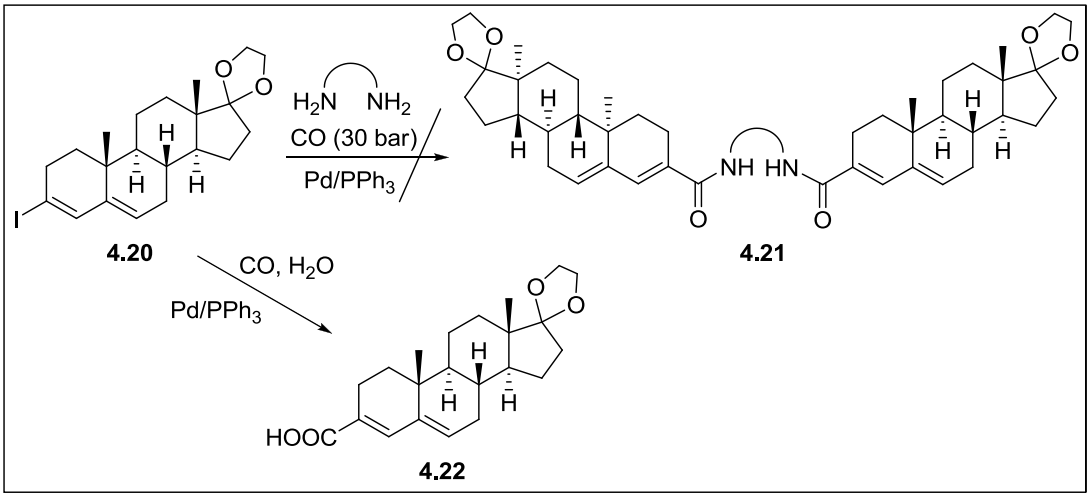


Figure 4.8 – ^{13}C NMR spectrum of *N*,*N*'-(butane-1,4-diyl)-5α-diandrost-16-ene-17-carboxamide (**4.19i**), in $CDCl_3$.

The ^{13}C NMR spectrum (**Figure 4.8**), shows a signal δ = 166.5 ppm, typical of carboxamide carbon resonance. At δ = 150.8 ppm the signal was assigned to the saturated olefinic C17/C17' carbon atoms, while the more intense and higher field signal at δ = 135.8 ppm was assigned to the olefinic C16/C16' carbon atoms. All the other carbon atoms of steroidal skeleton and *n*-butyl group gave rise to 18 signals in the aliphatic region between 12.3 ppm and 57.0 ppm.

In order to expand this family of steroid dimers to a different type of 3,3'-dicarboxamide, the methodology was applied to 3-iodo-androst-3,5-diene-17-ketal (**4.20**),[95] **Scheme 4.12**.



Scheme 4.12

By reacting 3-iodo-androst-3,5-diene-17-ketal (**4.20**), under identical conditions to those previously used (100°C, 30 bar CO), in the presence of diamines **a**, **c**, **d** and **e** as *N*-nucleophiles, no isolable carboxamide or dicarboxamide products, such as the expected dicarboxamide dimers of type **4.21** were achieved. However, in elevated reaction times, instead of aminocarbonylated products, a complex mixture was obtained, whose ^{1}H and ^{13}C NMR spectra confirmed the presence of androst-3,5-diene-17-ketal-3-carboxylic acid **4.22** (**Scheme 4.12**).

A similar phenomenon has already been observed with 17-iodo-5α-androst-16-ene, in the absence of an *N*-nucleophile, in long reaction times.[98] In our case, due to the low reactivity of 3-iodo-3,5-diene functionality towards diamines, a side hydroxycarbonylation reaction becomes favored in presence of water, resulting in the corresponding 3-carboxylic acid derivative. Since DMF was previously dried with sodium, the water content of the solvent itself could not result in **4.22**, so the formation of the 3-carboxylic acid steroid derivative might be enabled by moisture adsorption by the substrate.

The biological evaluation of the steroidal and non-steroidal dicarboxamide compounds, as cytotoxic agents against *A549* tumor cells, is currently underway in a cooperation project with Doctor J. M. Dąbrowski (University of Kraków, Poland). Preliminary studies, have already demonstrated that the butane-1,4-diyl (**4.19i**) and the 1,4-phenylene derived (**4.19k**) steroidal carboxamide dimers and are the ones with

lower values of IC50 inhibitory concentration on *A549* tumor cells (in the range of 40μM). These promising results open new horizons, regarding the application of the catalytic diaminocarbonylation reactions for preparation of new dimeric compounds with high potentialities for medical use.[62]

4.5 Conclusions

The new tris-binaphthyl phosphites have been effectively applied as ligands in palladium-catalyzed aminocarbonylation of iodobenzene and 1-iodo-cyclohexene. The Pd/monophosphite **L2**-OBn complexes formed *in situ* provided active catalytic systems in the aminocarbonylation of iodobenzene. Carboxamides were the only products obtained with aromatic amines, while keto-carboxamides were the major products when primary and secondary aliphatic amines were employed as *N*-nucleophiles. 1-Iodo-cyclohexene has been double carbonylated for the first time, through the use of Pd/monophosphite *in situ* catalysts. While the structure of the phosphite ligand had practically no effect either on catalytic activity or chemoselectivity, low temperature (30°C) and high carbon monoxide pressure (110 bar) were demonstrated to be the most favorable conditions for double carbonylation. Under these optimal reaction conditions, the use of *tert*-butylamine, morpholine and piperidine as nucleophiles led to cyclohexenyl-glyoxylamides with unprecedented structures, in isolated yields of 60-66%.

Furthermore, an effective route for a family of chiral conduritol-derived carboxamides was developed through catalytic coupling reactions of halogenated cyclohexenetetraol derivatives with CO and different amines, in presence of *in situ* Pd/PPh_3 catalysts. The aminocarbonylation of cyclitol derivatives possessing a bromoalkene functionality, under 30 bar CO pressure and 100°C, provided the corresponding carboxamides in moderate isolated yields. The stereochemistry of the acetate substituents at the substrates did not affect the reactivity, whereas significant differences in product yields were apparently related with the nucleophile, being considerably higher with aliphatic amines. Moreover, the aminocarbonylations of the iodo-cyclohexenetetraol analogue was efficiently carried out, under mild reaction

conditions, using two different amino acid methyl esters, yielding target carboxamides in good isolated yields. Thus, the versatility of this methodology for the preparation of conduritol-derived carboxamides was demonstrated by the diverse range of *N*-nucleophiles, as well as the possibility of using either vinyl iodides or vinyl-bromides as substrates.

The one-step catalytic synthesis of dicarboxamides was performed through the pioneering use of diamines in aminocarbonylation reactions, also in presence of catalysts formed *in situ* from palladium(II) acetate and triphenylphosphine. The diaminocarbonylation of 1-iodo-cyclohexene, at 100°C and 30 bar CO, using different diamines as nucleophiles, proceeded in all cases with complete conversions, and high chemoselectivity regarding the transformation of the iodoalkenyl substrate into bis(carboxamides), with lack of double carbonyl insertion. However, the corresponding dicarboxamides were isolated in moderate yields, after purification procedures. Furthermore, the presence of amino-monocarboxamide products, which might play a key-role as intermediate species in the diaminocarbonylation catalytic cycle, was suggested by GC-MS techniques. The Pd/PPh_3 catalyzed diaminocarbonylation of iodobenzene proceeded also with high conversions, leading to the corresponding dibenzamides in low to moderate yields, possibly due to the concomitant formation of carboxamide-ketocarboxamide and bis(ketocarboxamide) compounds as products.

Finally, this synthetic strategy provided a new and atom economic methodology for preparation of valuable steroid dimers. The one-step carbonylative dimerization reaction of 17-iodo-5α-androst-16-ene, performed under relatively mild conditions (30 bar CO, 100°C), led to a set of dimeric androst-16-enes, with structurally different achiral or chiral dicarboxamide “bridges” at C-17, in excellent isolated yields. However, the attempts to aminocarbonylate the steroidal substrate 3-iodo-androst-3,5-diene-17-ketal, under the same conditions, led to the corresponding 3-carboxylic acid steroidal derivative, as result of hydroxycarbonylation as side reaction, favored in presence of water traces.

Promising results have been obtained in preliminary biological tests, which demonstrated the high cytotoxic effects *in vitro* of the dicarboxamide compounds on human lung carcinoma *A549* cells.

4.6 References

1. L. Kollár (Ed.), *Modern Carbonylation Methods*, Wiley-VCH, Weinheim, **2008**.

2. R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515.

3. B. Cornils, W. A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, **1996**.

4. R. Skoda-Földes, L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097.

5. H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation. Direct Synthesis of Carbonyl Compounds*, Plenum, New York and London, **1991**.

6. A. Takács, A. Petz, L. Kollár, *Tetrahedron* **2010**, *66*, 4479.

7. M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis (Vol. I-II.),* Wiley-VCH, Weinheim, **1998**.

8. A. Brennführer, H. Neumann, M. Beller, *Angew. Chem., Int. Ed*. **2009**, *48*, 4114.

9. R. Skoda-Földes, L. Kollár, *Lett. Org. Chem.* **2010**, *7*, 621.

10. E. Müller, G. Péczely, R. Skoda-Földes, E. Takács, G. Kokotos, E. Bellis, L. Kollár, *Tetrahedron* **2005**, *61*, 797.

11. A. Takács, A. Petz, L. Kollár, *Tetrahedron* **2008**, *64*, 8726.

12. P. W. Miller, L E. Jennings, A. J. de Mello, A. D. Gee, N. J. Long, R. Vilar, *Adv. Synth. Catal.* **2009**, *351*, 3260.

13. (a) P. Rattanaburi, B. Khumraksa, M. Pattarawarapan, *Tetrahedron Lett.* **2012**, *53*, 2689; (b) L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2002**, *67*, 6272.

14. T. Zhou, Z.-C. Chen, *J. Chem. Research (S)* **2001**, 116.

15. T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, N. Kasai, *J. Org. Chem.* **1972**, *37*, 3810.

16. P. E. Herrington, M. A. Tius, *Org. Lett.* **2000**, *2*, 2447.

17. A. R. Katritzky, Z. Wang, S. Slavov, M. Tsikolia, D. Dobchev, N. G. Akhmedov, C. D. Hall, U. R. Bernier, G. G. Clark, K. J. Linthicum, *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 7359.

18. C. Amatore, E. Carre, A. Jutand, M. A. M'Barki, G. Meyer, *Organometallics* **1995**, *14*, 5605.

19. Z. Csákai, R. Skoda-Földes, L. Kollár, *Inorg. Chim. Acta* **1999**, *286*, 93.

20. F. Ozawa, T. Sugimoto, T. Yamamoto, A. Yamamoto, *Organometallics* **1984**, *3*, 692.

21. T. Son, H. Yanagihara, F. Ozawa, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1251.

22. S. Cantekin, A. Baran, R. Çalişkan, M. Balci, *Carbohydr. Res.* **2009**, *344*, 426.

23. V. Cerè, G. Mantovani, F. Peri, S. Pollicino, A. Ricci, *Tetrahedron* **2000**, *56*, 1225.

24. G. Mehta, D. S. Reddy, S. S. Ramesh, U. Tatu, *Tetrahedron Lett.* **1999**, *40*, 9141.

25. W. Xu, S. A. Springfield, J. T. Koh, *Carbohydr. Res.* **2000**, *325*, 169.

26. S. Ogawa, *Trends Glycosci. Glycotechnol.* **2004**, *16*, 33.

27. V. Nagy, M. Benltifa, S. Vidal, E. Berzsényi, C. Teilhet, K. Czifrák, G. Batta, T. Docsa, P. Gergely, L. Somsák, J.-P. Praly, *Bioorg. Med. Chem.* **2009**, *17*, 5696.

28. P. Compain, O. R. Martin, *Bioorg. Med. Chem.* **2001**, *9*, 3077.

29. L. E. Blidi, D. Crestia, E. Gallienne, C. Demuynck, J. Bolte, M. Lemaire, *Tetrahedron: Asymmetry* **2004**, *15*, 2951.

30. O. Arjona, A. M. Gómez, J. C. López, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919.

31. T. Mahmud, *Nat. Prod. Rep.* **2003**, *20*, 137.

32. A. M. Gómez, E. Moreno, C. Uriel, S. Jarosz, S. Valverde, J. C. López, *Tetrahedron: Asymmetry* **2005**, *16*, 2401.

33. G. Mehta, S. Lakshminath, P. Talukdar, *Tetrahedron Lett.* **2002**, *43*, 335.

34. X. Chen, Y. Fan, Y. Zheng, Y. Shen, *Chem. Rev.* **2003**, *103*, 1955.

35. D. R. Boyd, N. D. Sharma, C. A. Acaru, J. F. Malone, C. R. O'Dowd, C. C. R. Allen, P. J. Stevenson, *Org. Lett.* **2010**, *12*, 2206.

36. D. R. Boyd, N. D. Sharma, N. M. Llamas, J. F. Malone, C. R. O'Dowd, C. C. R. Allen, *Org. Biomol. Chem.* **2005**, *3*, 1953.

37. J.-J. Shie, J.-M. Fang, C.-H. Wong, *Angew. Chem., Int. Ed.* **2008**, *47*, 5788.

38. (a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 9750; (b) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2005**, *11*, 2276.

39. V. Heguaburu, *Preparación de sintones para la obtención de epoxienonas diméricas naturales y análogos. Introducción de sus cadenas laterales*, PhD Thesis, Universidad de la Republica, Montevideo, **2010**.

40. T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichim. Acta* **1999**, *32*, 35.

41. T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent, J. D. Price, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2907.

42. T. Hudlicky, J. D. Price, F. Rulin, T. Tsunoda, *J. Am. Chem. Soc.* **1990**, *112*, 9439.

43. R. M. B. Carrilho, V. Heguaburu, V. Schapiro, E. Pandolfi, L. Kollár, M. M. Pereira, *Tetrahedron* **2012**, *68*, 6935.

44. M. Adolph, T. A. Zevaco, O. Walter, E. Dinjus, M. Döring, *Polyhedron* **2012**, *48*, 92.

45. P. Chen, M. Gao, D. X. Wang, L. Zhao, M. X. Wang, *Chem Commun.* **2012**, *48*, 3482.

46. A. Amiri, M. Amirnasr, S. Meghdadi, K. Mereiter, V. Ghodsi, A. Gholami, *Inorg. Chim. Acta* **2009**, *362*, 3934.

47. P. Chen, M. Gao, D.-X. Wang, L. Zhao, M. X. Wang, *J. Org. Chem*. **2012**, *77*, 4063.

48. Y.-T. Shen, C.-H. Li, K.-C. Chang, S.-Y. Chin, H.-A. Lin, Y.-M. Liu, C.-Y. Hung, H.-F. Hsu, S.-S. Sun, *Langmuir* **2009**, *25*, 8714.

49. A. Dorazco-Gonzalez, H. Hopfl, F. Medrano, A. K. Yatsimirsky, *J. Org. Chem*. **2010**, *75*, 2259.

50. I. Stolic, K. Molcanov, G. Kovacevic, B. Kojic-Prodic, M. Bajic, *Struct. Chem*. **2012**, *23*, 425.

51. P. Prediger, R. Brandão, C. W. Nogueira, G. Zeni, *Eur. J. Org. Chem*. **2007**, *32*, 5422.

52. R. Solinas, J. C. DiCesare, P. W. Baures, *Molecules* **2009**, *14*, 352.

53. A. V. Wiznyczia, J.-R. Rush, P. W. Baures, *J. Org. Chem*. **2004**, *69*, 8489.

54. M. Porcs-Makkay, B. Volk, Z. Mucsi, G. Simig *Tetrahedron* **2010**, *66*, 7017.

55. H. Kitajima, K. Ito, Y. Aoki, T. Katsuki, *Bull. Chem. Soc. Japan* **1997**, *70*, 207.

56. P. Kapoor, A. P. S. Pannu, M. Sharma, G. Hundal, R. Kapoor, M. S. Hundal, *J. Coord. Chem*. **2011**, *64*, 256.

57. E. M. Perchellet, J. P. Perchellet, P. W. Baures, *J. Med. Chem*. **2005**, *48*, 5955.

58. H. Sawanishi, S. Wakusawa, R. Murakami, K. Miyamoto, K. Tanaka, S. Yoshifuji, *Chem. Pharm. Bull.* **1994**, *42*, 1459.

59. A. Szilágyi, R. Farkas, A. Petz, L. Kollár, *Tetrahedron* **2009**, *65*, 4484.

60. B. Gabriele, G. Salerno, R. Mancuso, M. Costa, *J. Org. Chem*. **2004**, *69*, 4741.

61. A. R. Danko, F. C. Curran, C. Copin, L. McElwee-White, *Tetrahedron* **2011**, *67*, 3976.

62. R. M. B. Carrilho, M. Kiss, J. M. Dabrowski, M. J. S. M. Moreno, R. Skoda-Földes, M. M. Pereira, L. Kollár, "*Synthesis and biological evaluation of carboxamide dimers*", in preparation, **2013**.

63. R. M. B. Carrilho, M. M. Pereira, A. Takács, L. Kollár, *Tetrahedron* **2012**, *68*, 204.

64. A. Primo, E. Aguado, H. Garcia, *ChemCatChem* **2013**, *5*, 1020.

65. R. A. Maurya, P. H. Hoanga, D.-P. Kim, *Lab. Chip.* **2012**, *12*, 65.

66. A. R. Jacobson, A. N. Makris, L. M. Sayre *J. Org. Chem.* **1987**, *52*, 2592.

67. P. M. Anarjan, N. Noshiranzadeh, R. Bikas, M. Woińska, K. Wozniak, *Acta Cryst.* **2013**, *E69*, o102.

68. L. Yu, H.-J. Schneider, *Eur. J. Org. Chem.* **1999**, 1619.

69. R. J. Gaymans, S. Harkema, *J. Polym. Sci. Polym. Phys. Ed.* **1977**, *15*, 587.

70. S. Harkema, R. J. Gaymans, *Acta Cryst.* **1977**, *B33*, 3609.

71. R. A. Rebelo, M. C. Rezende, F. Nome, C. Zucco, *Synth. Commun.* **1987**, *17*, 1741.

72. M. Taddei, F. Tempesti, *Synth. Commun.* **1985**, *15*, 1019.

73. R. Maltais, D. Poirier, *Steroids* **2011**, *76*, 929.

74. D. A. Ross, J. S. Cetas, *J. Neurooncol.* **2012**, *109*, 439.

75. L. Nahar, S. D. Sarker, *Steroid dimers. Chemistry and applications in drug delivery*, John Wiley & Sons, Chichester, **2012**.

76. Y. Li, J. R. Dias, *Chem. Rev.* **1997**, *97*, 283.

77. L. Nahar, S. D. Sarker, A. B. Turner, *Curr. Med. Chem.* **2007**, *14*, 1349.

78. D. F. Taber, J.-M. Joerger, *J. Org. Chem.* **2008**, *73*, 4155.

79. S. T. Phillips, M. D. Shair, *J. Am. Chem. Soc.* **2007**, *129*, 6589.

80. N. López-Antón, A. Rudy, N. Barth, L. M. Schmitz, G. R. Pettit, K. Schulze-Osthoff, V. M. Dirsch, A. M. Vollmar, *J. Biol. Chem.* **2006**, *281*, 33078.

81. B. R. Moser, *J. Nat. Prod.* **2008**, *71*, 487.

82. J. McKenna, J. M. McKenna, D. W. Thornthwaite, *J. Chem. Soc. Chem.Commun.* **1977**, 809.

83. P. A. Clemons, *Curr. Opin. Chem. Biol.* **1999**, *3*, 112.

84. S. T. Diver, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 5106.

85. T. Thiemann, V. Vill, *J. Phys. Chem. Ref. Data* **1997**, *26*, 291.

86. J. P. Guthrie, J. Cossar, B. A. Dawson, *Can. J. Chem.* **1986**, *64*, 2456.

87. V. Janout, B. W. Jing, S. L. Regen, *Bioconjug. Chem.* **2002**, *13*, 351.

88. D. B. Salunke, B. G. Hazra, V. S. Pore, M. K. Bhat, P. B. Nahar, M. V. Despande, *J. Med. Chem.* **2004**, *47*, 1591.

89. Shamsuzzaman, M. G. Alam, T. Siddiqui, *J. Chem. Sci.* **2011**, *123*, 491.

90. D. Fournier, D. Poirier, *Bioorg. & Med. Chem. Lett.* **2009**, *19*, 693.

91. Z. Paryzek, M. Piasecka, R. Joachimiak, E. Luks, W. Radecka-Paryzek, *J. Rare Earths* **2010** (*Spec. Issue*) *28*, 56.

92. R. Joachimiak, M. Piasecka, Z. Paryzek, *J. Chem. Res.* **2008**, *5*, 260.

93. V. C. Edelsztein, P. H. Di Chenna, G. Burton, *Tetrahedron* **2009**, *65*, 3615.

94. R. Skoda-Földes, L. Kollár, *Chem. Rev.* **2003,** *103,* 4095.

95. P. Ács, E. Müller, G. Czira, S. Mahó, M. M. Pereira, L. Kollár, *Steroids* **2006**, *71*, 875.

96. A. Takács, P. Ács, Z. Berente, J. Wölfling, G. Schneider, L. Kollár, *Steroids* **2010**, *75*, 1075.

97. P. Ács, A. Takács, M. Kiss, N. Pálinkás, S. Mahó, L. Kollár, *Steroids* **2011**, *76*, 280.

98. R. Skoda-Földes, Z. Csákai, L. Kollár, G. Szalontai, J. Horváth, Z. Tuba, *Steroids* **1995**, *60*, 786.

99. D. H. R. Barton, B. Bashiardes, J. L. Fourrey, *Tetrahedron Lett.* **1983**, *24*, 1605.

100. R. M. B. Carrilho, M. M. Pereira, M. J. S. M. Moreno, A. Takács, L. Kollár, *Tetrahedron Lett.* **2013**, *54*, 2763.

CHAPTER 5

EXPERIMENTAL

5.1 General

In this section, general information is provided, regarding materials, reagents and solvents, as well as the techniques and instruments used during the experimental work.

5.1.1 Reagents, materials and solvents

All chemicals were commercially obtained from Merck, Fluka, Strem or Sigma-Aldrich, except when indicated. The steroid 17β-acetoxyandrost-4-ene **3.11** was kindly provided by Doctor A. Peixoto (University of Coimbra). 1-Iodo-cyclohexene **4.4** and the iodoalkenyl steroids **4.18** and **4.20**, prepared from the corresponding ketones by modified Barton's procedure,[1] were kindly provided by Prof. L. Kollár (University of Pécs, Hungary) and Prof. R. Skoda-Földes (University of Veszprém, Hungary). The halogenated cyclohexenetetraol derivatives **4.8**, **4.9** and **4.10**, synthesized via biotransformation of bromo- or iodobenzene with *Pseudomonas putida* F39/D,[2] were kindly provided by Prof. E. Pandolfi (UdeLaR, Montevideo, Uruguay).

Air and moisture sensitive reagents and solutions were handled under nitrogen or argon atmosphere, in a vacuum system, using *Schlenk* techniques.[3] All the glassware was dried by heating. Thin layer chromatography (TLC) was performed using aluminum plates coated with silica gel 60 (Fluka) with fluorescent indicator UV_{254} and $UV_{366.}$ Column chromatography was performed, using silica gel 60 (particle size 0.06-0.20 mm), which was carefully dried prior to use, as the stationary phase.

The solvents were purified by simple distillation or, when necessary, properly dried and distilled by the standard procedures,[4] described below.

Methanol and benzyl alcohol

5.0 g of magnesium flakes and 0.5 g of iodine were placed in a two liter round-bottom flask. 50 mL of the desired alcohol was added and the mixture was heated until the disappearance of iodine brown color. After magnesium had been totally consumed, approximately 950 mL of the corresponding alcohol were then added and the mixture was kept under reflux for 2 hours, followed by distillation from molecular sieves (3Å).

Tetrahydrofuran (THF) and diethyl ether

The solvent was placed in a round-bottom flask, with sodium flakes and benzophenone. The mixture was kept under reflux, at the boiling temperature (66°C for THF and 35°C for diethyl ether), until a strong blue color was observed. After distillation, the solvent was collected and stored, under nitrogen atmosphere, in a vessel containing activated molecular sieves (3Å). (CAUTION: Diethyl ether and tetrahydrofuran are susceptible to peroxide formation, which are higher boiling and contact explosives when dry.)

Dichloromethane and chloroform

The chlorinated solvent was placed in a round-bottom flask, with anhydrous calcium chloride and pumice stone. The mixture was kept under reflux, at the boiling temperature (40°C for dichloromethane and 61°C for chloroform), for two hours. After

distillation, the solvent was collected and passed through a column of basic alumina (grade I) and stored in a flask containing activated molecular sieves (3Å). For experiments, which were highly water sensitive, dichloromethane was dried with calcium hydride, under reflux, at the boiling temperature, for three hours. After distillation, the solvent was collected and stored, under nitrogen atmosphere, in a vessel containing activated molecular sieves (3Å).

Ethyl acetate

Ethyl acetate was placed in a round-bottom flask, with anhydrous calcium chloride and pumice stone. The mixture was kept under reflux, at the boiling temperature (77°C), for two hours. After distillation, the solvent was collected and passed through a column of basic alumina (grade I) and stored in a flask containing activated molecular sieves (3Å).

Hexane

n-Hexane was placed in a round-bottom flask, with anhydrous calcium chloride and pumice stone. The mixture was kept under reflux, at the boiling temperature (68-69°C), for three hours. After distillation, the solvent was collected and passed through a column of basic alumina (grade I) and stored in a flask containing activated molecular sieves (3Å). For experiments which were highly water sensitive, *n*-hexane was dried with sodium/benzophenone, under reflux, at the boiling temperature, until a strong blue color was observed. After distillation, the solvent was collected and stored, under nitrogen atmosphere, in a vessel containing activated molecular sieves (3Å).

Triethylamine

Triethylamine was placed in a round-bottom flask, with sodium flakes and benzophenone. The mixture was kept under reflux, at the boiling temperature (89-90°C), until a strong blue color was observed. After distillation, the solvent was collected and stored, under nitrogen atmosphere, in a vessel containing activated molecular sieves (3Å).

N,N-Dimethylformamide (DMF)

DMF was placed in a round-bottom flask equipped with a reflux condenser, with calcium hydride and the mixture was kept at 80°C, for 6 hours. After distillation under reduced pressure, the solvent was collected and stored in a container with activated molecular sieves (3Å).

Toluene

Toluene was placed in a round-bottom flask, with sodium flakes and benzophenone. The mixture was kept under reflux, at the boiling temperature (110°C), until a strong blue color was observed. After distillation, the solvent was collected and stored, under nitrogen atmosphere, in a vessel containing activated molecular sieves (3Å).

5.1.2 Instrumentation

A – *Nuclear Magnetic Resonance Spectroscopy* (NMR)

NMR spectra were recorded on *Bruker Avance 400* spectrometer (Department of Chemistry, University of Coimbra), *Varian Inova 400* spectrometer (Department of Inorganic Chemistry, University of Pécs), *Varian XL-500* and *Mer-400* spectrometers (Department of Inorganic Chemistry, University of Barcelona), using $CDCl_3$ as deuterated solvent (unless otherwise stated). The ^{1}H and ^{13}C chemical shifts, expressed in ppm, are generally relative to a TMS internal standard, while for ^{31}P, an 85% solution of phosphoric acid was used as external standard.

B – *Gas Chromatography* (GC)

Gas chromatography was carried out on an *Agilent-7820A* apparatus equipped with a non-polar capillary *HP-5* column (5% diphenyl and 95% dimethylpolysiloxane), with 30 m length and 0.32 mm inside diameter and an *Agilent-6890* apparatus equipped with a chiral capillary column *Supelco* β-*Dex 120* (20% β-cyclodextrins) with 30 m length and 0.25 mm of inside diameter, both with FID detectors, belonging to Department of Chemistry from the University of Coimbra. The GC analysis used in

catalytic hydrovinylation was carried out in *Agilent-5890 Series II* instruments, equipped with HP5 (30 m long, 0.32 mm) and *Astec Chiraldex DM* (25 m long, 0.25 mm) columns, with helium as a carrier gas, belonging to Department of Inorganic Chemistry from the University of Barcelona. The GC analysis regarding catalytic aminocarbonylation reactions was performed in a *Hewlett Packard 5830A* apparatus fitted with a capillary column coated with *OV-1*, belonging to Department of Inorganic Chemistry from the University of Pécs.

C – *Gas Chromatography coupled with Mass Spectrometry* (GC-MS)

GC-MS analysis was performed using a *Agilent 7820 GC System Technologies* gas chromatograph equipped with a *HP-5 MS* capillary column coupled to a mass spectrometer *Agilent 5975 MSD System Technologies*, belonging to Department of Chemistry, from the University of Coimbra, or a *Hewlett Packard 5830A* gas chromatograph coupled to an *Agilent 5975B inert Serie*s apparatus, belonging to Department of Inorganic Chemistry from the University of Pécs.

D – *Mass Spectrometry* (MS)

High-resolution mass spectrometry was carried out on a *Bruker Microtof* apparatus, equipped with selective ESI detector, belonging to *Unidade de Masas e Proteómica* from the University of Santiago de Compostela.

E – *Infrared Spectroscopy* (IR)

The FT-IR spectra were taken in KBr pellets using an *IMPACT 400* (Nicolet) equipped with a DTGS detector, belonging to Department of Inorganic Chemistry from the University of Pécs, or in a Thermo Scientific Nicolet 380 spectrometer, belonging to Department of Chemistry from the University of Coimbra.

F – *Elemental Analysis*

Elemental analyses for carbon, hydrogen and nitrogen were measured on *EA1108-CHNS-O Fisons Instruments* apparatus, belonging to Department of Chemistry,

from the University of Coimbra and *Carlo Erba 1108* apparatus, belonging to Department of Inorganic Chemistry, from the University of Pécs.

G – *Melting Points*

Melting points, with uncorrected values, were determined in a capillary microscope *Electrothermal Melting Point* apparatus, belonging to the Department of Chemistry from the University of Coimbra or in a *Gallenkamp 5A 6797 digital Melting-Point* apparatus, belonging to the Department of Inorganic Chemistry from the University of Pécs.

H – *Polarimetry*

The specific rotation [α] was measured in an electrical polarimeter *Optical Activity AA-5*, belonging to the Department of Chemistry from the University of Coimbra.

I – *Computational Calculations*

The minimized-energy structure of the complex *trans*-[$HRh(CO)_2$(**L3**-$OCHPh_2$)] was performed by Doctor Tamás Kégl, in the University of Pécs. The calculations were done by employing the two-layer ONIOM method, in which the inner layer (including the $HRh(CO)_2$ moiety, as well as the oxygen atoms of phosphite neighboring to phosphorus) was handled at the BP86 DFT functional in combination with the SDD basis set. The remainder of the complex was treated by molecular mechanics, with the Universal Force Field (UFF).

5.2 Experimental (referring to Chapter 2)

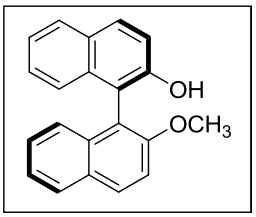
In this section, the synthetic procedures of binaphthyl-based derivatives and monophosphite ligands (described in Chapter 2) are provided, as well as their full characterization.

5.2.1 Synthesis of mono-protected BINOL derivatives

The BINOL-derived mono-alkyl ethers **2.1**-**2.4** were synthesized via Mitsunobu reaction,[5] according to a slightly modified literature procedure.[6] In a typical experiment, to a solution of (*S*)- or (*R*)-BINOL (5.0 g, 17 mmol), dried azeotropically with toluene, PPh_3 (4.5 g, 17 mmol) and the desired alcohol (20 mmol), in dry THF (100 mL), diethyl azodicarboxylate (DEAD) (40% in toluene, 7.5 mL, 17 mmol) was added dropwise, at 0 °C and the mixture was stirred at 25°C, for 48 h. After quenching with water, the solvent was evaporated under reduced pressure and the crude mixture was dissolved in dichloromethane (50 mL). The organic layer was washed with brine (3×50 mL) and water (3×50 mL). The organic layers were then combined and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the products **2.1-2.4** were isolated by column chromatography on silica gel, using mixtures of CH_2Cl_2/*n*-hexane as eluent, and were further purified by recrystallization from toluene/*n*-hexane. (Note: DEAD is highly toxic, so the appropriate safety procedures were taken for its manipulation.(*R*: 5-11-20-36/37/38-48/20-63-65-67; *S*: 26-36/37-62).

(*R*)-2'-methoxy-1,1'-binaphthyl-2-ol ((*R*)-2.1)

Following the above described procedure, 1.6 mL (40 mmol) of methanol was used, with complete conversion in 48 hours. After work-up, purification by column chromatography on silica gel (using a 1:1 mixture of CH_2Cl_2/*n*-hexane as eluent) and recrystallization (from toluene/*n*-hexane), the final product (*R*)-**2.1** with white crystalline aspect was obtained in 84% yield (4.289 g, 14.3 mmol). Spectroscopic data is in agreement with that previously reported.[6]

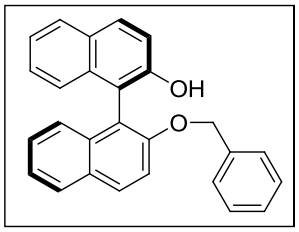


(*R*)-**2.1**

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.85 (1H, d, 9.2 Hz, Ar), 7.70-7.76 (3H, m, Ar), 7.26 (1H, d, 8.8 Hz, Ar), 7.05-7.23 (6H, m, Ar), 6.93 (1H, d, 8.0 Hz, Ar), 4.83 (1H, s, O*H*), 3.59 (3H, s, OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 156.1, 151.4, 134.2, 133.9, 131.1, 129.9, 129.5, 129.3, 128.3, 128.2, 127.4, 126.5, 125.0, 124.9, 124.3, 123.3, 117.6, 115.5, 115.1, 113.9 (Ar*C*) 56.7 (O*C*H_3); **HRMS (ESI)**: m/z calcd. for $C_{21}H_{16}O_2Na$ $[M+Na]^+$: 323.1043, found: 323.1033; **Elem. Anal.** calcd. for $C_{21}H_{16}O_2$: C 83.98, H 5.37, found: C 83.17, H 6.69; **Mp**: 105-107 °C; **$[\alpha]_D^{25}$**: + 35 (*c* 1.0, CH_2Cl_2).

(*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-ol ((*R*)-2.2)

Following the same procedure, 2.1 mL (20 mmol) of benzyl alcohol was used. Complete conversion of reactants into products has occurred in 48 hours. After work-up, purification by column chromatography on silica gel (using a 2:1 mixture of CH_2Cl_2/*n*-hexane as eluent) and recrystallization (from toluene/*n*-hexane), the final product (*R*)-**2.2** with white crystalline aspect was obtained in 87% yield (5.568 g, 14.8 mmol). Spectroscopic data is in agreement with that previously reported.[6] Crystallographic data is presented in **Annex 1**.

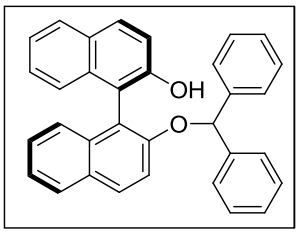


(*R*)-**2.2**

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.88 (1H, d, 9.2 Hz, Ar), 7.83 (1H, d, 8.8 Hz, Ar), 7.78 (2H, d, 8.0 Hz, Ar), 7.36 (1H, d, 9.2 Hz, Ar), 7.07-7.29 (9H, m, Ar), 7.00 (1H, d, 8.4 Hz, Ar), 6.94-6.96 (2H, m, Ar), 5.02 (1H, d, 12.8 Hz, OCH_2Ph), 4.97 (1H, d, 12.8 Hz, OCH_2Ph), 4.85 (1H, br s, O*H*); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 155.1, 151.5, 137.1, 134.2, 134.0, 131.0, 130.0, 129.8, 129.3, 129.2, 128.5, 128.4, 128.3, 127.8, 127.4, 127.0, 126.5, 125.4, 125.2, 125.1, 124.6, 123.4, 117.7, 117.0, 116.1, 115.2 (Ar*C*), 71.3 (O*C*H_2Ph); **HRMS (ESI)**: m/z calcd. for $C_{27}H_{20}O_2Na$ $[M+Na]^+$: 399.1356, found: 399.1348; **Elem. Anal.** calcd. for $C_{27}H_{20}O_2 \cdot ½\ H_2O$: C 84.13, H 5.49, found: C 84.08, H 6.08; **Mp**: 112-114 °C; **$[\alpha]_D^{25}$**: + 15 (*c* 1.0, CH_2Cl_2).

(*R*)-2'-(diphenylmethoxy)-1,1'-binaphthyl-2-ol ((*R*)-2.3)

Following the above described procedure, 3.69 g (20 mmol) of diphenylmethanol was used (reaction time = 72 h). After work-up, purification by column



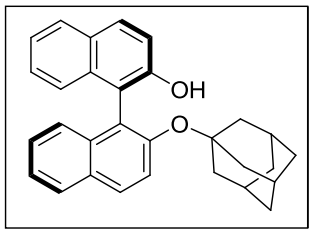
(*R*)-**2.3**

chromatography on silica gel (CH_2Cl_2/*n*-hexane 2:1) and recrystallization (from toluene/*n*-hexane), the final product (*R*)-**2.3** with white crystalline aspect was obtained in 63% yield (4.847 g, 10.7 mmol). Spectroscopic data is in good agreement with that previously reported.[6]

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.93 (1H, d, 8.8 Hz, Ar), 7.88 (2H, d, 8.8 Hz, Ar) 7.83 (1H, d, 8.0 Hz, Ar), 7.41 (1H, d, 8.8 Hz, Ar), 7.00-7.38 (15H, m, Ar), 6.93 (2H, d, 7.2 Hz), 6.24 (1H, s, C*H*Ph_2), 4.96 (1H, s, O*H*); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 154.1, 151.6, 141.4, 141.2, 134.2, 134.0, 130.7, 130.0, 129.8, 129.3, 128.6 (double intensity), 128.3 (double intensity), 128.2, 128.1, 127.7, 127.5, 127.4, 126.7 (double intensity), 126.5 (double intensity), 126.4, 125.4, 125.3, 124.6, 123.4, 117.8, 117.7, 117.1, 115.4 (Ar*C*), 82.4 (OC*H*Ph_2); **HRMS (ESI)**: m/z calcd. for $C_{33}H_{24}O_2Na$ $[M+Na]^+$: 475.1669, found: 475.1662; **Elem. Anal.** calcd. for $C_{33}H_{24}O_2 \cdot ½\ H_2O$: C 85.87, H 5.46, found: C 86.24, H 6.08; **Mp**: 69-71 °C; **$[\alpha]_D^{25}$**: - 20 (*c* 1.0, CH_2Cl_2).

(*R*)-2'-(1-adamantyloxy)-1,1'-binaphthyl-2-ol ((*R*)-2.4)

Following the same procedure, 3.05 g (20 mmol) of 1-adamantanol was used (reaction time = 96 h). After work-up, purification by column chromatography on silica gel (using CH_2Cl_2/*n*-hexane 2:1 as eluent) and recrystallization (from toluene/*n*-hexane), the final product (*R*)-**2.4** with white crystalline aspect was obtained in 52% yield (3.718 g, 8.84 mmol).[7]

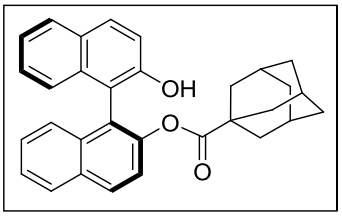


(*R*)-**2.4**

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.69-7.76 (4H, m, Ar), 7.33 (1H, d, 9.2 Hz, Ar), 7.04-7.25 (6H, m, Ar), 6.99 (1H, d, 8.4 Hz, Ar), 5.53 (1H, s, O*H*), 1.80 (3H, br s, Ad), 1.46 (6H, br s, Ad), 1.31 (3H, d, 12.4 Hz, Ad), 1.20 (3H, d, 12.0 Hz, Ad); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 152.0, 151.7, 134.0, 133.9, 130.9, 129.8, 129.5, 129.1, 128.1 (double intensity), 126.7, 126.4, 126.1, 125.9, 124.9 (double intensity), 124.0, 123.1, 118.4, 117.0, 80.6, 43.1, 35.9, 30.9; **HRMS (ESI)**: m/z calcd. for $C_{30}H_{28}O_2Na$ $[M+Na]^+$: 443.1982, found: 443.1988; **Mp**: 85-87 °C; **$[\alpha]_D^{25}$**: - 130 (*c* 2.0, CH_2Cl_2).

(*S*)-2'-(1-adamantanoyloxy)-1,1'-binaphthyl-2-ol (2.5)

The (*S*)-BINOL-derived mono-ester **2.5** was synthesized, according to a literature procedure.[8] A dried round-bottom flask was charged with (*S*)-BINOL (5.0 g, 17 mmol), 4-dimethylaminopyridine (DMAP) (0.17 mmol), and triethylamine (22.1 mmol, 3.1 mL) in 75 mL THF. The mixture was cooled to 0°C and a solution of 1-adamantanoyl chloride (17 mmol, 3.38 g) in THF (10 mL) was added dropwise. Once the addition was complete, the reaction mixture was left at room temperature for 30 h. After nearly complete disappearance of the starting material (observed by TLC), the reaction was quenched with distilled water and the mixture was extracted with ethyl acetate. The combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$, brine, water, and then dried over Na_2SO_4. After filtration and solvent removal *in vacuo*, the crude product was purified by column chromatography on silica gel, using dichloromethane/*n*-hexane (3:1) as eluent, providing (*S*)-**2.5** in 82% isolated yield (13.94 mmol, 6.245 g). Spectral data is in agreement with literature values.[8]



2.5

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 8.06 (1H, d, 8.8 Hz, Ar), 7.97 (1H, d, 8.1 Hz, Ar), 7.88 (1H, d, 12.1 Hz, Ar), 7.83 (1H, d, 8.0 Hz, Ar), 7.49-7.53 (1H, m, Ar), 7.24-7.38 (6H, m, Ar), 7.05 (1H, d, *J* = 8.0 Hz, Ar), 5.17 (1H, s, O*H*), 1.77 (3H, s, Ad), 1.55-1.60 (4H, m, Ad), 1.39-1.46 (8H, m, Ad); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 177.0 (C=O), 151.8, 148.3, 133.6, 133.5, 132.2, 130.7, 130.2, 129.0, 128.3, 127.9, 127.4, 126.6, 126.2, 125.6, 124.6, 123.5, 123.0, 121.9, 118.3, 114.3 (Ar*C*), 40.7, 38.0, 36.2, 27.6; **HRMS (ESI)**: m/z calcd. for $C_{31}H_{28}O_3Na$ $[M+Na]^+$: 471.1931, found: 471.1936.

The (*S*)-BINOL derived (*S*)-**2.1**, (*S*)-**2.2**, (*S*)-**2.3**, and (*S*)-**2.4** have also been synthesized, in similar yields, and with spectroscopic data in accordance with (*R*)-analogues.[6,7,10]

(*S*)-2'-methoxy-1,1'-binaphthyl-2-ol ((*S*)-2.1)

Yield: 83% (4.237 g, 14.11 mmol); $[\alpha]_D^{25}$: - 40 (*c* 1.0, $CHCl_3$).

(*S*)-2'-(benzyloxy)-1,1'-binaphthyl-2-ol ((*S*)-2.2)

Yield: 85% (5.439 g, 14.45 mmol); $[\alpha]_D^{25}$: - 15 (*c* 1.0, CH_2Cl_2).

(*S*)-2'-(diphenylmethoxy)-1,1'-binaphthyl-2-ol ((S)-2.3)

Yield: 57% (4.378 g, 9.69 mmol); $[\alpha]_D^{25}$: + 10 (*c* 1.0, CH_2Cl_2).

(*S*)-2'-(1-adamantyloxy)-1,1'-binaphthyl-2-ol ((*S*)-2.4)

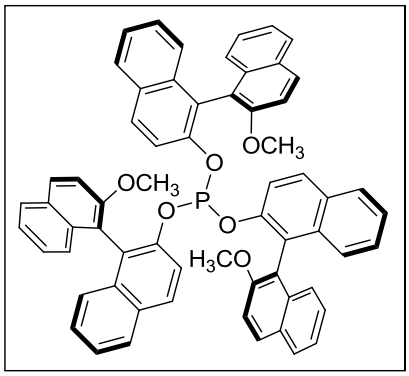
Yield: 51% (3.646 g, 8.67 mmol); $[\alpha]_D^{25}$: + 55 (*c* 1.0, CH_2Cl_2).

5.2.2 Synthesis of monophosphite ligands

The preparation of monophosphite ligands was performed, according to conventional procedures for synthesis of tris-arylphosphites.[9] It should be mentioned that triethylamine (Et_3N) and phosphorus trichloride (PCl_3) were distilled prior to use. In a typical experiment,[10] a dried Schlenk flask was charged with the desired mono-protected BINOL derivative (*R*)- or (*S*)-**2.1**-**2.5** (6.9 mmol), which was azeotropically dried with toluene, then placed under nitrogen atmosphere and dissolved in dry triethylamine (15 mL). The solution was cooled to 0 °C and PCl_3 (0.2 mL, 2.3 mmol) was slowly added. The reaction progress was followed by TLC and ^{31}P NMR. After stirring for 3-5 h, the solvent was evaporated under reduced pressure. Then, the residue was dissolved in dichloromethane/*n*-hexane (1:1) and purified by a silica gel column chromatography, using dichloromethane/*n*-hexane (1:1) as eluent, and further purified by recrystallization in diethyl ether/*n*-hexane, always under nitrogen atmosphere.

Tris[(*R*)-2'-methoxy-1,1'-binaphthyl-2-yl] phosphite ((*R*)-L1-OMe)

Following the above described procedure, the final product (*R*)-**L1**-OMe, with white crystalline aspect was obtained in 83% yield (1.773 g, 1.91 mmol).[11]

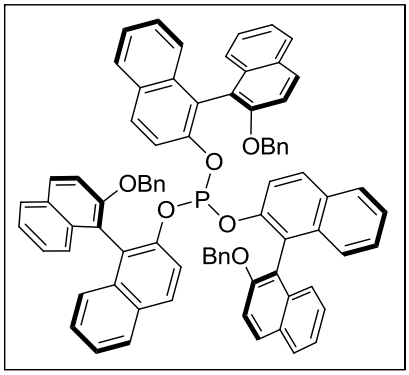


(*R*)-**L1**-OMe

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.89 (3H, d, 9.2 Hz, Ar), 7.82 (3H, d, 8.4 Hz, Ar), 7.75 (3H, d, 8.4 Hz, Ar), 7.31 (3H, t, 7.4 Hz, Ar), 7.18-7.27 (9H, m, Ar), 7.15 (3H, t, 7.8 Hz, Ar), 7.05 (3H, t, 7.8 Hz, Ar), 7.01 (3H, d, 8.4 Hz, Ar), 6.84 (3H, d, 8.4 Hz, Ar), 6.34 (3H, d, 8.8 Hz, Ar), 3.45 (9H, s, OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 155.0, 147.5, 133.9, 133.7, 130.3, 129.7, 129.0, 128.7, 127.8, 127.7, 126.3, 126.0, 125.8, 125.4, 124.3, 123.4, 120.7, 120.6, 118.5, 113.9, 56.3; **^{31}P NMR (161 MHz, $CDCl_3$), δ/ppm**: 131.5; **HRMS (ESI)**: m/z calcd. for $C_{63}H_{45}O_6PNa$ $[M+Na]^+$: 951.2846, found: 951.2828; **Elem. Anal.** calcd. for $C_{63}H_{45}O_6P \cdot 2H_2O$: C 78.41, H 5.12, found: C 78.61, H 5.58; **Mp**: 153-155 °C; **$[\alpha]_D^{25}$**: + 30 (*c* 1.0, toluene).

Tris[(*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl] phosphite ((*R*)-L2-OBn)

Following the above described procedure, the final product (*R*)-**L2**-OBn, with white crystalline aspect was obtained in 81% yield (2.156 g, 1.86 mmol).[11]

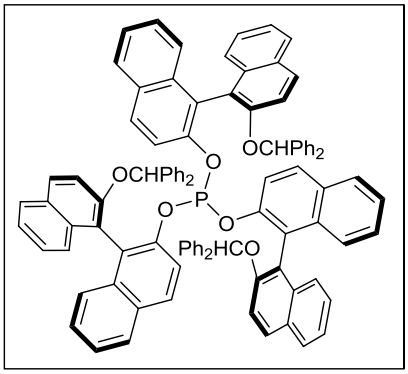


(*R*)-**L2**-OBn

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.71-7.77 (9H, m, Ar), 7.32 (3H, t, 7.4 Hz, 3H), 7.23 (3H, t, 7.6 Hz, Ar), 7.11-7.17 (6H, m, Ar), 6.99-7.01 (18H, m, Ar), 6.88 (3H, d, 8.4 Hz, Ar), 6.79 (6H, d, 6.4 Hz, Ar), 6.20 (3H, d, 8.8 Hz, Ar), 4.73 (6H, s, OCH_2Ph); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 154.3, 147.6, 137.6, 134.1, 133.8, 130.5, 129.7, 129.4, 128.8, 128.2, 127.9, 127.8, 127.3, 126.9, 126.4, 126.1, 126.0, 125.7, 124.4, 123.7, 123.0, 120.6, 119.7, 115.8, 71.0; **^{31}P NMR (161 MHz, $CDCl_3$), δ/ppm**: 132.6; **HRMS (ESI)**: m/z calcd. for $C_{81}H_{58}O_6P$ $[M+H]^+$: 1157.3996, found: 1157.3932; **Elem. Anal.** calcd. for $C_{81}H_{57}O_6P \cdot 2H_2O$: C 81.53, H 5.15, found: C 81.42, H 4.70; **Mp**: 113-115 °C; **$[\alpha]_D^{25}$**: + 15 (*c* 1.0, toluene).

Tris[(*R*)-2'-(diphenylmethoxy)-1,1'-binaphthyl-2-yl] phosphite ((*R*)-L3-OCHPh$_2$)

Following the above described procedure, the final product (*R*)-**L3**-OCHPh$_2$, with white crystalline aspect was obtained in 77% yield (2.454 g, 1.77 mmol).[11]

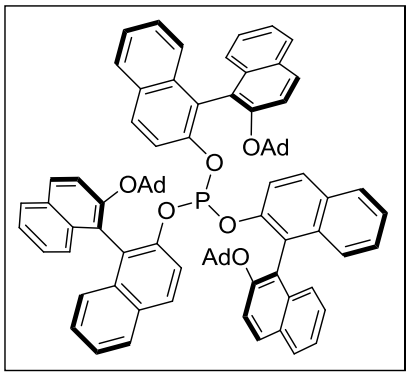


(*R*)-**L3**-OCHPh$_2$

^{1}H NMR (400 MHz, CDCl$_3$), δ/ppm: 7.64-7.71 (9H, m, Ar), 7.30 (3H, t, 7.4 Hz, Ar), 7.19 (6H, d, 9.2 Hz, Ar), 7.10-7.15 (9H, m, Ar), 7.01 (6H, t, 7.2 Hz, Ar), 6.80-6.97 (27H, m, Ar), 6.74 (3H, d, 8.4 Hz, Ar), 6.17 (3H, d, 9.2 Hz, Ar); 6.05 (3H, s, OC*H*Ph$_2$); **^{13}C NMR (100 MHz, CDCl$_3$), δ/ppm**: 153.2, 147.5, 141.5, 134.0, 133.6, 130.3, 129.2, 129.1, 128.7, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 127.1, 126.7, 126.5, 126.4, 126.1, 126.0, 125.7, 124.1, 123.5, 120.4, 116.7, 81.9; **^{31}P NMR (161 MHz, CDCl$_3$), δ/ppm**: 134.2; **HRMS (ESI)**: m/z calcd. for $C_{99}H_{70}O_6P$ $[M+H]^+$: 1386.4938, found: 1386.4909; **Elem. Anal.** calcd. for $C_{99}H_{69}O_6P \cdot 2H_2O$: C 83.64, H 5.18, found: C 82.98, H 4.62; **Mp**: 142-144 °C; **$[\alpha]_D^{25}$**: - 20 (*c* 1.0, toluene).

Tris[(*R*)-2'-(1-adamantyloxy)-1,1'-binaphthyl-2-yl] phosphite ((*R*)-L4-OAd)

Following the above described procedure, the final product (*R*)-**L4**-OAd, with white crystalline aspect was obtained in 76% yield (2.253 g, 1.75 mmol).[7]

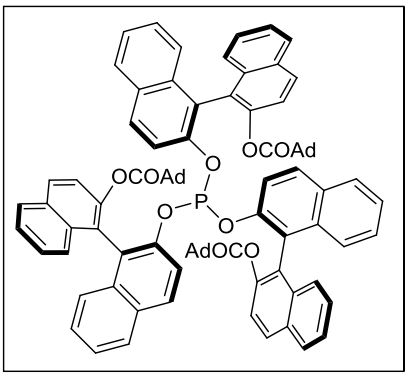


(*R*)-**L4**-OAd

^{1}H NMR (400 MHz, CDCl$_3$), δ/ppm: 7.70 (3H, d, 8.8 Hz, Ar), 7.68 (3H, d, 7.6 Hz, Ar), 7.64 (3H, d, 8.4 Hz, Ar), 7.29 (3H, d, 8.8 Hz, Ar), 6.89-7.22 (18H, m, Ar), 6.77 (3H, d, 8.4 Hz, Ar), 6.44 (3H, d, 8.8 Hz, Ar), 1.80 (12H, br s, Ad), 1.32-1.42 (33H, m, Ad); **^{13}C NMR (100 MHz, CDCl$_3$), δ/ppm**: 152.1, 147.9, 134.2, 133.8, 130.2, 130.1, 128.6, 128.3, 127.8, 127.7, 126.6, 126.6, 126.0, 125.6, 125.5, 124.5, 124.0, 124.0, 120.5, 120.4, 78.9, 43.2, 36.2, 31.0; **^{31}P NMR (161 MHz, CDCl$_3$), δ/ppm**: 132.2; **HRMS (ESI)**: m/z calcd. for $C_{90}H_{81}O_6PNa$ $[M+Na]^+$: 1311.5663, found: 1311.5628; **Mp**: 158-160°C; **$[\alpha]_D^{25}$**: - 160 (*c* 2.0, CH_2Cl_2).

Tris[(*S*)-2'-(1-adamantanoyloxy)-1,1'-binaphthyl-2-yl]phosphite (L5-OCOAd)

Following the above described procedure, the final product (*S*)-**L5**-OCOAd, with white crystalline aspect was obtained in 74% yield (2.338 g, 1.70 mmol). The spectroscopic data is in agreement with that previously reported.[8]



L5-OCOAd

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.85 (3H, d, 8.8 Hz, Ar), 7.72 (6H, t, 9.4 Hz, Ar), 7.23-7.34 (12H, m, Ar), 7.15 (3H, t, 7.6 Hz, Ar), 7.00 (3H, t, 7.6 Hz, Ar), 6.94 (3H, d, 8.4 Hz, Ar), 6.66 (3H, d, 8.4 Hz, Ar), 6.46 (3H, d, 8.8 Hz, Ar), 1.71 (9H, br s, Ad), 1.45 (18H, dd, 11.6 Hz, 55.6 Hz, Ad), 1.23 (18H, br s, Ad); **^{31}P NMR (161 MHz, $CDCl_3$), δ/ppm**: 136.2; **HRMS (ESI)**: m/z calcd. for $C_{93}H_{81}O_9PNa$ $[M+Na]^+$: 1396.5568, found: 1396.5549; **Mp**: 259-261 °C.

The monophosphite ligands (*S*)-**L1**-OMe, (*S*)-**L2**-OBn, (*S*)-**L3**-$OCHPh_2$, (*S*)-**L4**-OAd have also been synthesized, from the corresponding (*S*)-BINOL mono-ethers, in similar isolated yields and spectroscopic data in accordance with (*R*) analogues.[7,10,11]

Tris[(*S*)-2'-methoxy-1,1'-binaphthyl-2-yl] phosphite ((S)-L1-OMe)

Yield: 82% (1.752 g, 1.89 mmol); $[\alpha]_D^{25}$: - 35 (*c* 1.0, CH_2Cl_2).

Tris[(*S*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl] phosphite ((*S*)-L2-OBn)

Yield: 78% (2.076 g, 1.79 mmol); $[\alpha]_D^{25}$: - 15 (*c* 1.0, toluene).

Tris[(*S*)-2'-(diphenylmethoxy)-1,1'-binaphthyl-2-yl] phosphite ((*S*)-L3-$OCHPh_2$)

Yield: 72% (2.295 g, 1.66 mmol); $[\alpha]_D^{25}$: + 15 (*c* 1.0, toluene).

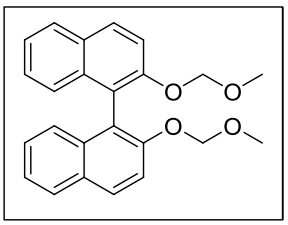
Tris[(*S*)-2'-(1-adamantyloxy)-1,1'-binaphthyl-2-yl] phosphite ((S)-L4-OAd)

Yield: 74% (2.195 g, 1.70 mmol); $[\alpha]_D^{25}$: $[\alpha]_D^{25}$: + 65 (*c* 1.0, CH_2Cl_2).

5.2.3 Synthesis of 3-methyl binaphthyl derivatives

The syntheses of 3-methyl binaphthyl derivatives were performed through slightly modified literature procedures.[12,13]

2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (2.6)


2.6

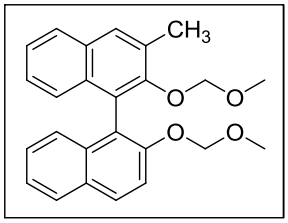
In a typical procedure, racemic 1,1'-binaphthol (6.0 g, 21 mmol) was added to a stirring suspension of NaH (1.11 g, 46.2 mmol) in anhydrous THF (60 mL) at 0°C, under a nitrogen atmosphere. This solution was stirred for 15 min, and then methoxymethyl chloride (4.0 mL, 53 mmol) was slowly added. The mixture was allowed to warm up to room temperature and stirred for 5 h. After washing and drying the organic layers by standard procedures, the solvent was removed and the target compound **2.6** with white crystalline aspect was recrystallized from toluene/*n*-hexane, with 88% isolated yield (6.920 g, 18.5 mmol). Spectroscopic data is in agreement with literature values.[14,15,16]

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.90 (2H, d, 8.8 Hz, Ar), 7.82 (2H, d, 8.0 Hz, Ar), 7.55 (2H, d, 9.2 Hz, Ar), 7-29 (2H, t, 6.4 Hz, Ar), 7.14-7.20 (4H, m, Ar), 5.04 (2H, d, 6.8 Hz, OCH_2O), 4.93 (2H, d, 6.8 Hz, OCH_2O), 3.10 (6H, s, OCH_3); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 152.6, 134.0, 129.9, 129.4, 127.8, 126.3, 125.5, 124.0, 121.3, 117.2, 95.1, 55.7; **MS (EI)**: m/z = 374.1516 (M^+).

2,2'-bis(methoxymethoxy)-3-methyl-1,1'-binaphthyl (2.7)

In a standard procedure,[13,17] *n*-BuLi (1.6 M in hexane, 11.3 mL, 18 mmol) was added to a solution of 2,2'-bis(methoxymethoxy)-1,1'-binaphthyl **2.6** (5.5 g, 15 mmol) in anhydrous THF (90 mL), under a nitrogen atmosphere, at room temperature. The mixture was stirred for 4 h, which produced a grey suspension. After the mixture was cooled to 0°C, iodomethane (1.2 mL, 19 mmol) was added. The reaction was allowed to warm up to room temperature and stirred for 5 h. After quenching by a saturated solution of NH_4Cl (50 mL), the aqueous layer was extracted with ethyl acetate (2×50 mL) and the organic layers were combined and dried over Na_2SO_4. After removal of the

solvent, the residue was purified by column chromatography on silica gel, using a mixture of *n*-hexane/ethyl acetate (10:1) as eluent, which rendered the target compound **2.7**, as a white crystalline solid in 70% isolated yield (4.096 g, 10.5 mmol). Spectroscopic data is in agreement with that reported in literature.[13] Crystallographic data is presented in **Annex 2**.

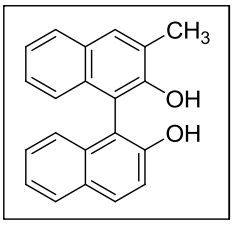


2.7

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.95 (1H, d, 9.2 Hz, Ar), 7.86 (1H, d, 8.0 Hz, Ar), 7.79-7.81 (2H, m, Ar), 7.57 (1H, d, 8.8 Hz, Ar), 7.33-7.36 (2H, m, Ar), 7.24-7.27 (1H, m, Ar), 7.12-7.18 (3H, m, Ar), 5.12 (1H, d, 7.2 Hz, OC*H*$_2$O), 5.01 (1H, d, 6.8 Hz, OC*H*$_2$O), 4.64 (1H, d, 5.6 Hz, OC*H*$_2$O), 4.55 (1H, d, 5.6 Hz, OC*H*$_2$O), 3.16 (3H, s, OC*H*$_3$), 2.89 (3H, s, OC*H*$_3$), 2.58 (3H, s, C*H*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 153.1, 152.8, 134.1, 132.8, 131.6, 131.1, 129.7 (double intensity), 129.5, 127.8, 127.1, 126.6, 125.7, 125.7, 125.3, 125.1, 124.8, 124.1, 121.2, 116.7, 98.7 (O*C*H$_2$), 95.0 (O*C*H$_2$), 56.5 (O*C*H$_3$), 55.9 (O*C*H$_3$), 17.9 (*C*H$_3$); **MS (EI)** m/z = 388.1671 (M^+).

3-methyl-1,1'-binaphthyl-2,2'-diol (2.9)

In a standard procedure,[18] to a solution of 2,2'-bis(methoxymethoxy)-3-methyl-1,1'-binaphthyl **2.7** (3.50 g, 9.0 mmol) in methanol, 0.25 mL of HCl 37% was added and the mixture was stirred under reflux at 60°C, for 30 minutes. Then, the mixture was poured into water, extracted with ethyl acetate and after work-up, the residue was purified by column chromatography on silica gel, using as eluent a mixture of *n*-hexane/ethyl acetate (6:1), which furnished the target compound **2.9** as a white solid, in 95% isolated yield (2.570 g, 8.55 mmol). Spectroscopic data is in agreement with the literature.[19]

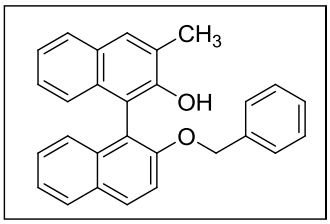


2.9

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.98 (1H, d, 8.8 Hz, Ar), 7.90 (1H, d, 8.0 Hz, Ar), 7.81-7.83 (2H, m, Ar), 7.22-7.40 (5H, m, Ar), 7.15 (1H, d, 8.0 Hz, Ar), 7.08 (1H, d, 8.8 Hz, Ar), 5.12 (1H, s, O*H*), 5.07 (1H, s, O*H*); 2.52 **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 152.8, 152.0, 133.5, 132.1, 131.4, 130.8, 129.5, 129.4, 128.4, 127.6, 127.5, 127.0, 126.4, 124.3, 124.02, 123.99, 123.96, 117.8, 111.1, 110.2, 17.0; **MS (EI)**: m/z = 300.1150 (M^+).

2'-(benzyloxy)-3-methyl-1,1'-binaphthyl-2-ol (2.10)

To a solution of 3-methyl-1,1'-binaphthyl-2,2'-diol **2.9** (2.0 g, 6.7 mmol), PPh_3 (1.8 g, 6.7 mmol) and benzyl alcohol (7.9 mmol, 0.8 mL), in dry THF (40 mL), DEAD (40% in toluene, 3.0 mL, 6.7 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature, for 48 h. After work-up and purification by chromatography in silica gel, using CH_2Cl_2/*n*-hexane (2:1) as eluent, the product **2.10** was obtained as a white solid, in 48% isolated yield (1.255 g, 3.22 mmol).

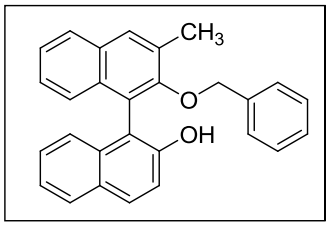


2.10

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.90 (1H, d, 9.2 Hz, Ar), 7.80 (1H, d, 8.0 Hz, Ar), 7.72 (1H, d, 8.0 Hz, Ar), 7.67 (1H, s, Ar), 7.38 (1H, d, 8.8 Hz, Ar), 7.29 (1H, t, 7.2 Hz, Ar), 7.06-7.22 (7H, m, Ar), 6.92-6.97 (3H, m, Ar), 4.97-5.04 (2H, m, OC*H*$_2$Ph), 4.90 (1H, s, O*H*), 2.44 (3H, s, C*H*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 155.0, 150.6, 137.0, 134.2, 132.6, 130.8, 129.7, 129.3, 129.1, 128.3 (double intensity), 128.1, 127.6, 127.3, 127.2 (double intensity), 126.9, 126.6, 125.4, 125.2, 124.7, 124.4, 123.2, 117.2, 116.0, 114.5 (Ar*C*), 71.2 (O*C*H$_2$Ph), 17.1 (*C*H$_3$); **HRMS (ESI)**: m/z calcd. for $C_{28}H_{22}O_2Na$ $[M+Na]^+$: 413.1512, found: 413.1516; **Mp**: 123-125 °C; **Rf**: 0.39 (CH_2Cl_3:*n*-hexane 2:1).

2'-(benzyloxy)-3'-methyl-1,1'-binaphthyl-2-ol (2.11)

In the same procedure above described, the product **2.11** was also obtained as a beige solid product, in 33% isolated yield (0.861 g, 2.21 mmol).



2.11

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.85 (1H, d, 8.8 Hz, Ar), 7.78 (3H, t, 8.0 Hz, Ar), 7.32-7.37 (1H, m, Ar), 7.05-7.30 (9H, m, Ar), 6.71 (2H, br d, 6.4 Hz, Ar), 5.08 (1H, s, O*H*), 4.44 (1H, d, 10.4 Hz, OC*H*$_2$Ph), 4.32 (1H, d, 10.4 Hz, OC*H*$_2$Ph), 2.45 (3H, s, C*H*$_3$); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 155.5, 151.2, 136.9, 134.1, 132.8, 132.2, 131.6, 131.0, 130.3, 129.2, 128.3 (double intensity), 128.1 (double intensity), 128.0, 127.6, 126.9, 126.3, 125.6, 125.6, 125.3, 123.5, 122.0, 118.0, 115.5 (Ar*C*), 75.1 (O*C*H$_2$Ph), 17.6 (CH_3); **HRMS (ESI)**: m/z calcd. for $C_{28}H_{22}O_2Na$ $[M+Na]^+$: 413.1512, found: 413.1511; **Rf**: 0.65 (CH_2Cl_3:*n*-hexane 2:1).

5.3 Experimental (referring to Chapter 3)

In this section, the specific procedures of the asymmetric catalytic reactions (reported in Chapter 3) are described, as well as the preparation of *in situ* rhodium/monophosphite complexes, and the synthesis and characterization of chloro-allylpalladium/monophosphite complexes.

5.3.1 Rhodium-catalyzed hydroformylation

The rhodium-catalyzed hydroformylation reactions were performed in a high pressure system, belonging to the Chemistry Department in the University of Coimbra (**Figure 5.1**).

Figure 5.1 – High-pressure system for catalytic hydroformylation, in the Chemistry Department, University of Coimbra.

In a typical hydroformylation experiment, the autoclave was charged with the appropriate amount of monophosphite ligand and after three cycles of *syngas*/vacuum, the rhodium precursor $Rh(CO)_2(acac)$, in toluene, was then introduced via *cannula*. The reactor was pressurized with the desired pressure of an equimolar mixture of CO/H_2, and kept at 80^oC for 1 hour. After the incubation, the autoclave was slowly depressurized and set to the working temperature. Then, the substrate was introduced through the inlet *cannula* and the *syngas* pressure was set to the desired value for each experiment (**Figure 5.2**).

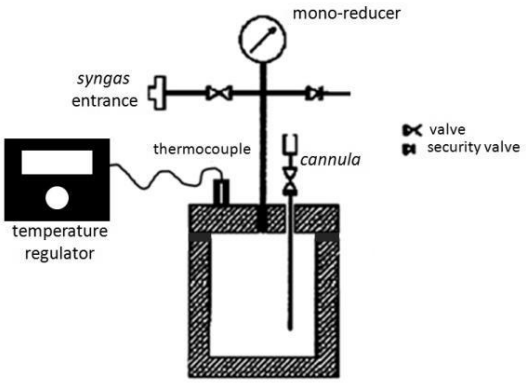


Figure 5.2 – Schematic representation of the autoclave for high-pressure hydroformylation reactions.

After the reactions were finalized, the autoclave was slowly depressurized and the samples were analyzed by GC, in order to determine conversion, chemo- and regioselectivity, through the following expressions.

$$Conversion\,(\%) = \left(\frac{total\ peaks\ area\ -\ substrate\ peak\ area}{total\ peak\ area} \right) \times 100$$

$$Chemoselectivity\,(\%) = \left(\frac{aldehydes\ peaks\ areas}{sum\ of\ all\ products\ peaks\ areas} \right) \times 100$$

$$Regioselectivity\,(\%) = \left(\frac{major\ aldehyde\ peak\ area}{aldehydes\ peaks\ areas} \right) \times 100$$

5.3.1.1 General procedure for hydroformylation of aryl olefins

The autoclave was charged with the desired monophosphite ligand **L1**-OMe, **L2**-OBn, **L3**-$OCHPh_2$ or **L4**-OAd (0.0145 mmol) and the system was purged by three cycles of *syngas* and vacuum. Then, a solution of $Rh(CO)_2(acac)$ (0.75 mg, 0.0029 mmol) in toluene (3mL) was introduced via *cannula*, under vacuum. After 1 h incubation at 80°C and 40 bar of *syngas*, the substrate (2.32 mmol), previously passed through an aluminum oxide (grade I) column was dissolved in toluene (4 mL) and subsequently introduced through the inlet *cannula*. Then, pressure was set to the desired value, and the mixture was magnetically stirred for the selected time. The conversion, chemo-

and regioselectivity throughout the reactions were determined by gas chromatography analysis of aliquots from the reaction mixture (*Agilent-7820A* chromatographer equipped with *HP-5* column; injector temperature = 200°C; oven: starting temperature 100°C (hold-time 10 min), heating rate 20°C/min until 280°C (hold-time 10 min), heating rate 5°C/min until 300°C (hold-time 5 min); detector temperature 250°C; carrier gas: nitrogen).

Retention times

trans-1-phenylpropene (**3.1**): 3.5 min;

2-phenylbutanal (**3.2**): 6.4 min;

2-methyl-3-phenylpropanal (**3.3**): 7.1 min.

2-phenylpropene (**3.4**): 3.1 min;

3-phenylbutanal (**3.5**): 7.2 min;

2-methyl-2-phenylpropanal (**3.6**): 5.7 min.

styrene (**3.7**): 2.4 min;

2-phenylpropanal (**3.8**): 4.5 min;

3-phenylpropanal (**3.9**): 5.7 min.

For kinetic studies, samples were taken at no more than 20% conversions, in order to determine the initial rates, without product interferences. The turnover frequencies (TOF's), in h^{-1}, were calculated as the number of mmol of substrate converted into aldehydes, per mmol of rhodium, per hour.

To analyze the enantiomeric excesses, aldehydes were oxidized into the corresponding carboxylic acids. Following a standard procedure,[20,21] the aldehydes (1 mL in toluene) were added to a solution containing $KMnO_4$ (0.2 g, 1.3 mmol) and $MgSO_4$ (0.2 g, 1.7 mmol) in acetone (20 mL), and the mixture was stirred at room temperature, for 15-30 minutes. Then, the solvent was evaporated in vacuum and the residue was dissolved in H_20 (25 mL), at 70°C. The solution was washed with dichloromethane (3×25 mL) to remove unreacted alkenes and/or non-oxidized aldehydes, and the aqueous phase was then acidified with 10% HCl solution to ensure the protonation of carboxylates. After checking the acidic pH of the solution, the

extraction of carboxylic acids was performed with dichloromethane (3×25 mL). The organic phases were collected and dried over anhydrous magnesium or sodium sulfate. After filtration, the solvent was removed under vacuum, and the resulting oil (or solid) was dissolved in 1 mL of CH_2Cl_2. Finally, 0.5 µL of this sample was injected in the chromatograph (*Agilent-6890* equipped with a *Supelco* β-*Dex 120* column; injector temperature = 220°C; program: isotherm 150°C; detector temperature 240°C; carrier gas: helium; flow: 1 mL/min). The enantiomeric excesses were determined according to the expression:

$$enantiomeric\ excess(\%) = \left(\frac{major\ enantiomer\ -\ minor\ enantiomer}{major\ enantiomer\ +\ minor\ enantiomer} \right) \times 100$$

Retention times

(*S*)-2-phenylbutanoic acid: 96.2 min;

(*R*)-2-phenylbutanoic acid: 100.7 min.

(*S*)-3-phenylbutanoic acid: 59.8 min;

(*R*)-3-phenylbutanoic acid: 61.1 min.

(*S*)-2-phenylpropanoic acid: 36.5 min;

(*R*)-2-phenylpropanoic acid: 38.8 min.

5.3.1.2 Hydroformylation of 17β-acetoxyandrost-4-ene

The steroid 17β-acetoxyandrost-4-ene **3.11**, prepared from the respective 3-ketone through a literature procedure,[22] was kindly provided by Doctor A. Peixoto (University of Coimbra). The autoclave was charged with (*R*)- or (*S*)- **L2**-OBn (0.110 g, 0.095 mmol) and $[Rh(CO)_2(acac)]$ (0.005 g, 0.019 mmol), and toluene (3 mL) was added under vacuum. After incubation, at 40 bar *syngas* and 80°C, during 1h, the steroid 17β-acetoxyandrost-4-ene **3.11** (0.948 mmol, 0.300 g), dissolved in toluene (3 mL) was introduced via *cannula*, and the reaction was conducted at 100°C and 25 bar *syngas*, for 48h.[23,24] After the reaction was finished, the autoclave was cooled, slowly depressurized, and toluene was evaporated under reduced pressure. The identification of products was performed by NMR and MS (EI), and the quantification of chemo-,

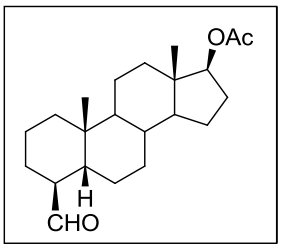
regio- and diastereoselectivity was carried out based by GC analysis and ^{1}H and ^{13}C NMR spectroscopy, based on the previously performed assignments.[23] (*Agilent-6890* chromatograph equipped with *HP-5* column; injector temperature = 280°C; oven: starting temperature 250°C (hold-time 4 min), heating rate 20°C/min until 280°C (hold-time 10 min), heating rate 20°C/min until 300°C (hold-time 10 min); detector temperature 300°C; carrier gas: nitrogen).

Retention times

17β-acetoxyandrost-4-ene (**3.11**): 4.1 min;

4β-formyl-17β-acetoxy-5β-androstane (**3.12**): 5.7 min;

4α-formyl-17β-acetoxy-5α-androstane (**3.13**): 6.1 min.



3.12

The major product was identified as being 4β-formyl-17β-acetoxy-5β-androstane **3.12** (95% conversion, 86% chemoselectivity, 100% of 4-formyl regioselectivity and 70% of β-diastereoselectivity. Spectroscopic data is in agreement with the literature values. **MS (EI)**: m/z = 346 (M^{+}).[23]

5.3.2 Preparation of *in situ* Rh(I)(CO)(acac)(monophosphite) complexes

In a typical experiment, a dried NMR tube was charged with $Rh(CO)_2(acac)$ (2.6 mg, 0.01 mmol) and each monophosphite ligand **L1**-OMe, **L2**-OBn, **L3**-$OCHPh_2$ and **L4**-OAd (0.01 mmol), under an argon or nitrogen atmosphere.

The solids were dissolved in 0.5 mL $CDCl_3$ at 25°C, and the mixture was subjected to magnetic stirring for 1 h. Then, the ^{31}P NMR spectra of the resulting solutions were registered. After the addition of a second molar equiv of monophosphite ligand, the ^{31}P NMR spectra of the resulting solutions were registered again.

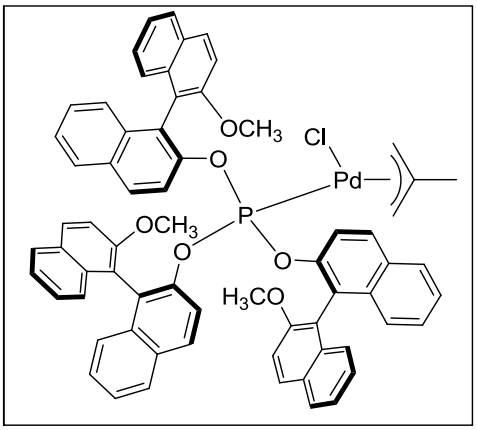
5.3.3 Synthesis of Pd(II)(chloro)(methylallyl)(monophosphite) complexes

The palladium precursor $[PdCl(\eta^3\text{-2-Me-allyl})]_2$, prepared from Na_2PdCl_4 and β-methylallyl chloride, by a standard procedure[25] was kindly provided by Doctor A. Grabulosa, from the group of Prof. G. Muller (Department of Inorganic Chemistry, University of Barcelona).

In a typical complexation reaction,[26,27] $[PdCl(\eta^3\text{-2-Me-allyl})]_2$ (39.3 mg, 0.1 mmol) and the monophosphite ligand **L1**-OMe, **L2**-OBn, **L3**-$OCHPh_2$, **L4**-OAd or **L5**-OCOAd (0.21 mmol) were dissolved in 10 ml of dichloromethane and stirred for 1 h, under nitrogen atmosphere, at room temperature. The solvent was removed *in vacuo* and the pale brown foam was suspended in *n*-pentane, filtered and washed with pentane.

Chloro(η^3-2-Me-allyl)[tris((*S*)-2'-methoxy-1,1'-binaphthyl-2-yl)phosphite] palladium (II) (Pd1)

Following the above described procedure, using $[PdCl(\eta^3\text{-2-Me-allyl})]_2$ (39.3 mg, 0.1 mmol) and (*S*)-**L1**-OMe (195 mg, 0.21 mmol), the target complex **Pd1** (in a 4:1 ratio diastereomeric mixture) was obtained as a fine white solid, in 71 % isolated yield (160 mg, 0.14 mmol).



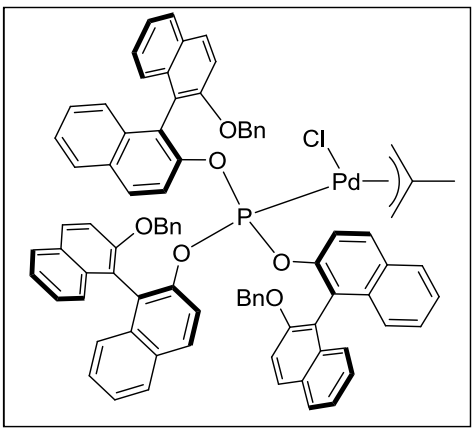
Pd1

^{1}H NMR (500 MHz, $CDCl_3$), δ/ppm: 6.82-7.97 (36H, m, Ar), 4.12 minor (1H, d, 9.0 Hz, *syn-trans*-C*H*); 3.89 major (1H, d, 9.5 Hz, *syn-trans*-C*H*); 3.58 minor (3H, s, OCH_3); 3.44 major (3H, s, OCH_3), 3.02 minor (1H, d, 16.5 Hz, *anti-trans*-C*H*); 2.54 major (1H, d, 17.0 Hz, *anti-trans*-C*H*); 2.51 minor (1H, s, *syn-cis*-C*H*); 2.09 major (1H, s, *syn-cis*-C*H*); 1.45 minor (1H, s, *anti-cis*-C*H*); 1.04 minor, 1.01 major (3H, s, allyl-CH_3); 0.61 major (1H, s, *anti-cis*-C*H*); **^{13}C NMR (125.7 MHz, $CDCl_3$), δ/ppm**: 155.0 (*C*OCH_3); 146.9 (*C*OP); 133.7, 133.5 (*C* Naph); 117.7 (*C* Binaph); 79.6 minor (d, 51.0 Hz, *trans*-*C*H_2); 78.3 major (d, 52.0 Hz, *trans*-*C*H_2); 58.2 major (*cis*-*C*H_2); 57.4 minor (*cis*-*C*H_2); 56.3 minor, 56.0 major (O*C*H_3); 22.1 minor, 22.0 major (allyl-*C*H_3); **^{31}P NMR (121 MHz, $CDCl_3$), δ/ppm**: 121.0 major, minor; **Elem. Anal.** calcd. for $C_{67}H_{52}ClO_6PPd$: C 71.47, H 4.65; found C 69.57, H 4.77.

Chloro(η^3-2-Me-allyl)[tris((*S*)-2'-(benzyloxy)-1,1'-binaphthyl-2-yl)phosphite] palladium (II) (Pd2)

Following the same procedure, but using [PdCl(η^3-2-Me-allyl)]$_2$ (37.8 mg, 0.096 mmol) and (*S*)-**L2**-OBn (233 mg, 0.20 mmol), the target complex **Pd2** (in a 3.7:1 ratio diastereomeric mixture) was obtained as a fine white solid, in 66 % isolated yield (170 mg, 0.13 mmol).

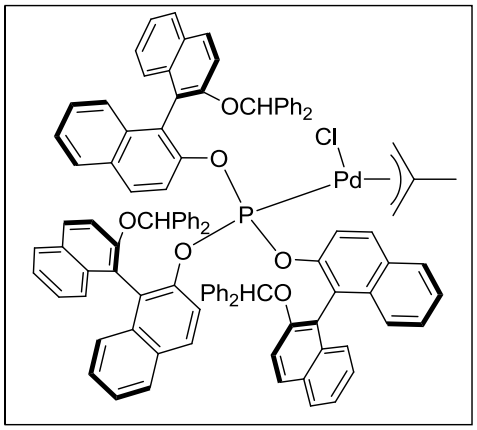
^{1}H NMR (400.1 MHz, $CDCl_3$), δ/ppm: 6.76-7.90 (51H, m, Ar); 4.83 minor, (1H, d, 12.4 Hz, OC*H*$_2$Ph); 4.79 major, (1H, d, 12.4 Hz, OC*H*$_2$Ph); 4.77 minor (1H, d, 12.4 Hz, OC*H*$_2$Ph); 4.75 major (1H, d, 12.4 Hz, OC*H*$_2$Ph); 4.04 minor (1H, d, 11.0 Hz, *syn-trans*-C*H*); 3.85 major (1H, d, 10, 1Hz, *syn-trans*-C*H*); 2.82 minor (1H, d, 16.4 Hz, *anti-trans*-C*H*); 2.51 major (1H, d, 17.0 Hz, *anti-trans*-C*H*); 2.31 minor (1H, s, *syn-cis*-C*H*); 2.13 major (1H, s, *syn-cis*-C*H*); 1.19 minor (1H, s, *anti-cis*-C*H*); 0.65 major, 0.94 minor (3H, s, allyl-C*H*$_3$); 0.48 major (1H, s, *anti-cis*-C*H*); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 154.2 (*C*OCH$_2$Ph); 146.9 (*C*OP); 137.26, 133.7 (*C* Naph); 118.7 (*C* Binaph); 78.9 major (d, 52.0 Hz, *trans*-*C*H$_2$); 71.0 minor, 70.8 major (O*C*H$_2$Ph); 57.9 major (*cis*-*C*H$_2$); 22.0 minor, 21.6 major (allyl-*C*H$_3$); **^{31}P NMR (121 MHz, $CDCl_3$), δ/ppm**: 121.9 major, 121.6 minor; **Elem. Anal.** calcd. for $C_{85}H_{64}ClO_6PPd$: C 75.39, H 4.76; found C 75.19, H 4.61.



Pd2

Chloro(η^3-2-Me-allyl)[tris((*R*)-2'-(diphenylmethoxy)-1,1'-binaphthyl-2-yl)phosphite] palladium (II) (Pd3)

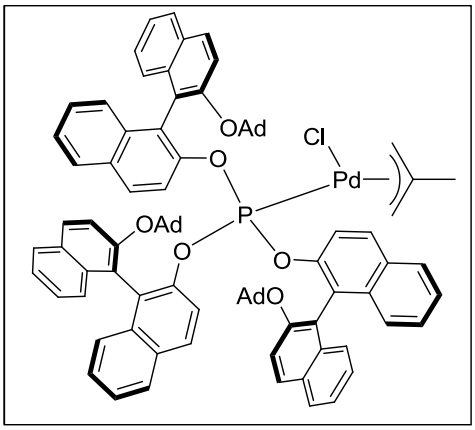
Following the same procedure, but using [PdCl(η^3-2-Me-allyl)]$_2$ (11.5 mg, 0.029 mmol) and (*R*)-**L3**-OCHPh$_2$ (85 mg, 0.061 mmol), the target complex **Pd3** (in a 1.5:1 ratio diastereomeric mixture) was obtained as a fine white solid, in 50 % isolated yield (46 mg, 0.029 mmol).



Pd3

^{1}H NMR (500 MHz, $CDCl_3$), δ/ppm: 6.30-8.00 (66H, m, Ar); 6.11 major, 6.03 minor (1H, s, OC*H*Ph_2); 4.05 minor (1H, d, 10.0 Hz, *syn-trans*-C*H*); 3.87 major (1H, d, 9.5 Hz, *syn-trans*-C*H*); 2.72 minor (1H, d, 17.0 Hz, *anti-trans*-C*H*); 2.45 major (1H, d, 17.0 Hz, *anti-trans*-C*H*); 2.28 minor (1H, s, *syn-cis*-C*H*); 1.87 major (1H, s, *syn-cis*-C*H*); 1.16 minor (1H, s, *anti-cis*-C*H*); 1.05 minor, 0.99 major (3H, s, allyl-CH_3); 0.51 major (1H, s, *anti-cis*-C*H*); **^{13}C NMR (125.7 MHz, $CDCl_3$), δ/ppm**: 153.3 (*C*OCHPh$_2$); 147.3 (*C*OP); 141.8, 141.4 (*C* Naph); 82.4 (s, O*C*HPh$_2$); 79.2 minor (d, 50.0 Hz, *trans*-*C*H$_2$); 78.7 major (d, 56.0 Hz, *trans*-*C*H$_2$); 58.5 minor (*cis*-*C*H$_2$); 58.1 major (*cis*-*C*H$_2$); 22.3 minor, 22.3 major (s, allyl-*C*H$_3$); **^{31}P NMR (121 MHz, $CDCl_3$), δ/ppm**: 120.2 (major), 119.4 (minor); **Elem. Anal.** calcd. for $C_{103}H_{76}ClO_6PPd$: C 78.17, H 4.84; found C 76.30, H 5.12.

Chloro(η^3-2-Me-allyl)[tris((*S*)-2'-(1-adamantyloxy)-1,1'-binaphthyl-2-yl)phosphite] palladium (II) (Pd4)



Pd4

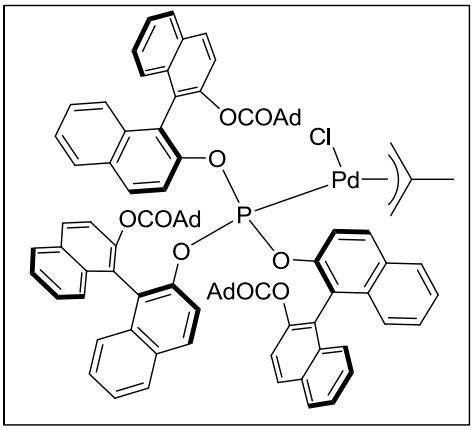
Following the same procedure, but using [PdCl(η^3-2-Me-allyl)]$_2$ (19.7 mg, 0.05 mmol) and (*S*)-**L4**-OAd (135.4 mg, 0.11 mmol), the target complex **Pd4** (in a 2.2:1 ratio diastereomeric mixture) was obtained as a fine white solid, in 64 % isolated yield (95 mg, 0.064 mmol).

^{1}H NMR (400.1 MHz, $CDCl_3$), δ/ppm: 6.85-7.90 (36H, m, Ar); 4.03 minor (1H, d, 10.4 Hz, *syn-trans*-C*H*); 3.82 major (1H, d, 12.0 Hz *syn-trans*-C*H*); 3.00 minor (1H, d, 16.4 Hz, *anti-trans*-C*H*); 2.42 major (1H, d, 17.2 Hz, *anti-trans*-C*H*); 2.13 minor (1H, s, *syn-cis*-C*H*); 0.81-1.88 (45H, m, major and minor adamantyl protons; ov. 3H, allyl-CH_3 , ov. minor 1H, *anti-cis*-C*H*, ov. major 1H, *syn-cis*-C*H*); 0.50 major (1H, s, *anti-cis*-C*H*); **^{13}C NMR (100.5 MHz, $CDCl_3$), δ/ppm**: 151.9 (*C*OAd); 147.6 (*C*OP); 120.1-133.8 (*C*, *C*H Naph); 78.5

(*C*1 OAd); 77.2 major (*trans*-*C*H_2 ov. $CDCl_3$); 58.9 major (*cis*-*C*H_2); 43.3, 36.0, 30.8, (*C*2, *C*4, *C*3 Ad); 22.6 major (allyl-*C*H_3); **^{31}P NMR (121 MHz, $CDCl_3$), δ/ppm**: 118.9 minor, 118.2 major; **Elem. Anal.** calcd. for $C_{94}H_{88}ClO_6PPd$: C 75.95, H 5.97; found C 72.64, H 6.24.

Chloro(η^3-2-Me-allyl)[tris((*S*)-2'-(1-adamantanoyloxy-1,1'-binaphthyl-2-yl) phosphite] palladium (II) (Pd5)

Following the same procedure, but starting from [PdCl(η^3-2-Me-allyl)]$_2$ (19.7 mg, 0.05 mmol) and (*S*)-**L5**-OCOAd (144.0 mg, 0.105 mmol), the target complex **Pd5** (in a 2.5:1 ratio diastereomeric mixture) was obtained as a fine white solid, in 70 % isolated yield (109 mg, 0.070 mmol).



Pd5

^{1}H NMR (400.1 MHz, $CDCl_3$), δ/ppm: 6.73-7.90 (36H, m, Ar); 4.29 minor (1H, d, 12.0 Hz, *syn-trans*-C*H*); 3.86 major (1H, d, 12.0 Hz, *syn-trans*-C*H*); 3.13 minor (1H, d, 16.0 Hz, *anti-trans*-C*H*); 1.87 major (1H, d, 16.0 Hz, *anti-trans*-C*H*); 1.23-1.78 (45H, m, major and minor adamantyl protons; ov. minor 1H, *anti-cis* C*H*; ov. minor 3H, allyl-C*H*$_3$; ov. 1H, *syn-cis* C*H*); 1.14 major (3H, s, allyl-C*H*$_3$); 0.85 major (1H, s, *anti-cis* C*H*); **^{13}C NMR (100.5 MHz, $CDCl_3$), δ/ppm**: 175.6 (*C*OO); 147.0 (*C*O Ad); 146.9 (*C*OP); 118.8-133.4 (*C*, *C*H Naph); 80.7 major (d, 50.0 Hz, *trans*-*C*H_2); 57.4 major (*cis*-*C*H_2); 40.5, 37.9, 36.1, 27.6 (*C*1, *C*2, *C*4, *C*3 Ad); 22.7 major (allyl-*C*H_3); **^{31}P NMR (121 MHz, $CDCl_3$), δ/ppm**: 118.9 minor, 118.0 major; **Elem. Anal.** calcd. for $C_{97}H_{88}ClO_9PPd$: C 74.18, H 5.65; found C 74.19, H 6.50.

5.3.4 Palladium-catalyzed hydrovinylation

The catalytic hydrovinylation experiments were performed, in the scope of a cooperation project, in the laboratory of Prof. Guillermo Muller, from the University of Barcelona. The reactions were carried out in a stainless-steel autoclave fitted with an external jacket connected to an ethanol bath and a thermocouple device, which controls the internal temperature, using a thermostat to ± 0.5°C (**Figure 5.3**).

5.3.4.1 General procedure of Pd-catalyzed hydrovinylation of styrene

In a typical procedure,[27,28] the desired chloro-allylpalladium complex **Pd1**-**Pd5** (0.035 mmol), $AgBF_4$ (1.1 molar equiv with respect to Pd) and styrene (35 mmol, 4.0 mL) were dissolved in 15 mL of dichloromethane and stirred for 10 min, sheltered from light. After filtering off the formed AgCl, the solution was placed, by syringe, into the autoclave, which had been purged by successive vacuum/nitrogen cycles and thermostated to 25°C. Then, ethylene was admitted until a pressure of 16 bar was reached.

Figure 5.3 – High-pressure system for catalytic hydrovinylation, in the Department of Inorganic Chemistry, University of Barcelona.

After the selected time, the autoclave was slowly depressurized and 10 mL of a 10% aqueous NH_4Cl solution was added. The mixture was stirred for 10 min in order to quench the catalyst. The organic layer was separated, dried with Na_2SO_4, filtered through a plug of silica gel and subjected to GC analysis, to determine the products

distribution and enantiomeric excesses, using *Agilent HP-5* and *Astec Chiraldex DM* columns. The program conditions for each instrument and the respective retention times are presented below.

Achiral GC (*Agilent-5890 Series II* chromatographer equipped with *HP-5* column; program: starting temperature 40°C (hold-time 2 min), heating rate 10°C/min until 250°C (hold-time 20 min); carrier gas: helium).

styrene (**3.7**): 14.2 min;

3-phenylbut-1-ene (**3.14**): 16.8 min;

(*Z*)-2-phenylbut-2-ene (**3.15**): 16.9 min;

(*E*)-2-phenylbut-2-ene (**3.16**): 18.6 min:

cis-1,3-diphenylbut-1-ene (**3.17**): 30.0 min.

Chiral GC (*Agilent-5890 Series II* chromatographer equipped with *Astec Chiraldex DM* column; program: starting temperature 60°C (hold-time 30 min), heating rate 10°C/min until 120°C (hold-time 20 min); carrier gas: helium).

(*R*)-3-phenylbut-1-ene ((*R*)-**3.14**): 18.9 min;

(*S*)-3-phenylbut-1-ene ((*S*)-**3.14**): 19.4 min.

The conversions, chemo- and enantioselectivity were calculated through the following expressions:

$$Conversion\,(\%) = \left(\frac{total\ peak\ area\ -\ substrate\ peak\ area}{total\ peak\ area} \right) \times 100$$

$$Chemoselectivity\,(\%) = \left(\frac{3\text{-}phenylbut\text{-}1\text{-}ene\ peak\ area}{sum\ of\ all\ \ products\ peaks\ areas} \right) \times 100$$

$$enantiomeric\ excess(\%) = \left(\frac{major\ enantiomer\ -\ minor\ enantiomer}{major\ enantiomer\ +\ minor\ enantiomer} \right) \times 100$$

5.4 Experimental (referring to Chapter 4)

In this section, the specific procedures for each catalytic aminocarbonylation reaction (reported in Chapter 4) are described, as well as the full characterization of the new carboxamide-functionalized products.

5.4.1 General procedure of Pd-catalyzed aminocarbonylation reactions

The catalytic aminocarbonylation reactions were performed in both Coimbra and Pécs laboratories, following standard procedures.[29,30]

Figure 5.4 – Autoclave for high-pressure catalytic aminocarbonylation reactions in the Department of Inorganic Chemistry, University of Pécs.

Catalytic aminocarbonylation under high carbon monoxide pressure

In a typical experiment,[29] the palladium precursor $Pd(OAc)_2$, 2 molar equiv. phosphorus ligand, the iodo-substrate (1 mmol), the *N*-nucleophile (1.1 – 3 molar equiv. of monoamine, or 0.5 molar equiv. of diamine) and triethylamine (0.5 mL) were dissolved in DMF under argon in a stainless steel autoclave. The autoclave was pressurized with the desired pressure of carbon monoxide. The reaction was conducted for the given reaction time, upon stirring at the selected temperature, and subsequently analyzed by GC, GC-MS and NMR. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform and washed with

water. The organic phase was dried over Na_2SO_4, filtered and evaporated to a crystalline material or to a waxy residue. All compounds were subjected to column chromatography (silica gel 60 (Merck), 0.063-0.200 mm), or simply recrystallized from solvents (the exact ratios are specified below for each compound).

Catalytic aminocarbonylation under atmospheric carbon monoxide pressure

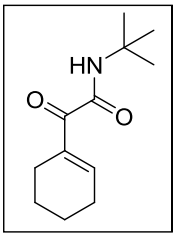
In a typical experiment,[30] $Pd(OAc)_2$, phosphorus ligand, iodo-substrate, *N*-nucleophile and triethylamine were dissolved in DMF (in similar quantities used for high pressure experiments – *see above*), under argon in a 100 mL three-necked flask equipped with a gas inlet, reflux condenser with a balloon (filled with argon) at the top. Then, the atmosphere was changed to carbon monoxide. Finally, the reaction was conducted for the given reaction time, upon stirring at the selected temperature, and subsequently analyzed by GC-MS and NMR. At the end of the reactions, the mixture was evaporated to dryness and worked-up as previously described.

5.4.2 Synthesis of cyclohexenyl-glyoxylamides

Following the typical procedure described above, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), monophosphite ligand (**L2**-OMe) (57.9 mg, 0.05 mmol), 1-iodocyclohexene (1 mmol), amine nucleophile (1.1-3.0 mmol) and 0.5 ml triethylamine were dissolved in DMF (10 mL), under argon, in a 100 mL autoclave. The autoclave was pressurized with 110 bar of carbon monoxide, and the reaction was conducted for 2 h, upon stirring at 30°C.[31]

***N*-*tert*-butyl-2-(cyclohex-1-enyl)-2-oxoacetamide (4.6a)**

1-Iodocyclohexene **4.4** was aminocarbonylated, using 3 mmol of *tert*-butylamine **a**, as *N*-nucleophile. When the reaction was finished, the solvent was evaporated under reduced pressure and the residue was dissolved in chloroform (20 ml) and washed with water (3x20 mL). After drying over Na_2SO_4, filtration and solvent evaporation, the mixture was subjected to column chromatography in silica gel, using a 2% EtOAc/$CHCl_3$ mixture as eluent. The target compound **4.6a** was obtained as a beige crystalline solid, in 60% isolated yield (0.125 g, 0.60 mmol).[31]

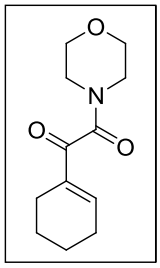


4.6a

^{1}H NMR (400.1 MHz, $CDCl_3$), δ/ppm: 7.80 (1H, br s, =C*H*), 6.68 (1H, br s, N*H*), 2.32 (2H, m, CH_2), 2.23 (2H, br s, CH_2); 1.65 (4H, m, 2xCH_2); 1.39 (9H, s, C(CH_3)$_3$); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 189.1, 162.0, 149.7, 135.5, 51.4, 28.3, 26.7, 23.1, 21.7, 21.2; **IR (KBr (cm^{-1}))**: 3274 (NH); 1669 (CO); 1646 (CON); **MS m/z (rel. int.)**: 209 (12%), 194 (2%), 153 (18%), 109 (100%), 81(46%); 57 (32%); **Elem. Anal.** calcd. for $C_{12}H_{19}NO_2$: C 68.87, H 9.15, N 6.69; found: C 68.72, H 9.01; N 6.40; **Mp**: 81-82°C; **Rf:** 0.48 (2% EtOAc/$CHCl_3$).

1-cyclohexenyl-2-morpholinoethane-1,2-dione (4.6c)

A similar procedure was carried out, but using 1.5 mmol of morpholine **c**, as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a 20% EtOAc/$CHCl_3$ mixture as eluent, the target compound **4.6c** was obtained as an off-white crystalline solid, in 62% isolated yield (0.138 g, 0.62 mmol).[31]



4.6c

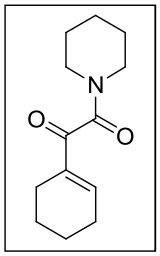
^{1}H NMR (400.1 MHz, $CDCl_3$), δ/ppm: 6.93 (1H,br s, =C*H*), 3.64-3.74 (6H, m, 3xCH_2), 3.30 (2H, t, 4.8 Hz, NCH_2), 2.35 (2H, br s, CH_2), 2.26 (2H, br s, CH_2), 1.66 (4H, m, 2xCH_2); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 193.1, 166.1, 148.9, 137.0, 66.7, 66.6, 46.3, 41.4, 26.5, 21.8, 21.4, 21.3; **IR (KBr (cm^{-1}))**: 1654 (CO); 1644 (CON); 1626 (C=C); **MS m/z (rel. int.)**: 223 (31%), 194 (2%), 109 (100%), 81(49%), 70 (19%), 53(10%); **Elem. Anal.** calcd. for $C_{12}H_{17}NO_3$: C 64.55, H 7.67, N 6.27; found: C 64.37, H 7.51 N, 6.05; **Mp**: 109-110°C; **Rf**: 0.40 (20% EtOAc/$CHCl_3$).

1-cyclohexenyl-2-(piperidin-1-yl)ethane-1,2-dione (4.6d)

The same procedure was carried out, but using 1.5 mmol of piperidine **d**, as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a 10% EtOAc/$CHCl_3$ mixture as eluent, the target compound **4.6d** was obtained as a yellow crystalline solid, in 66% isolated yield (0.146 g, 0.66 mmol).[31]

^{1}H NMR (400.1 MHz, $CDCl_3$), δ/ppm: 6.29 (1H, br s, =C*H*), 3.61 (2H, t, 5.2Hz, NCH_2), 3.21 (2H, t, 5.2 Hz, NCH_2), 2.38 (4H, m, 2xCH_2), 1.56-1.65 (10H, m, 5xCH_2); **^{13}C NMR (100.6 Hz, $CDCl_3$), δ/ppm**: 193.9, 166.1, 148.2, 136.9, 47.1, 42.0, 26.5, 26.2, 25.4, 24.4,

21.8, 21.4, 21.3; **IR (KBr (cm^{-1}))**: 1658 (CO), 1641 (CON); **MS m/z (rel. int.)**: 221 (28%), 192 (6%), 109 (100%), 81(48%), 69 (46%), 53(15%); **Elem. Anal.** calcd. for $C_{13}H_{19}NO_2$: C 70.56, H 8.65, N 6.33; found: C 70.40, H 8.77, N 6.17; **Mp**: 77-78°C; **Rf**: 0.48 (10% EtOAc/$CHCl_3$).



4.6d

5.4.3 Synthesis of conduritol-derived carboxamides

The halogenated cyclohexenetetraol derivatives **4.8**, **4.9** and **4.10** were synthesized via biotransformation of bromo- or iodobenzene with *Pseudomonas putida* F39/D,[2] by Doctor V. Schapiro and Doctor V. Heguaburu,[32] in the laboratory of Prof. Doctor E. Pandolfi (UdeLaR, Montevideo, Uruguay).

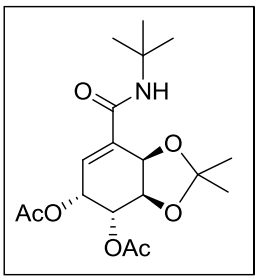
In a typical aminocarbonylation reaction, $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), PPh_3 (7.9 mg, 0.05 mmol) and the halogenated cyclohexenetetraol derivative (0.30 mmol), were placed in the autoclave. After three cycles of CO/vacuum, the amine nucleophile (0.33-0.90 mmol) and 0.25 ml triethylamine dissolved in DMF (7 mL) under N_2 atmosphere were added via *cannula*, and the autoclave was pressurized with 30 bar of carbon monoxide. The reaction was conducted for 24 h, upon stirring at 100°C.

(3a*R*,4*R*,5*R*,7a*R*)-7-(*tert*-butylcarbamoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate (4.11a)

The aminocarbonylation of **4.8** was carried out, using 0.9 mmol of *tert*-butylamine **a**, as *N*-nucleophile. At the end of the reaction, palladium metallic particles were filtered off. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL), then washed with water (3×20 mL), dried over Na_2SO_4 and concentrated to a red/orange waxy oil. After purification by column chromatography in silica gel, using a mixture of ethyl acetate/*n*-hexane (2:3) as eluent, the target compound **4.11a** was obtained as a yellow oil, in 50% isolated yield (0.055 g, 0.15 mmol).[33]

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.64 (1H, d, 4.8 Hz, C*H*=C), 6.60 (1H, br s, N*H*), 5.67 (1H, dd, 3.8 Hz, 4.8 Hz, C=CH-C*H*-OAc), 5.40 (1H, dd, 3.8 Hz, 6.6 Hz, C-O-CH-C*H*-OAc), 4.87 (1H, d, 5.8 Hz, CH=C-C*H*-O-C), 4.44 (1H, dd, 5.8 Hz, 6.6Hz, AcO-CH-C*H*-O-C), 2.07

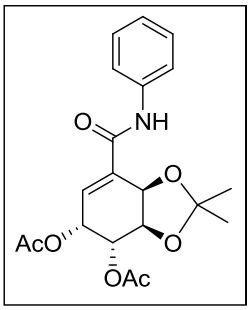
(3H, s, O=C-CH_3), 2.05 (3H, s, O=CCH_3), 1.44 (3H, s, O-C-CH_3), 1.42 (3H, s, O-C-CH_3), 1.40 (9H, s, *t*-Bu); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 170.2 (O-*C*=O), 169.9 (O-*C*=O), 164.4 (NH-*C*=O), 134.8 (CH=*C*-C=O), 131.0 (AcO-CH-*C*H=C), 110.7 (O-*C*-O), 73.4 (AcO-CH-*C*H-O-C), 71.5 (CH=C-*C*H-O-C), 69.5 (AcO-*C*H-CH-O-C), 68.2 (C=CH-*C*H-OAc), 51.4 (*C*(CH_3)$_3$), 28,7 (3C, C(*C*H_3)$_3$), 27.6 (O-C-*C*H_3), 26.1 (O-C-*C*H_3), 20.8 (O=C-*C*H_3), 20.7 (O=C-*C*H_3); **HRMS (ESI):** m/z calcd. for $C_{18}H_{27}NO_7Na$ $[M+Na]^+$: 392.1680, found: 392.1684; **$[\alpha]_D^{25}$**: - 50.0 (*c* 0.5, CH_2Cl_2); **Rf**: 0.35 (EtOAc/*n*-hexane 2:3).



4.11a

(3a*R*,4*R*,5*R*,7a*R*)-2,2-dimethyl-7-(phenylcarbamoyl)-3a,4,5,7a-tetrahydrobenzo[*d*] [1,3]dioxole-4,5-diyl diacetate (4.11b)

The aminocarbonylation of **4.8** was carried out, using 0.6 mmol of aniline **b**, as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a mixture of ethyl acetate/*n*-hexane (1:9) as eluent, the target compound **4.11b** was obtained as a yellow oil, in 45% isolated yield (0.053 g, 0.136 mmol).[33]

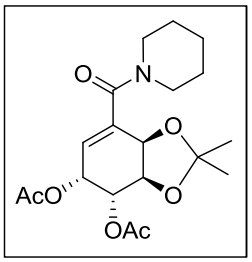


4.11b

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 8.69 (1H, br s, N*H*), 7.57-7.58 (2H, m, Ar), 7.33-7.36 (2H, m, Ar), 7.12-7.16 (1H, m, Ar), 6.82 (1H, d, 3.3 Hz, C*H*=C), 5.75 (1H, dd, 3.3 Hz, 3.7 Hz, C=CH-C*H*-OAc), 5.52 (1H, dd, 3.7 Hz, 6.0 Hz, C-O-CH-C*H*-OAc), 5.01 (1H, d, 5.5 Hz, CH=C-C*H*-O), 4.51 (1H, dd, 5.5 Hz, 6.0 Hz, AcO-CH-C*H*-O-C), 2.08 (3H, s, O=C-CH_3), 2.07 (3H, s, O=C-CH_3), 1.48 (3H, s, O-C-CH_3), 1.47 (3H, s, O-C-CH_3); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 170.1 (O-*C*=O), 169.9 (O-*C*=O), 166.3 (NH-*C*=O), 137.6 (AcO-CH-*C*H=C), 133.7 (CH=*C*-C=O), 133.2 (C_{Ar}), 129.1 (C_{Ar}), 124.8 (C_{Ar}), 120.3 (C_{Ar}), 111.7 (O-*C*-O), 73.6 (AcO-CH-*C*H-O-C), 71.2 (CH=C-*C*H-O-C), 69.2 (AcO-*C*H-CH-O-C), 65.7 (C=CH-*C*H-OAc), 27.1 (O-C-*C*H_3), 26.2 (O-C-*C*H_3), 20.8 (2C, O=C-*C*H_3); **HRMS (ESI)**: m/z calcd. for $C_{20}H_{23}NO_7Na$ $[M+Na]^+$: 412.1367, found: 412.1355; $[\alpha]_D^{25}$: - 30.0 (*c* 0.7, CH_2Cl_2); **Rf**: 0.50 (EtOAc/*n*-hexane 1:9).

(3a*R*,4*R*,5*R*,7a*R*)-2,2-dimethyl-7-(piperidine-1-carbonyl)-3a,4,5,7a-tetrahydrobenzo [*d*][1,3]dioxole-4,5-diyl diacetate (4.11d)

The aminocarbonylation of **4.8** was carried out, using 0.45 mmol of piperidine **b**, as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a mixture of chloroform/EtOAc 5:1 as eluent, the target compound **4.11d** was obtained as an orange oil, in 56% isolated yield (0.064 g, 0.168 mmol).[33]



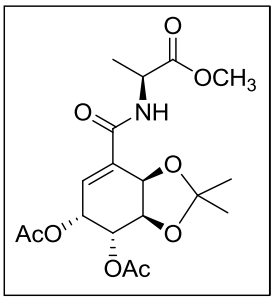
4.11d

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 5.77 (1H, d, 4.8 Hz, C*H*=C), 5.49 (1H, dd, 3.6 Hz, 4.8 Hz, C=CH-C*H*-OAc), 5.12 (1H, dd, 3.6 Hz, 8.0 Hz, C-O-CH-C*H*-OAc), 5.03 (1H, d, 6.0 Hz, CH=C-C*H*-O), 4.44 (1H, dd, 6.0 Hz, 8.0 Hz, AcO-CH-C*H*-O-C), 3.39-3.51 (4H, m, CH_2-N-CH_2), 2.03 (3H, s, O=C-CH_3), 1.98 (3H, s, O=C-CH_3), 1.45-1.53 (6H, m, N-CH_2-(CH_2)$_3$-CH_2), 1.37 (3H, s, O-C-CH_3), 1.30 (3H, s, O-C-CH_3); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 169.5 (O-*C*=O), 169.1 (O-*C*=O), 166.1 (N-*C*=O), 135.6 (CH=*C*-C=O), 132.0 (AcO-CH-*C*H=C), 109.2 (O-*C*-O), 71.6 (AcO-CH-*C*H-O-C), 71.5 (CH=C-*C*H-O-C), 69.8 (AcO-*C*H-CH-O-C), 64.7 (C=CH-*C*H-OAc), 45.8 (N-*C*H_2), 39.6 (N-*C*H_2), 26.5 (O-C-*C*H_3), 25.5 (N-CH_2-*C*H_2) 25.3 (N-CH_2-*C*H_2), 24.4 (O-C-*C*H_3), 24.1 (N-CH_2-CH_2-*C*H_2), 19.9 (O=C-*C*H_3), 19.7 (O=C-*C*H_3); **HRMS (ESI)**: m/z calcd. for $C_{19}H_{27}NO_7Na$ $[M+Na]^+$: 404.1680, found: 404.1666; **$[\alpha]_D^{25}$**: - 55.0 (*c* 1.0, CH_2Cl_2); **Rf**: 0.52 ($CHCl_3$:EtOAc 5:1).

(3a*R*,4*R*,5*R*,7a*R*)-7-((*S*)-1-methoxy-1-oxopropan-2-ylcarbamoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate (4.11e)

The aminocarbonylation of **4.10** was carried out, under 1 bar CO and 50°C, using 0.33 mmol of L-alanine methyl ester **e** (hydrochloride salt), as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a mixture of chloroform/EtOAc 5:1 as eluent, the target compound **4.11e** was obtained as a yellow oil, in 85% isolated yield (0.102 g, 0.255 mmol).[33]

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.24 (1H, d, 6.8 Hz, N*H*), 6.72 (1H, d, 3.2 Hz, C*H*=C), 5.69 (1H, br s , C=CH-C*H*-OAc), 5.43-5.45 (1H, m, C-O-CH-C*H*-OAc), 4.94 (1H, d, 5.4 Hz, CH=C-C*H*-O), 4.64-4.71 (1H, m, CH_3-C*H*-NH), 4.45 (1H, dd, 5.4 Hz, 6.0 Hz, AcO-CH-C*H*-O-C), 3.77 (3H, s, NH-COOCH_3), 2.06 (3H, s, O=C-CH_3), 2.05 (3H, s, O=C-CH_3), 1.46 (3H, s, HN-CH-CH_3), 1.45 (3H, s, O-C-CH_3), 1.44 (3H, s, O-C-CH_3); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 173.0 (O=*C*-OCH_3), 169.8 (O-*C*=O), 169.6 (O-*C*=O), 164.3 (HN-*C*=O), 133.2

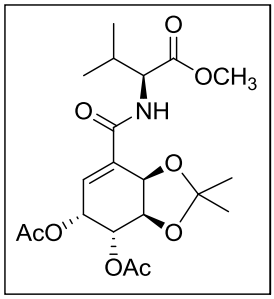


4.11e

(CH=*C*-C=O), 132.1 (AcO-CH-*C*H=C), 110.7 (O-*C*-O), 73.2 (AcO-CH-*C*H-O-C), 70.9 (CH=C-*C*H-O-C), 69.2 (AcO-*C*H-CH-O-C), 65.7 (C=CH-*C*H-OAc), 52.3 (O*C*H_3), 48.1 (HN-*C*H-CH_3) 27.4 (O-C-*C*H_3), 25.9 (O-C-*C*H_3), 20.6 (O=C-*C*H_3), 20.5 (O=C-*C*H_3), 18.1 (HN-CH-*C*H_3); **HRMS (ESI)**: m/z calcd. for $C_{18}H_{25}NO_9Na$ $[M+Na]^+$: 422.1422, found: 422.1437; **$[\alpha]_D^{25}$**: - 50.0 (*c* 2.0, $CHCl_2$); **Rf**: 0.45 ($CHCl_3$/EtOAc 5:1).

(3a*R*,4*R*,5*R*,7a*R*)-7-((*S*)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)-2,2-dimethyl -3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate (4.11f)

The aminocarbonylation of **4.10** was carried out, under 1 bar CO and 50°C, using 0.33 mmol of L-valine methyl ester **f** (hydrochloride salt), as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a mixture of chloroform/EtOAc 6:1 as eluent, the target compound **4.11f** was obtained as a yellow oil, in 66% isolated yield (0.085 g, 0.199 mmol).[33]

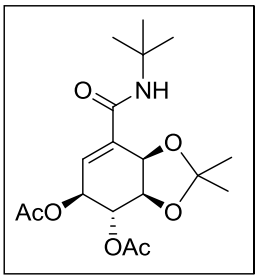


4.11f

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.23 (1H, d, 8.4 Hz, N*H*), 6.72 (1H, br s, C*H*=C), 5.70 (1H, br s, C=CH-C*H*-OAc), 5.46 (1H, br s, C-O-CH-C*H*-OAc), 4.95 (1H, d, 4.8 Hz, CH=C-C*H*-O), 4.61-4.64 (1H, m, (NH-C*H*-CH(CH_3)$_2$), 4.46 (1H, dd, 5.6 Hz, 5.6 Hz, AcO-CH-C*H*-O-C), 3.75 (3H, s, NH-COOC*H*$_3$), 2.22-2.26 (1H, m, NH-CH-C*H*(CH_3)$_2$) 2.06 (3H, s, O=C-C*H*$_3$), 2.05 (3H, s, O=C-C*H*$_3$), 1.43 (6H, s, O-C-C*H*$_3$), 0.94 (6H, dd, 6.8 Hz, 2.2 Hz, NH-CH-CH(C*H*$_3$)$_2$); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 171.9 (O=*C*-OCH$_3$), 169.8 (O-*C*=O), 169.5 (O-*C*=O), 164.4 (HN-*C*=O), 132.9 (CH=*C*-C=O), 132.1 (AcO-CH-*C*H=C), 110.6 (O-*C*-O), 73.2 (AcO-CH-*C*H-O-C), 71.0 (CH=C-*C*H-O-C), 69.0 (AcO-*C*H-CH-O-C), 65.6 (C=CH-*C*H-OAc), 57.1 (NH-*C*H-CH-(CH_3)$_2$), 51.9 (O*C*H_3), 30.8 (HN-CH-*C*H-(CH_3)$_2$), 27.4 (O-C-*C*H_3), 25.9 (O-C-*C*H_3), 20.5 (O=C-*C*H_3), 20.4 (O=C-*C*H_3), 18.0 (HN-CH-CH-(*C*H_3)$_2$), 16.7 (HN-CH-CH-(*C*H_3)$_2$); **HRMS (ESI)**: m/z calcd. for $C_{20}H_{30}NO_9$ $[M+H]^+$: 428.1915, found: 428.1915; **$[\alpha]_D^{25}$**: - 45.0 (*c* 2.0, $CHCl_2$); **Rf**: 0.45 ($CHCl_3$/EtOAc 6:1).

(3a*R*,4*R*,5*S*,7a*R*)-7-(*tert*-butylcarbamoyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate (4.12a)

The aminocarbonylation of **4.9** was performed, using 0.9 mmol of *tert*-butylamine **a**, as *N*-nucleophile After work-up and purification by column chromatography in silica gel, using a mixture of EtOAc/*n*-hexane 2:3 as eluent, the target compound **4.12a** was obtained as a yellow oil, in 52% isolated yield (0.058 g, 0.156 mmol).[33]



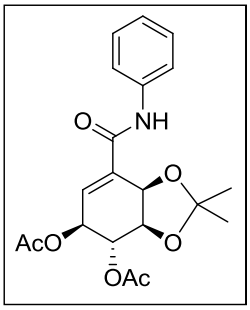
4.12a

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.63 (1H d, 2.0 Hz, C*H*=C), 6.48 (1H, br s, N*H*), 5.49 (1H, dd, *2*.0 Hz, 8.8 Hz, C=CH-C*H*-OAc), 5.23 (1H, dd, 8.8 Hz, 9.2 Hz, C-O-CH-C*H*-OAc), 4.82 (1H, d, 6.0 Hz CH=C-C*H*-O-C), 4.29 (1H, dd, 6.0 Hz, 9.2 Hz, AcO-CH-C*H*-O-C), 2.10 (3H, s, O=C-CH_3), 2.09 (3H, s, O=C-CH_3), 1.55 (3H, s, O-C-CH_3), 1.44 (3H, s, O-C-CH_3), 1.39 (9H, s, *t*-Bu); **^{13}C NMR (100 MHz, $CDCl_3$), δ/ppm**: 170.2 (O-*C*=O), 170.1 (O-*C*=O), 163.8 (NH-*C*=O), 135.0 (AcO-CH-*C*H=C), 132.1 (CH=*C*-C=O), 111.9 (O-*C*-O), 75.6 (AcO-CH-*C*H-O-C), 71.8 (CH=C-*C*H-O-C), 71.4 (AcO-*C*H-CH-O-C), 69.9 (C=CH-*C*H-OAc), 51.4 (*C*$(CH_3)_3$), 28.6 (3C, C(*C*$H_3)_3$), 27.8 (O-C-*C*H_3), 26.4 (O-C-*C*H_3), 20.9, 20.8 (2C, O=C-*C*H_3); **HRMS (ESI)**: m/z calcd. for $C_{18}H_{27}NO_7Na$ $[M+Na]^+$: 392.1680. Found: 392.1672; **$[\alpha]_D^{25}$**: + 100.0 (*c* 0.6, CH_2Cl_2); **Rf**: 0.42 (EtOAc/*n*-hexane 2:3).

(3a*R*,4*R*,5*S*,7a*R*)-2,2-dimethyl-7-(phenylcarbamoyl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diyl diacetate (4.12b)

The aminocarbonylation of **4.9** was carried out, using 0.6 mmol of aniline **b**, as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a mixture of ethyl acetate/*n*-hexane (1:9) as eluent, the target compound **4.12b** was obtained as a yellow oil, in 27% isolated yield (0.032 g, 0.082 mmol).[33]

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 8.40 (1H, br s, N*H*), 7.47-7.49 (2H, m, Ar), 7.26-7.30 (2H, m, Ar), 7.06-7.10 (1H, m, Ar), 6.75 (1H, d, 1.2 Hz, C*H*=C,), 5.49 (1H, d, 8.8 Hz, C=CH-C*H*-OAc), 5.21 (1H, dd, 8.8Hz, 9.2 Hz, C-O-CH-C*H*-OAc), 4.91 (1H, d, 6.0 Hz, CH=C-C*H*-O-C), 4.39 (1H, dd, 6.0 Hz, 9.2 Hz, AcO-CH-C*H*-O-C), 2.05 (3H, s, O=C-CH_3), 2.02 (3H, s,

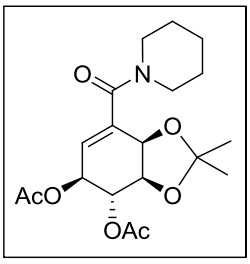


4.12b

O=C-C*H*$_3$), 1.53 (3H, s, O-C-C*H*$_3$), 1.43 (3H, s, O-C-C*H*$_3$); **^{13}C NMR (100 MHz, CDCl$_3$), δ/ppm**: 169.3 (2C, O-*C*=O), 161.9 (NH-*C*=O), 136.8 (CH=*C*-C=O), 136.1 (AcO-CH-*C*H=C), 130.9 (C$_{Ar}$), 128.4 (C$_{Ar}$), 124.1 (C$_{Ar}$), 119.6 (C$_{Ar}$), 111.7 (O-*C*-O), 74.9 (AcO-CH-*C*H-O-C), 71.0 (CH=C-*C*H-O-C), 70.5 (AcO-*C*H-CH-O-C), 69.0 (C=CH-*C*H-OAc), 26.8 (O-C-*C*H$_3$), 25.5 (O-C-*C*H$_3$), 19.9 (O=C-*C*H$_3$), 19.7 (O=C-*C*H$_3$); **HRMS (ESI)**: m/z calcd. for $C_{20}H_{23}NO_7Na$ [M+Na]$^+$: 412.1367, found: 412.1357; **[α]$_D^{25}$**: + 110.0 (*c* 0.5, CH_2Cl_2); **Rf**: 0.45 (EtOAc/*n*-hexane 1:9).

(3a*R*,4*R*,5*S*,7a*R*)-2,2-dimethyl-7-(piperidine-1-carbonyl)-3a,4,5,7a-tetrahydrobenzo [*d*][1,3]dioxole-4,5-diyl diacetate (4.12d)

The aminocarbonylation of **4.9** was carried out, using 0.45 mmol of piperidine **b**, as *N*-nucleophile. After work-up and purification by column chromatography in silica gel, using a mixture of chloroform/EtOAc 5:1 as eluent, the target compound **4.12d** was obtained as an orange oil, in 53% isolated yield (0.061 g, 0.136 mmol).[33]



4.12d

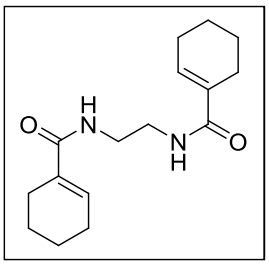
^{1}H NMR (400 MHz, CDCl$_3$), δ/ppm): 5.66 (1H,br s, C*H*=C), 5.31 (1H, d, 8.8 Hz C=CH-C*H*-OAc), 5.22 (1H, dd, 8.8 Hz, 9.0 Hz, C-O-CH-C*H*-OAc), 4.98 (1H, d, 6.4 Hz, CH=C-C*H*-O), 4.28 (1H, dd, 6.4 Hz, 9.0 Hz, AcO-CH-C*H*-O-C), 3.49-3.52 (2H, m, C*H*$_2$-N-CH$_2$), 3.26-3.28 (2H, m, CH$_2$-N-C*H*$_2$), 2.08 (3H, s, O=C-C*H*$_3$), 2.04 (3H, s, O=C-C*H*$_3$), 1.42-1.62 (6H, m, N-CH$_2$-(C*H*$_2$)$_3$-CH$_2$), 1.48 (3H, s, O-C-C*H*$_3$), 1.33 (3H, s, O-C-C*H*$_3$); **^{13}C NMR (100 MHz, CDCl$_3$), δ/ppm)**: 169.4 (O-*C*=O), 169.2 (O-*C*=O), 167.2 (N-*C*=O), 131.8 (CH=*C*-C=O), 131.0 (AcO-CH-*C*H=C), 110.5 (O-*C*-O), 74.1 (AcO-CH-*C*H-O-C), 71.7 (CH=C-*C*H-O-C), 70.8 (AcO-*C*H-CH-O-C), 69.4 (C=CH-*C*H-OAc), 46.2 (N-*C*H$_2$), 40.8 (N-*C*H$_2$), 26.8 (O-C-*C*H$_3$), 25.4 (N-CH$_2$-*C*H$_2$), 25.1 (O-C-*C*H$_3$), 24.3 (N-CH$_2$-*C*H$_2$), 23.4 (N-CH$_2$-CH$_2$-*C*H$_2$), 20.0 (O=C-*C*H$_3$), 19.8 (O=C-*C*H$_3$); **HRMS (ESI)**: m/z calcd. for $C_{19}H_{27}NO_7Na$ [M+Na]$^+$: 404.1680, found: 404.1677; **[α]$_D^{25}$**: + 115 (*c* 1.0, CH_2Cl_2); **Rf**: 0.40 ($CHCl_3$/EtOAc 5:1).

5.4.4 Synthesis of dicarboxamides

In a typical experiment,[34] $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), triphenylphosphine (13.2 mg, 0.05 mmol), the iodo-substrate (1 mmol), diamine nucleophile (0.5 mmol) and triethylamine (0.5 ml) were dissolved in DMF (10 mL), under argon, in a 100 mL autoclave. The autoclave was then pressurized to 30 bar of carbon monoxide and the reaction was conducted for 3 h (or 5 h), upon stirring at 100°C.

N,*N*'-(ethane-1,2-diyl)dicyclohex-1-enecarboxamide (4.13g)

The diaminocarbonylation of substrate **4.4** was carried out, using 0.5 mmol of 1,2-diaminoethane **g**, as *N*-nucleophile. After 3h, the autoclave was slowly depressurized and palladium metallic particles were filtered off. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL), then washed with water (3×20 mL), dried over Na_2SO_4 and concentrated to a solid material. After purification by column chromatography in silica gel, using as eluent a mixture of ethyl acetate/chloroform (2:1), the target compound **4.13g** was obtained as a white solid, in 58% isolated yield (0.080 g, 0.29 mmol).



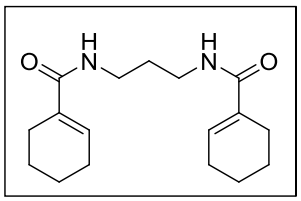
4.13g

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.67 (2H, br s, C=C*H*), 6.53 (2H, br s, N*H*), 3.47 (4H, d, 2.4 Hz, N-CH_2CH_2-N), 2.19-2.24 (4H, m, CH=CCH_2), 2.12-2.18 (4H, m, C=CHCH_2), 1.65-1.71 (4H, m, CH=CCH$_2$CH_2), 1.55-1.61 (4H, m, C=CHCH$_2$CH_2); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 169.9, 134.5, 132.7, 40.7, 25.6, 24.3, 22.3, 21.7; **IR (KBr (cm^{-1}))**: 3298 (v br, NH), 1659 (CO), 1611 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{16}H_{25}N_2O_2$ $[M+H]^+$: 277.1911, found: 277.1908; **Mp**: 218-220°C; **Rf**: 0.20 (EtOAc/$CHCl_3$ 2:1).

N,*N*'-(propane-1,3-diyl)dicyclohex-1-enecarboxamide (4.13h)

Following a similar procedure, the diaminocarbonylation of **4.4** was carried out, using 0.5 mmol of 1,3-diaminopropane **h**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of chloroform/methanol

(25:1), the target compound **4.13h** was obtained as a beige solid, in 53% isolated yield (0.077 g, 0.265 mmol).

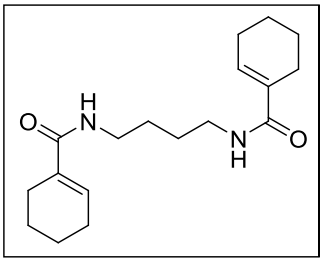


4.13h

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.71 (2H, br s, N*H*), 6.66 (2H, s, C=C*H*), 3.31 (4H, dd, 5.6 Hz, 11.2 Hz, N-CH_2CH$_2$CH_2-N), 2.21-2.28 (4H, m, CH=CCH_2), 2.10-2.16 (4H, m, C=CHCH_2); 1.61-1.69 (6H, m, CH=CCH$_2$CH_2 + N-CH$_2$CH_2CH$_2$-N), 1.54-1.60 (4H, m, C=CHCH$_2$CH_2); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 169.4, 133.9, 133.1, 35.8, 30.0, 25.5, 24.3, 22.3, 21.6; **IR (KBr (cm^{-1}))**: 3315 (v br, NH), 1659 (CO), 1617 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{17}H_{27}N_2O_2$ $[M+H]^+$: 291.2067, found: 291.2077; **Mp**: 110-112 °C; **Rf**: 0.50 ($CHCl_3$/CH_3OH 25:1).

N,*N*'-(butane-1,4-diyl)dicyclohex-1-enecarboxamide (4.13i)

Following a similar procedure, the diaminocarbonylation of **4.4** was carried out, using 0.5 mmol of 1,4-diaminobutane **i** (hydrochloride salt), as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of ethyl acetate/chloroform (2:1), the target compound **4.13i** was obtained as a white solid, in 69% isolated yield (0.105 g, 0.345 mmol).



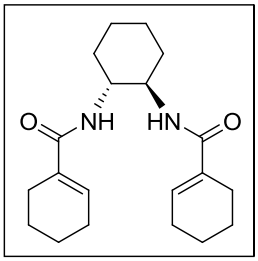
4.13i

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.64 (2H, s, C=C*H*), 5.91 (2H, br s, N*H*), 3.34-3-36 (4H, m, N-CH_2(CH$_2$)$_2$CH_2-N), 2.21-2.26 (4H, m, CH=CCH_2), 2.14-2.20 (4H, m, C=CHCH_2); 1.58-1.74 (12H, m, C=CHCH$_2$CH_2CH_2 + N-CH$_2$(CH_2)$_2$CH$_2$-N); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 168.9, 133.6, 133.2, 39.2, 27.2, 25.5, 24.4, 22.3, 21.7; **IR (KBr (cm^{-1}))**: 3344 (v, br, NH), 1662 (CO), 1616 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{18}H_{29}N_2O_2$ $[M+H]^+$: 305.2224, found: 305.2224; **Mp**: 202-205 °C; **Rf**: 0.25 (EtOAc/$CHCl_3$ 2:1).

N,*N*'-(cylohexane-*trans*-1,2-diyl)dicyclohex-1-enecarboxamide (4.13j)

Following a similar procedure, the diaminocarbonylation of **4.4** was carried out, using 0.5 mmol of *trans*-(±)-1,2-diaminocyclohexane **j**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of

chloroform/methanol (25:1), the target compound **4.13j** was obtained as a beige solid, in 52% isolated yield (0.086 g, 0.260 mmol).

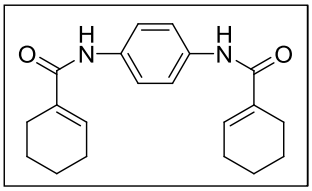


4.13j

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.58 (2H, s, C=C*H*), 6.20 (2H, br s, N*H*), 3.74 (2H, br s, N-C*H*-C*H*-N), 2.11-2.17 (8H, m, CH=CCH_2+C=CHCH_2), 1.54-1.78 (12H, m, C=CHCH_2CH_2CH_2 + N-CHCH_2(CH_2)$_2$CH_2CH-N), 1.24-1.39 (4H, m, N-CHCH_2(CH_2)$_2$CH_2CH-N); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 169.4, 134.1, 133.0, 54.0, 32.5, 25.6, 24.9, 24.3, 22.3, 21.7; **IR (KBr (cm^{-1}))**: 3320 (v br, NH), 1660 (CO), 1619 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{20}H_{31}N_2O_2$ $[M+H]^+$: 331.2380, found: 331.2377; **Mp**: 248-250°C; **Rf**: 0.55 ($CHCl_3$/CH_3OH 25:1).

N,*N*'-(1,4-phenylene)dicyclohex-1-enecarboxamide (4.13k)

Following a similar procedure, the diaminocarbonylation of **4.4** was carried out, using 0.5 mmol of 1,4-diaminobenzene **k**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of chloroform/methanol (10:1), the target compound **4.13k** was obtained as a beige solid, in 55% isolated yield (0.089 g, 0.274 mmol).



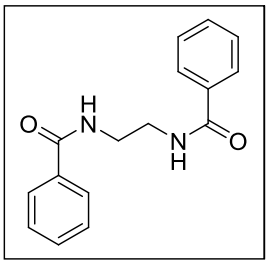
4.13k

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.52 (4H, s, Ph-*H*), 7.36 (2H, br s, N*H*), 6.74 (2H, br s, C=C*H*), 2.35 (4H, d, 2.0 Hz, CH=CCH_2), 2.22 (4H, d, 2.8 Hz, C=CHCH_2), 1.71-1.76 (4H, m, CH=CCH$_2$CH_2), 1.61-1.66 (4H, m, C=CHCH$_2$CH_2); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 166.7, 134.4, 134.1, 133.7, 120.7, 25.7, 24.5, 22.3, 21.6; **IR (KBr (cm^{-1}))**: 3320 (v br, NH), 1656 (CO), 1623 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{20}H_{25}N_2O_2$ $[M+H]^+$: 325.1911, found: 325.1917; **Mp**: 240-242 °C (decomp.); **Rf**: 0.20 ($CHCl_3$/CH_3OH 10:1).

N,*N*'-(ethane-1,2-diyl)dibenzamide (4.14g)

Following a similar procedure, the diaminocarbonylation of **4.1** was carried out, using 0.5 mmol of 1,2-diaminoethane **g**, as *N*-nucleophile. After recrystallization from

ethyl acetate/diethyl ether (1:2), the target compound **4.14g** was obtained as a white solid, in 42% isolated yield (0.056 g, 0.209 mmol).

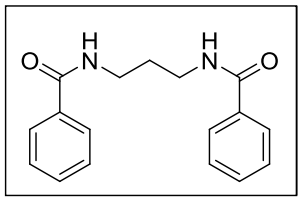


4.14g

^{1}H NMR (400 MHz, DMF-d$_7$), δ/ppm: 8.69 (2H, br s, N*H*), 7.97 (4H, d, 7.2 Hz, Ph-*ortho*), 7.46-7.58 (6H, m, Ph-*meta*,*para*), 3.60-3.64 (4H, m, N-C*H*$_2$C*H*$_2$-N); **^{13}C NMR (100.6 MHz, DMF-d$_7$), δ/ppm**: 167.9, 136.0, 132.2, 129.4, 128.3, 40.8; **IR (KBr (cm^{-1}))**: 3296 (v br, NH), 1633 (CO); **HRMS (ESI)**: m/z calcd. for $C_{16}H_{16}N_2O_2Na$ $[M+Na]^+$: 291.1104, found: 291.1096; **Mp**: 228-220°C.

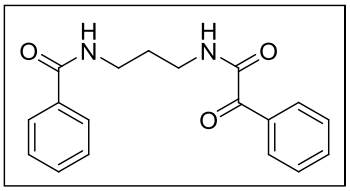
_N_,_N_'-(propane-1,3-diyl)dibenzamide (4.14h), _N_-(3-(2-oxo-2-phenylacetamido)propyl) benzamide (4.15h) and _N_,_N_'-(propane-1,3-diyl)bis(2-oxo-2-phenylacetamide) (4.16h)

The diaminocarbonylation of **4.1** was carried out, using 0.5 mmol of 1,3-diaminopropane **h**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of chloroform/ethyl acetate (2:1), three products were obtained: the target compound **4.14h**, as a beige solid in 35% isolated yield (0.049 g, 0.174 mmol); the compound **4.15h**, as a beige solid in 29% isolated yield (0.045 g, 0.145 mmol); and the compound **4.16h**, as a yellow oil, in 26% isolated yield (0.044 g, 0.130 mmol).



4.14h

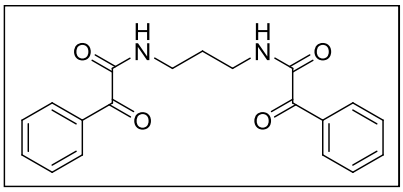
^{1}H NMR (400 MHz, CDCl$_3$), δ/ppm: 7.87 (4H, d, 7.2 Hz, Ph-*ortho*), 7.41-7.54 (6H, m, Ph-*meta*,*para*), 7.28 (2H, br s, N*H*), 3.51-3.58 (4H, m, N-C*H*$_2$CH$_2$C*H*$_2$-N), 1.75-1.85 (2H, m, N-CH$_2$C*H*$_2$CH$_2$-N); **^{13}C NMR (100.6 MHz, CDCl$_3$), δ/ppm**: 168.3, 134.4, 131.7, 128.7, 127.1, 36.4, 30.0; **HRMS (ESI)**: m/z calcd. for $C_{17}H_{19}N_2O_2$ $[M+H]^+$: 283.1441, found: 283.1434; **Mp**: 118-120°C; **Rf**: 0.15 ($CHCl_3$/EtOAc 2:1).



4.15h

^{1}H NMR (400 MHz, CDCl$_3$), δ/ppm: 8.25 (2H, d, 6.0 Hz, Ph-*ortho*), 7.89 (1H, br s, N*H*), 7.84 (2H, d, 6.0 Hz, Ph-*ortho*), 7.41-7.48 (5H, m, Ph-*meta*+Ph-*para*+N*H*), 7.37 (2H, t, 6.0 Hz, Ph-*meta*), 3.44-3.53 (4H, m, N-C*H*$_2$CH$_2$C*H*$_2$-N), 1.78-1.84 (2H, m, N-CH$_2$C*H*$_2$CH$_2$-N); **^{13}C NMR (100.6 MHz, CDCl$_3$), δ/ppm**: 188.0, 168.0, 163.3, 134.5, 134.4, 133.3, 131.5, 131.0, 128.6, 128.6, 127.1, 36.4, 36.2, 29.5; **HRMS**

(ESI): m/z calcd. for $C_{18}H_{18}N_2O_3$ $[M+H]^+$: 311.1390, found: 311.1395; **Mp**: 63-65 °C; **Rf**: 0.25 ($CHCl_3$/EtOAc 2:1).

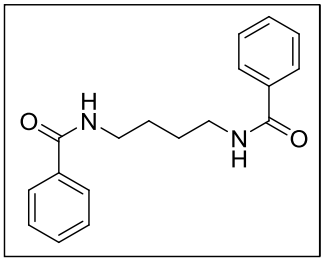


4.16h

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 8.33 (4H, d, 7.6 Hz, Ph-*ortho*), 7.60-7.64 (2H, m, Ph-*para*),7.45-7.50 (4H, m, Ph-*meta*), 7.40 (1H, br s, N*H*), 3.46-3.53 (4H, m, N-CH_2CH_2CH_2-N), 1.86-1.92 (2H, m, N-CH$_2$CH_2CH$_2$-N); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 187.7, 162.6, 134.6, 133.4, 131.3, 128.7, 36.4, 29.5; **HRMS (ESI)**: m/z found for $C_{19}H_{18}N_2O_4$ $[M+H]^+$: 339.1336; **Rf**: 0.5 ($CHCl_3$/EtOAc 2:1).

N,*N*'-(butane-1,4-diyl)dibenzamide (4.14i)

The diaminocarbonylation of **4.1** was performed, using 0.5 mmol of 1,4-diaminobutane **i** (hydrochloride salt), as *N*-nucleophile. After recrystallization from ethyl acetate/diethyl ether (1:2), the target compound **4.14i** was obtained as a white solid, in 45% isolated yield (0.067 g, 0.226 mmol).



4.14i

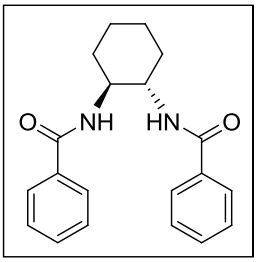
^{1}H NMR (400 MHz, DMF-d_7), δ/ppm: 8.49 (2H, br s, N*H*), 7.97 (4H, d, 7.2 Hz, Ph-*ortho*), 7.46-7.56 (6H, m, Ph-*meta*,*para*), 3.42-3.45 (4H, m, N-CH_2(CH$_2$)$_2$CH_2-N), 1.69 (4H, br s, N-CH$_2$(CH_2)$_2$CH$_2$-N); **^{13}C NMR (100.6 MHz, DMF-d_7), δ/ppm**: 167.5, 136.2, 132.1, 129.3, 128.3, 40.4, 28.1; **IR (KBr (cm^{-1}))**: 3318 (v br, NH), 1630 (CO); **HRMS (ESI)**: m/z calcd. for $C_{18}H_{20}N_2O_2Na$ $[M+Na]^+$: 319.1417, found: 319.1424; **Mp**: 172-174 °C.

N,*N*'-(cyclohexane-(1*S*,2*S*)-1,2-diyl)dibenzamide (4.14j)

The diaminocarbonylation of **4.1** was performed, using 0.5 mmol of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane **j**, as *N*-nucleophile. After recrystallization from ethyl acetate/diethyl ether (1:2), the target compound **4.14j** was obtained as a beige solid, in 39% isolated yield (0.063 g, 0.195 mmol).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.70 (4H, d, 7.2 Hz, Ph-*ortho*), 7.38-7.40 (2H, m, Ph-*para*), 7.28-7.33 (4H, m, Ph-*meta*), 6.96 (2H, br s, N*H*), 4.04 (2H, br s, N-C*H*-C*H*-N), 2.16-2.24 (2H, br s, N-CHCH_aH$_b$(CH$_2$)$_2$CH_aH$_b$CH-N), 1.85 (2H, br s, N-CHCH$_a$$H_b$(CH$_2$)$_2CH_a$$H_b$CH-

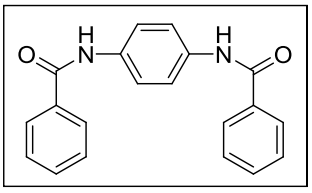
N), 1.41-1.51 (4H, m, N-CHCH$_2$(C*H*$_2$)$_2$CH$_2$CH-N); **^{13}C NMR (100.6 MHz, CDCl$_3$), δ/ppm**: 168.4, 134.3, 131.5, 128.6, 127.1, 54.6, 32.5, 25.0; **IR (KBr (cm^{-1}))**: 3309 (v br, NH), 1635 (CO); **HRMS (ESI)**: m/z calcd. for $C_{20}H_{23}N_2O_2$ $[M+H]^+$: 323.1754, found: 323.1760; **Mp**: 230-232 °C; **$[\alpha]_D^{20}$**: + 70 (*c* 0.5, $CHCl_3$).



4.14j

***N*,*N*'-(1,4-phenylene)dibenzamide (4.14k)**

The diaminocarbonylation of **4.1** was performed, using 0.5 mmol of 1,4-diaminobenzene **k**, as *N*-nucleophile. After recrystallization from chloroform/ethyl acetate (1:10), the target compound **4.14k** was obtained as a beige solid, in 65% isolated yield (0.103 g, 0.326 mmol).

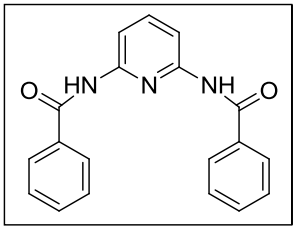


4.14k

^{1}H NMR (400 MHz, DMSO-d$_6$), δ/ppm: 10.24 (2H, s, N*H*), 7.96 (4H, d, 7.2 Hz, Ph-*ortho*), 7.75 (4H, s, phenylene *H*), 7.50-7.61 (6H, m, Ph-*meta*,*para*); **^{13}C NMR (100.6 MHz, DMSO-d$_6$), δ/ppm**: 165.4, 135.0 (double intensity), 131.5, 128.4, 127.6, 120.7; **HRMS (ESI)**: m/z calcd. for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317.1285, found: 317.1280; **Mp**: 320-322 °C.

***N*,*N*'-(pyridine-2,6-diyl)benzamide (4.14l)**

The diaminocarbonylation of **4.1** was performed, using 0.5 mmol of 2,6-diaminopyridine **l**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of chloroform/methanol (20:1), the target compound **4.14l** was obtained as a white solid, in 40% isolated yield (0.064 g, 0.202 mmol).



4.14l

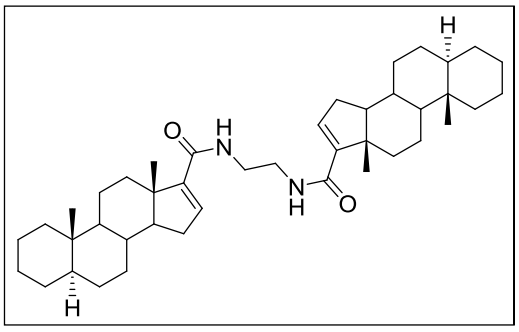
^{1}H NMR (400 MHz, CDCl$_3$), δ/ppm: 8.40 (2H, br s, N*H*), 8.08 (2H, d, 8.0 Hz, pyr-*meta*), 7.87 (4H, d, 7.6 Hz, Ph-*ortho*), 7.76 (1H, t, 8.2 Hz, pyr-*para*), 7.51-7.57 (2H, m, Ph-*para*), 7.43-7.49 (4H, m, Ph-*meta*); **^{13}C NMR (100.6 MHz, CDCl$_3$), δ/ppm**: 165.6, 149.8, 141.0, 134.2, 132.4, 128.9, 127.2, 110.0; **IR (KBr (cm^{-1}))**: 3338 (v br, NH), 1651 (CO); **HRMS (ESI)**: m/z calcd. for $C_{19}H_{16}N_3O_2$ $[M+H]^+$: 318.1237, found: 318.1244; **Mp**: 165-167 °C; **Rf**: 0.70 ($CHCl_3$/CH_3OH 20:1).

5.4.4.1 Synthesis of 17,17'-dicarboxamide steroid dimers

In a typical experiment,[35] $Pd(OAc)_2$ (2.6 mg, 0.0125 mmol), triphenylphosphine (6.6 mg, 0.025 mmol), 17-iodo-5α-androst-16-ene **4.18** (220 mg, 0.57 mmol), diamine nucleophile (0.285 mmol) and triethylamine (0.25 ml) were dissolved in DMF (5 mL), under argon, in a stainless steel autoclave. The atmosphere was pressurized to 30 bar of carbon monoxide. The reaction was conducted for 5 hours, upon stirring at 100°C. After cooling and venting the autoclave, the mixture was evaporated to dryness; the residue was dissolved in chloroform (20 ml) and washed with water (3x20 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to a crystalline material or to a waxy residue, which was subjected to column chromatography (silica gel 60, Merck, 0.063-0.200 mm), using as eluent EtOAc/$CHCl_3$ mixtures (exact ratios are specified for each compound), or simply washed with ethyl acetate.

N,N'-(ethane-1,2-diyl)-bis(5α-androst-16-ene-17-carboxamide) (4.19g)

The diaminocarbonylation of **4.18** (0.57 mmol) was performed, using 0.285 mmol of 1,2-diaminoethane **g**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of ethyl acetate/chloroform (2:1), the target compound **4.19g** was obtained as a white solid, in 91% isolated yield (0.163 g, 0.259 mmol).[35]

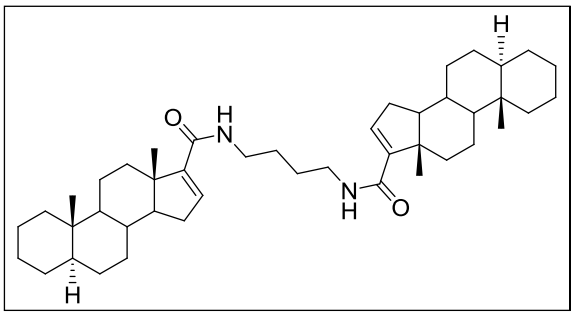


4.19g

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.35 (2H, br s, N*H*), 6.23 (2H, s, C=C*H*), 3.45 (2H, d, 9.6 Hz, N-C$H_a$$H_b$), 3.33 (2H, d, 9.6 Hz, N-C$H_a$$H_b$), 2.03-2.12 (4H, m, 15-$H_2$), 1.86 (2H, dd, 12.0 Hz, 15.2 Hz, 14-*H*), 0.88 (6H, s, 19-H_3), 0.74 (6H, s, 18-H_3), 0.65-1.60 (38H, m, *skeleton protons*); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 167.4, 150.4, 136.4, 56.9, 55.4, 47.3, 46.7, 39.8, 38.7, 36.6, 35.0, 33.9, 32.1, 31.8, 29.1, 29.0, 26.9, 22.3, 20.8, 16.6, 12.3; **IR (KBr (cm^{-1}))**: 3295 (v br, NH), 1645 (CO), 1591 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{42}H_{65}N_2O_2$ $[M+H]^+$: 629.5041, found 629.5038; **Mp**: 153-156 °C; **Rf**: 0.16 (EtOAc/$CHCl_3$ 2:1).

N,N'-(butane-1,4-diyl)-bis(5α-androst-16-ene-17-carboxamide) (4.19i)

The diaminocarbonylation of **4.18** (0.57 mmol) was performed, using 0.285 mmol of 1,4-diaminobutane **i** (hydrochloride salt), as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of ethyl acetate/chloroform (1:1), the target compound **4.19i** was obtained as a white solid, in 95% isolated yield (0.178 g, 0.271 mmol).[35]

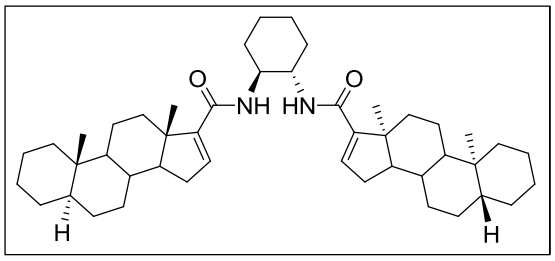


4.19i

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.25 (2H, s, C=C*H*), 5.80 (2H, br s, N*H*), 3.26 (4H, br s, NCH_2CH$_2$CH$_2$CH_2N), 2.02-2.15 (4H, m, 15-H_2), 1.88 (2H, dd, 11.6 Hz, 15.2 Hz, 14-*H*), 0.90 (6H, s, 19-H_3), 0.75 (6H, s, 18-H_3), 0.66-1.60 (42H, m, *skeleton protons* + NCH$_2$CH_2CH_2CH$_2$N); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 166.5, 150.8, 135.8, 57.0, 55.3, 47.4, 46.8, 38.7 (double intensity), 36.6, 35.2, 34.0, 32.1, 31.8, 29.2, 29.1, 27.2, 27.0, 22.3, 20.9, 16.7, 12.3; **IR (KBr (cm^{-1}))**: 3298 (v br, NH), 1639 (CO), 1594 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{44}H_{69}N_2O_2$ $[M+H]^+$: 657.5354, found: 657.5347; **Mp**: 179-182 °C; **Rf**: 0.15 (EtOAc/$CHCl_3$ 1:1).

N,N'-(cylohexane-(1*S*,2*S*)-diyl)-bis(5α-androst-16-ene-17-carboxamide) (4.19j)

The diaminocarbonylation of **4.18** (0.57 mmol) was performed, using 0.285 mmol of (*1S*,*2S*)-(+)-diaminocyclohexane **j**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent a mixture of chloroform/ethyl acetate (2:1), the target compound **4.19j** was obtained as a white solid, in 81% isolated yield (0.157 g, 0.230 mmol).[35]



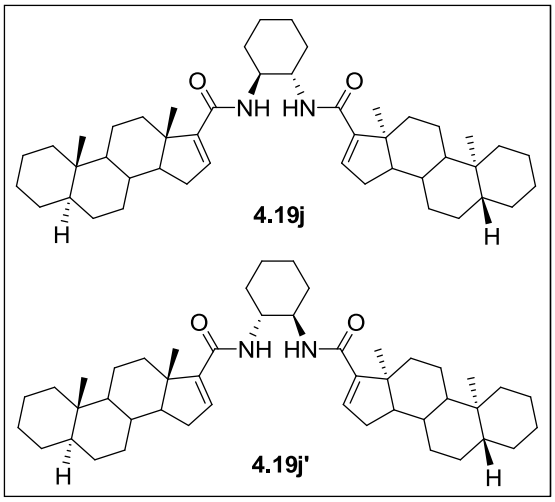
4.19j

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.23 (2H, br s, N*H*), 6.20 (2H, s, C=C*H*), 3.72 (2H, br s, N-CH_2), 2.03-2.16 (6H, m, 15-H_2 + NCHCH_aH$_b$, 1.93 (2H, dd, 12.3 Hz, 15.6 Hz, 14-*H*), 0.95 (6H, s, 19-H_3), 0.80 (6H, s, 18-H_3), 0.68-1.80 (44H, m, *skeleton protons* + NCHCH$_a$$H_bCH_2CH_2CH_a$$H_b$CHN); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 167.1; 150.8,

135.2, 56.8, 55.7, 53.6, 47.3, 46.9, 39.0, 36.7, 35.0, 33.9, 32.7, 32.1, 31.8, 29.2, 29.0 26.9, 25.0, 22.3, 20.8, 16.5, 12.3; **IR (KBr (cm^{-1}))**: 3340 (v br, NH), 1642 (CO), 1591 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{46}H_{71}N_2O_2$ $[M+H]^+$: 683.5510, found: 683.5528; **Mp**: 230-233 °C; **Rf**: 0.8 ($CHCl_3$/EtOAc 2:1); **$[\alpha]_D^{20}$**: + 40.0 (*c* 1.0, CH_2Cl_2).

N,N'-(cylohexane-*trans*-1,2-diyl)-bis(5α-androst-16-ene-17-carboxamide) (50:50 diastereomeric mixture of 4.19j and 4.19j')

The diaminocarbonylation of **4.18** (0.57 mmol) was performed, using 0.285 mmol of racemic *trans*-(±)-1,2-diaminocyclohexane **j**, as *N*-nucleophile. After purification by column chromatography in silica gel, using as eluent chloroform/ethyl acetate (8:1), an inseparable 50:50 mixture of **4.19j** and **4.19j'** diastereomers was obtained, as a white solid, in 66% isolated yield (0.129 g, 0.189 mmol).[34]

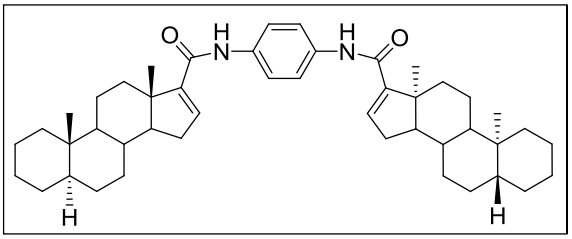


^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 6.25/6.01 (2H, br s, N*H*), 6.19 (2H, s, C=C*H*), 3.73 (2H, br s, N-C*H*), 0.95/0.89 (6H, s, 19-H_3), 0.80/0.79 (6H, s, 18-H_3), 0.72-2.15 (52H, m, *skeleton protons* + NCH($CH_{2)4}$CHN); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 167.1/166.8; 150.8/150.5, 135.9/135.2, 56.8/56.7, 55.6/55.3, 53.5/53.4, 47.4/47.3, 46.9/46.8, 39.0, 38.6, 36.6/36.6, 35.0/34.8, 33.9/33.8, 32.6, 32.1 (*double intensity*), 31.8, 29.2/29.1, 26.9, 25.0/24.9, 22.3, 20.8, 16.6/16.5, 12.3; **IR (KBr (cm^{-1}))**: 3340 (v br, NH), 1642 (CO), 1591 (C=C); **HRMS (ESI)**: m/z calcd. for $C_{46}H_{71}N_2O_2$ $[M+H]^+$: 683.5510, found: 683.5528; **Rf**: 0.30 ($CHCl_3$/EtOAc 8:1).

N,N'-(1,4-phenylene)-bis(5α-androst-16-ene-17-carboxamide) (4.19k)

The diaminocarbonylation of **4.18** (0.57 mmol) was performed, using 0.285 mmol of 1,4-diaminobenzene **k**, as *N*-nucleophile. After washing with ethyl acetate, the

target compound **4.19j** was obtained as a beige solid, in 48% isolated yield (0.092 g, 0.136 mmol).[35]



4.19k

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.50 (4H, s, aromatic *H*) 7.40 (2H, br s, N*H*), 6.44 (2H, s, C=C*H*), 2.19-2.28 (4H, m, 15-H_2), 2.02 (2H, dd, 9.4 Hz, 12.2 Hz, 14-*H*), 1.04 (6H, s, 19-H_3), 0.82 (6H, s, 18-H_3), 0.76-1.70 (38H, m, *skeleton protons*); **^{13}C NMR (100.6 MHz, $CDCl_3$), δ/ppm**: 164.1, 151.3, 136.8, 134.3, 120.4, 56.9, 55.3, 47.4, 47.0, 38.6, 36.6, 35.1, 34.0, 32.1, 32.0, 29.2, 29.0, 26.9, 22.3, 20.8, 16.7, 12.3; **IR (KBr (cm^{-1}))**: 3314 (v br, NH), 1665 (CO), 1594 (C=C); **HRMS (ESI)**: m/z calcd for $C_{46}H_{65}N_2O_2$ $[M+H]^+$: 677.5041, found: 677.5032; **Mp**: 316-319 °C (decomp.); **Rf:** 0.45 ($CHCl_3$/EtOAc 10:1).

5.5 References

1. D. H. R. Barton, R. E. O'Brien, S. Sternhell, *J. Chem. Soc*. **1962**, 470; (b) D. H. R. Barton, B. Bashiardes, J. L. Fourrey, *Tetrahedron Lett.* **1983**, *24*, 1605.

2. (a) D. T. Gibson, J. R. Koch, R. E. Kallio, *Biochemistry* **1968**, *7*, 2653; (b) T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichimica Acta* **1999**, *32*, 35; (c) D. R. Boyd, N. D. Sharma, B. Byrne, M. V. Hand, J. F. Malone, G. N. Sheldrake, J. Blacker, H. Dalton, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1935.

3. D. F. Shriver, M. A. Drezdzon, *The Manipulation of Air-Sensitive Compounds*, Wiley and Sons, New York, **1986**.

4. H. Burrows, M. M. Pereira (Eds.), *Síntese e Estrutura*, Escolar Editora, Lisboa, **2005**.

5. O. Mitsunobu, *Synthesis* **1981**, 1.

6. M. Takahashi, K. Ogasawara, *Tetrahedron: Asymmetry* **1997**, *8*, 3125.

7. R. M. B. Carrilho, A. C. B. Neves, M. A. O. Lourenço, A. R. Abreu, M. T. S. Rosado, P. E. Abreu, M. E. S. Eusébio, L. Kollár, J. C. Bayón, M. M. Pereira, *J. Organomet. Chem.* **2012**, *698*, 28.

8. M. T. Reetz, H. Guo, J.-A. Ma, R. Goddard, R. J. Mynott, *J. Am. Chem. Soc.* **2009**, *131*, 4136.

9. P. W. N. M. van Leeuwen, C. F. Roobeek, *J. Organomet. Chem.* **1983**, *258*, 343.

10. R. M. B. Carrilho, *Síntese de Monofosfitos Quirais. Aplicação em Reacções Catalíticas de Hidroformilação Assimétrica*, Tese de Mestrado (Master Thesis), Universidade de Coimbra, Coimbra, **2008**.

11. R. M. B. Carrilho, A. R. Abreu, G. Petöcz, J. C. Bayón, M. J. S. M. Moreno, L. Kollár, M. M. Pereira, *Chem. Lett.* **2009**, *38*, 844.

12. Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155.

13. P. J. Cox, W. Wang, V. Snieckus, *Tetrahedron Lett.* **1992**, *33*, 2253.

14. M. Shi, C. J. Wang, *Tetrahedron: Asymmetry* **2002**, *13*, 2161.

15. S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Lida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 2252.

16. H. Zhang, W. Huang, L. Pu, *J. Org. Chem.* **2001**, *66*, 481.

17. R. M. B. Carrilho, A. R. Abreu, M. M. Pereira, V. H. Rodrigues, *Acta Crystallogr. E* **2011**, *67*, o2370.

18. C. Qian, C. Zhu, T. Huang, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2131.

19. B. Saha, T. V. RajanBabu, *J. Org. Chem.* **2007**, *72*, 2357.

20. L. C. Serrano, *Hidroformilación Asimétrica de Olefinas con Catalisadores de Rodio y Difosfitos Metalamacrocíclicos*, PhD Thesis, Universidad Autònoma de Barcelona, **2007**.

21. J. E. Babin, G. T. Whiteker, *WO Patent* 9303839, **1992**.

22. J. R. Hanson, P. B. Hitchcock, M. D. Liman, S. Nagaratnam, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2183.

23. Z. Freixa, M. M. Pereira, J. C. Bayón, A. M. S. Silva, J. A. R. Salvador, A. M. Beja, J. A. Paixão, M. Ramos, *Tetrahedron: Asymmetry* **2001**, *12*, 1083.

24. A. F. Peixoto, M. M. Pereira, A. M. S. Silva, C. M. Foca, J. C. Bayón, M. J. S. M. Moreno, A. M. Beja, J. A. Paixão, M. R. Silva, *J. Mol. Catal. A: Chem.* **2007**, *275*, 121.

25. A. Grabulosa, *Compostos Organometàl-lics de Pd i Ru ambs Lligands Quirals P-Estereogènics: Preparació i Caracterització en Catàlisi Asimètrica*, PhD Thesis, Universidad de Barcelona, **2005**.

26. (a) A. Grabulosa, G. Muller, J. I. Ordinas, A. Mezzetti, M. A. Maestro, M. Font-Bardia, X. Solans, *Organometallics* **2005**, *24*, 4961; (b) R. M. Ceder, C. Garcia, A. Grabulosa, F. Karipcin, G. Muller, M. Rocamora, M. Font-Bardia, X. Solans, *J. Organomet. Chem.* **2007**, *692*, 4005.

27. R. M. B. Carrilho, G. N. Costa, M. M. Pereira, A. Grabulosa, J. C. Bayón, M. Rocamora, G. Muller, "*Asymmetric Hydrovinylation with Allyl-Palladium Complexes of C3-symmetry tris-Binaphthyl Monophosphites*", in preparation, **2013**.

28. (a) A. Grabulosa, A. Mannu, G. Muller, T. Calvet, M. Font-Bardia, *J. Organomet. Chem.* **2011**, *696*, 2338; (b) I. Ayora, R. M. Ceder, M. Espinel, G. Muller, M. Rocamora, M. Serrano, *Organometallics* **2011**, *30*, 115.

29. (a) A. Takács, A. R. Abreu, A. F. Peixoto, M. M. Pereira, L. Kollár, *Synth. Commun.* **2009**, *39*, 1534; (b) P. Ács, A. Takács, M. Kiss, N. Pálinkás, S. Mahó, L. Kollár, *Steroids* **2011**, *76*, 280.

30. (a) A. Takács, A. Petz, L. Kollár, *Tetrahedron* **2008**, *64*, 8726; (b) A. Takács, R. Farkas, L. Kollár, *Tetrahedron* **2008**, *64*, 61.

31. R. M. B. Carrilho, M. M. Pereira, A. Takács, L. Kollár, *Tetrahedron* **2012**, *68*, 204.

32. V. Heguaburu, *Preparación de sintones para la obtención de epoxienonas diméricas naturales y análogos. Introducción de sus cadenas laterales*, PhD Thesis, Universidad de la Republica, Montevideo, **2010**.

33. R. M. B. Carrilho, V. Heguaburu, V. Schapiro, E. Pandolfi, L. Kollár, M. M. Pereira, *Tetrahedron* **2012**, *68*, 6935.

34. R. M. B. Carrilho, M. Kiss, J. M. Dabrowski, M. J. S. M. Moreno, R. Skoda-Földes, M. M. Pereira, L. Kollár, "*Synthesis and biological evaluation of carboxamide dimers*", in preparation, **2013**.

35. R. M. B. Carrilho, M. M. Pereira, M. J. S. M. Moreno, A. Takács, L. Kollár, *Tetrahedron Lett.* **2013**, *54*, 2763.

ANNEX

ANNEX 1

Crystallographic data of (*R*)-2'-(benzyloxy)-1,1'-binaphthyl-2-ol (**2.2**)

Table A1. Crystal Data and Structure Refinement Parameters of (*R*)-**2.2**.

Empirical formula	$C_{27}H_{20}O_2$
Formula weight	376.43
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
***a* (Å)**	8.4850(3)
***b* (Å)**	11.3174(4)
***c* (Å)**	20.5379(7)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å^3)	1972.22(12)
Z	4
Calculated density (g/cm^3)	1.264
Absorption coefficient (mm^{-1})	0.079
F(000)	788
Refinement method	Full–matrix least–squares on F^2
Data/restraints/parameters	3759/0/266
Goodness–of–fit on F^2	0.947

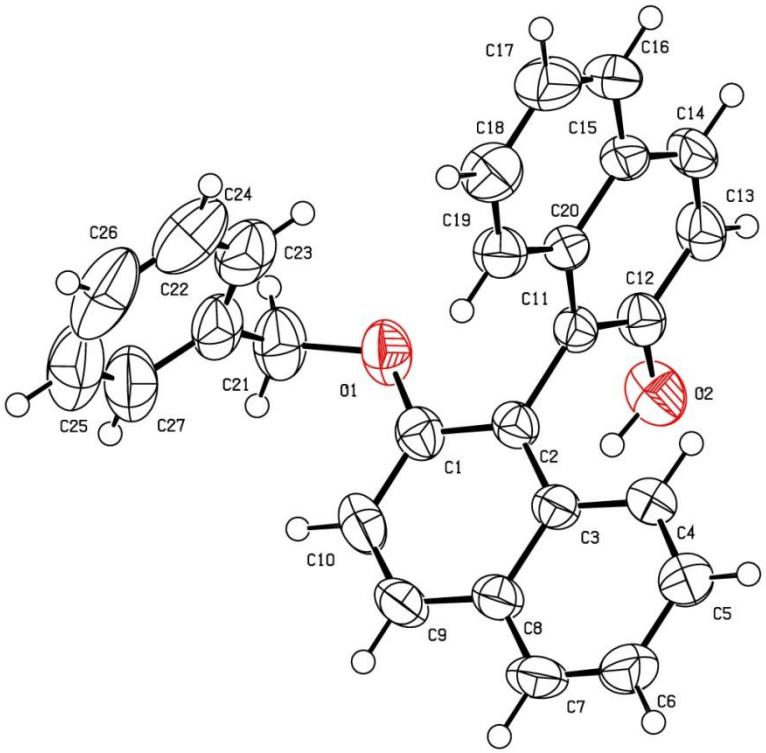


Fig. A1 – *ORTEP* plot of the compound (*R*)-**2.2**.

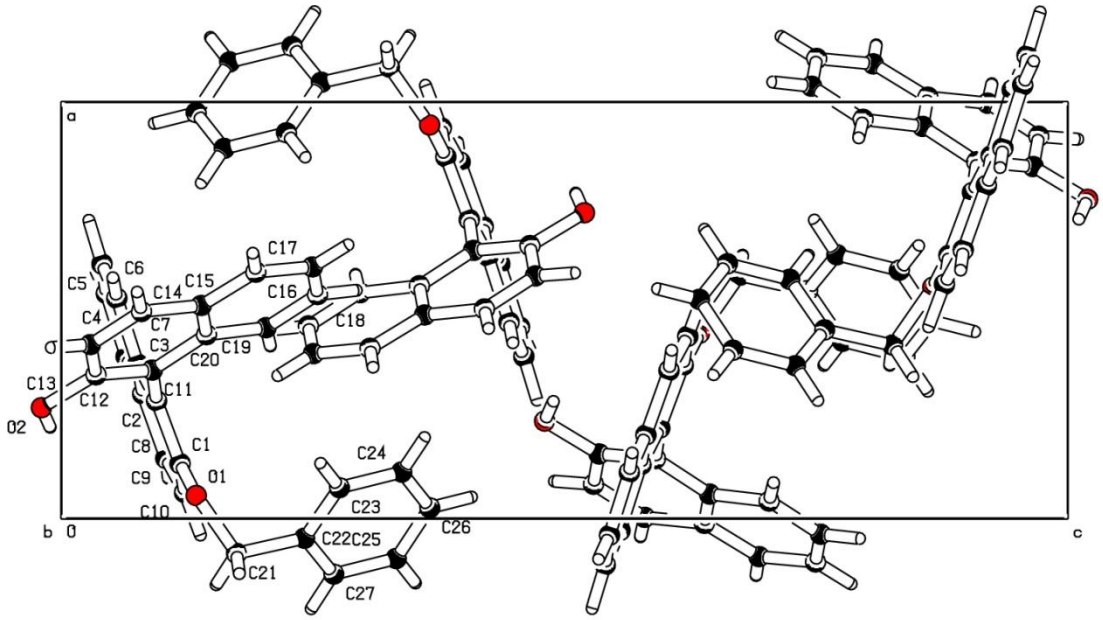


Fig. A2 – Unit cell of (*R*)-**2.2**.

ANNEX 2

Crystallographic data of 2,2'-bis(methoxymethoxy)-3-methyl-1,1'-binaphthyl **(2.7)**

Table A2. Crystal Data and Structure Refinement Parameters of **2.7**.

Empirical formula	$C_{25}H_{24}O_4$
Formula weight	388.43
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
***a* (Å)**	8.1928 (3)
***b* (Å)**	14.3757 (5)
***c* (Å)**	17.1839 (6)
***θ* (°)**	5.7 – 47.5
Volume (Å^3)	2023.87 (12)
Z	4
Calculated density (g/cm^3)	1.275
Absorption coefficient (mm^{-1})	0.090
F(000)	824
Refinement method	Full–matrix least–squares on F^2
Data/restraints/parameters	2046/0/265

Refinement: all H atoms were placed at idealized positions and refined as riding [C—H=0.93 (aromatic C), 0.97Å (CH_2) and 0.96Å (CH_3), U_{iso}(H)=1.2U_{eq}(C)]. The refined model structure is non-centrosymmetric with only atoms which are poor anomalous scatterers for the wavelength used. Friedel pairs were merged before the final refinement. The meaningless Flack parameter obtained without merging of Friedel pairs was -0.3 (11).

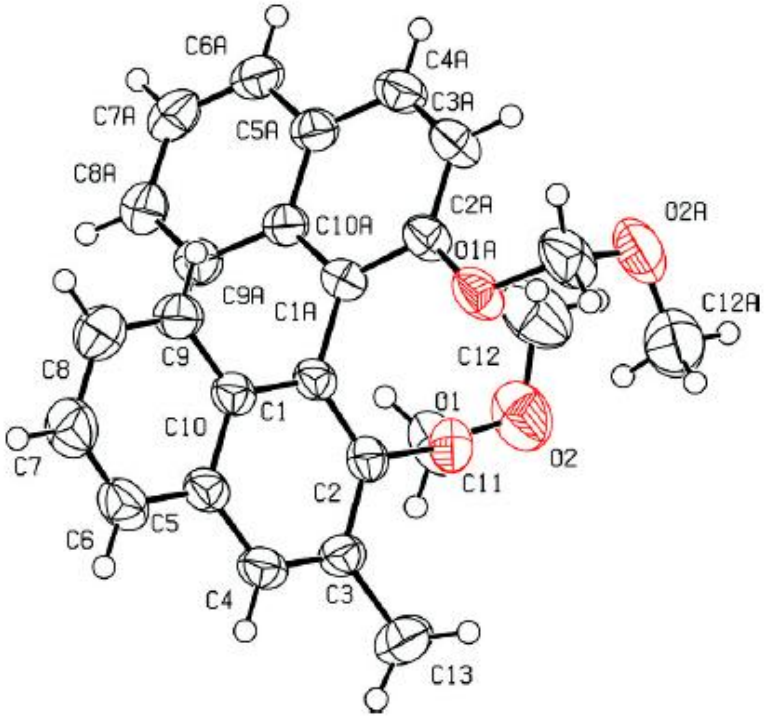


Fig. A3 – *ORTEPII* plot of the compound **2.7** (Displacement ellipsoids are drawn at the 50% level).