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PhD Thesis

MODULAR PHOSPHINOOXAZOLINES: SYNTHESIS AND EVALUATION IN ALLYLIC SUBSTITUTIONS

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Memoria presentada por Dana Madeleine Popa para optar al título de Doctor por la Universitat Rovira i Virgili.

Revisada por

Dr. Anton Vidal **Dr. Miquel A. Pericàs**

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ABBREVIATIONS

DIOP - ((4*R,5R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(diphenylphosphine)
PHOX – phosphinooxazoline
BOX – bisoxazoline
L – ligand
ee – enantiomeric excess
MW – microwave radiation
rt – room temperature
THF – tetrahydrofurane
^{i}PrOH – *iso*-propanol
MsCl - methanesulfonyl chloride
BSA – *N*,*O*- bis(trimethylsilyl)acetamide
$Eu(hcf)_3$-Europium(III)tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]
DMAP – 4-dimethylaminopyridine
NMR – Nuclear Magnetic Resonance
COSY – Correlation Spectroscopy
NOESY – Nuclear Overhauser Enhancement Spectroscopy
HPLC – High Performance Liquid Chromatography
GC – Gas Chromatography
DNA - Deoxyribonucleic acid
RNA - Ribonucleic acid
TS - Transition state
SPS - Solvent purification system
ESI - Electrospray ionization
EI - Electronic impact
IR - Infrared
Ac - Acetyl
DMF - N,N-dimethylformamide
Nu - Nucleophile
Temp - Temperature
Cat - Catalyst

Conv - Conversion

Boc - (*Tert*-Butoxy)-carbonyl

QUINAP - 1-(2-diphenylphosphino-1-naphthyl)isoquinoline

TBAF - Tetra-n-butylammonium fluoride

t_r - Retention time

CLRS - Chiral lanthanide shift reagent

CSA - Chiral solvating agent

CDA - Chiral derivatizing agent

MTPA - (α -methoxy- α -(trifluoromethyl)phenyl-acetic acid

CFPA - α-cyano-α-fluorophenylacetic acid

CFTA - α-cyano-α-fluoro-*p*-tolylacetic acid

CFNA - α-cyano-α-fluoro-2-naftylacetic acid

AFPA - (*R*)-2-fluorophenylacetic acid

ATEA - α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetic acid

TFLA - Trifluorolactic acid

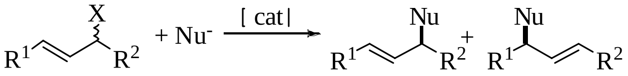
DHQD - bis(9-*O*-dihydroquinidyl)

TMS-trimethyl-silyl

CONTENTS

RESUMEN

La reacción de substitución alílica asimétrica representa un método importante para la generación de enlaces C-C y C-N de forma estereoselectiva (Esquema 1).



Esquema 1. Alquilación alílica enantioselectiva.

Las fosfinooxazolinas (Figura 1) fueron descritas originalmente en 1993 por Pfaltz Williams y Helmchen[1] de simultáneamente y han sido utilizadas en múltiples ejemplos de sustituciones alílicas enantioselectivas sobre una gran diversidad de sustratos.

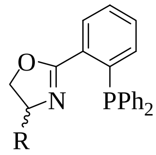
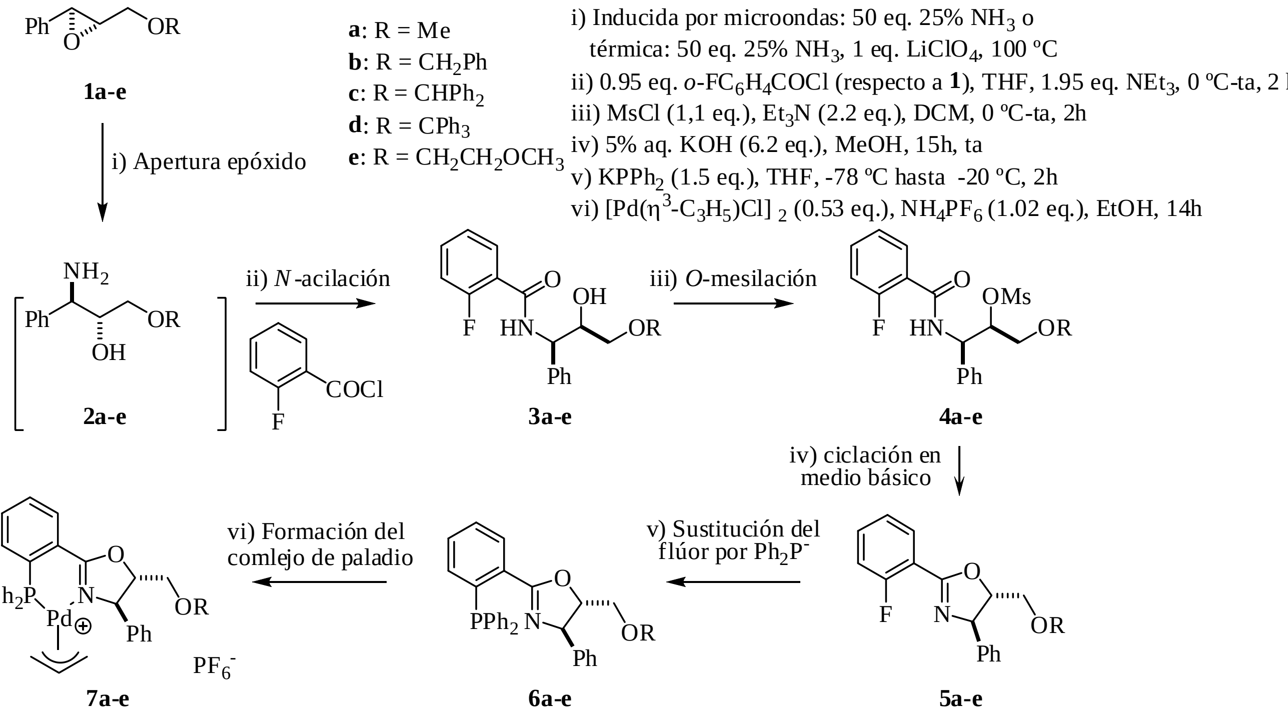


Figura 1. Ligandos de tipo fosfinooxazolina

En el primer capitulo de la Tesis, se recoge la síntesis y caracterización de una familia altamente modular de complejos de paladio-fosfinooxazolina. La metodología de síntesis empleada se describe en el Esquema 1.



a: R = Me
b: R = CH_2Ph
c: R = $CHPh_2$
d: R = CPh_3
e: R = $CH_2CH_2OCH_3$

i) Inducida por microondas: 50 eq. 25% NH_3 o
térmica: 50 eq. 25% NH_3, 1 eq. $LiClO_4$, 100 ºC
ii) 0.95 eq. *o*-FC_6H_4COCl (respecto a **1**), THF, 1.95 eq. NEt_3, 0 ºC-ta, 2
iii) MsCl (1,1 eq.), Et_3N (2.2 eq.), DCM, 0 ºC-ta, 2h
iv) 5% aq. KOH (6.2 eq.), MeOH, 15h, ta
v) $KPPh_2$ (1.5 eq.), THF, -78 ºC hasta -20 ºC, 2h
vi) $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.53 eq.), NH_4PF_6 (1.02 eq.), EtOH, 14h

Esquema 1. Síntesis de los complejos $[Pd(\eta^3\text{-alil})(PHOX)]PF_6$

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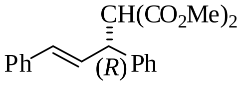
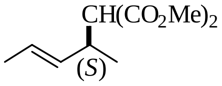
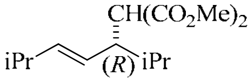
[1] von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1993**, *32*, 566-8; Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769-1772; Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149-3150.

La preparación de los epoxiéteres **1a-e** a partir del epoxido de Sharpless ha sido descrita con anterioridad en nuestro grupo de trabajo.[2] La apertura regioselectiva y estereoespecífica de los epoxiéteres con amoniaco (25% NH_3 en solución acuosa, en tubo de presión o en condiciones de irradiación en microondas) ha conducido a los amino alcoholes enantiopuros **2a-e** los cuales, sin previa purificación, han sido *N*-acilados seguido de activación del hidroxilo (como mesilato) y ciclación resultando las fluorooxazolinas **5a-e**. En el siguiente paso, la substitución del átomo de flúor por derivados de fósforo aniónicos ha conducido a los ligandos fosfinooxazolina que finalmente han sido transformados en los complejos de paladio **7a-e**. Los métodos preparativos empleados son fácilmente escalables y ha sido posible obtener con suma facilidad, en algunos casos, cantidades cercanas al gramo.

En el segundo capítulo de la Tesis están recogidos los resultados obtenidos en la alquilación alílica mediada por la nueva familia de complejos $[Pd(\eta^3\text{-alil})(PHOX)]PF_6$ **7a-e.** Los complejos descritos en este trabajo han mostrado una gran estereoselectividad en un amplio margen de temperaturas, sin prácticamente ninguna pérdida en la enantioselectividad en el rango de temperaturas comprendido entre temperatura ambiente y 130º C. En la Tabla 1 se resumen las mejores condiciones de reacción optimizadas para la alquilación alílica asimétrica de una serie de acetatos alílicos con nucleófilos derivados de ésteres malónicos. Se ha observado un caso sin precedentes de inversión de la enantioselectividad para el acetato de 1,3-dimetilalílo comparado con el substrato análogo difenil sustituído.

Tabla 1. Condiciones de reacción óptimas para la alquilación alílica mediada por **7a**

Entrada	Producto	Condiciones de reacción.	Conv. (%)	ee (%)
1		MeCN/55ºC, MW, 0.25h	99	95
2		CH_2Cl_2/25ºC, 24h	87	49
3		MeCN/80ºC, MW, 8h	54	92

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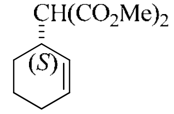
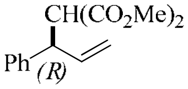
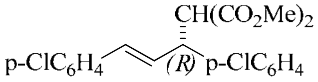
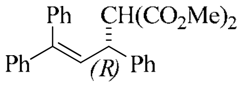
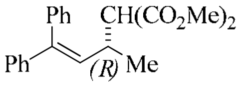
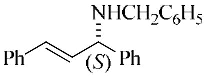
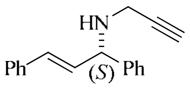
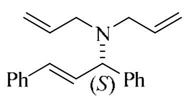
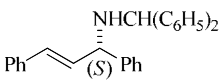
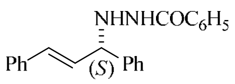
[2] Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970-4982.

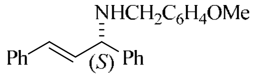
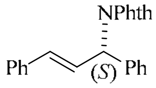
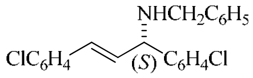
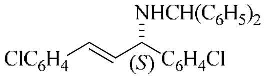
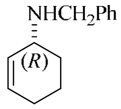
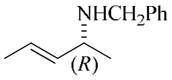
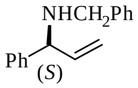
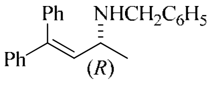
Entrada	Producto	Condiciones de reacción.	Conv. (%)	ee (%)
4		25ºC, 24h	40	56
5		25ºC, 4h	>99^b	82
6		THF/85ºC, MW 2.5 h	> 99	93
7		CH_3CN /130ºC, MW, 2h	99	94
8		CH_3CN /130ºC, MW, 2h	> 99	70

a) Condiciones de reacción: 3 eq.$CH_2(CO_2Me)_2$, 3 eq.BSA, 2.5 mol% KOAc, 2.5 mol% **7a**

En el tercer capítulo de la Tesis están recogidos los resultados obtenidos con la nueva familia de complejos Pd-PHOX en la aminacion asimétrica de varios substratos alílicos con nucleófilos nitrogenados. El grado de estereoinducción alcanzado con nuestros ligandos, en algunos de los casos, ha sido superior a los resultados descritos en la literatura. En la tabla 2 se resumen las mejores condiciones de reacción desarrolladas para la aminación alílica asimétrica de una serie de acetatos alílicos con una gran variedad de nucleófilos nitrogenados.

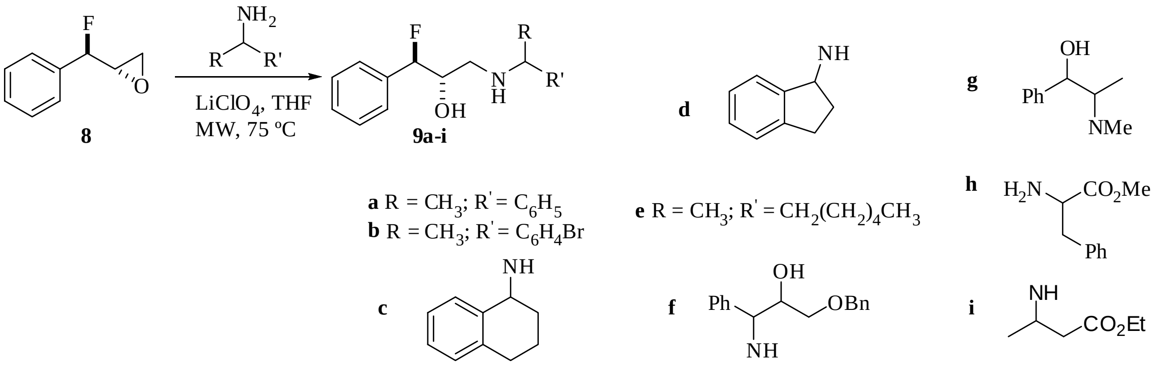
Tabla 2. Condiciones de reacción óptimas para la aminación alílica mediada por **7a**

Entrada	Producto	T(ºC)	Tiempo (h)	Conv. (%)^a	ee (%)
1		24	2	98	95
2		24	2	>99	97
3		24	4	>99	99.3
4		24	24	94	96
5		24	24	>99^b	94

Entrada	**Producto**	**T(°C)**	**Tiempo (h)**	**Conv. (%)**[a]	**ee (%)**
6		24	4	94	94
7		50	48	65	92
8		24	1	>99[c]	94
9		24	48	54	79
10		24	4	>99	37
11		24	4	>99	63
12		24	1	>99	74[e]
13		50	15	>99[d]	89

a) Condiciones de reacción generales: 2.5 mol % **7a**, 2.5 mol % KOAc, 3eq. nucleófilo, 3eq. BSA; b) 6eq. BSA; c) 6eq. nucleófilo, 6eq. BSA; d) 5eq. nucleophile, 3eq. BSA; e) Branch to Linial 0.36:99.64.

En el cuarto capítulo presentamos un nuevo agente chiral de resolucion, para la determinación de la pureza óptica de aminas quirales. Las aminas primarias y secundarias fueron derivatizadas con el reactivo quiral por apertura del agente de resolución (fluoro epóxido **8**) resultando en la formación de productos diastereoméricos los cuales son fáciles de identificar y cuantificar mediante ^{19}F, ^{1}H, ^{13}C NMR y HPLC (Esquema 2).



Esquema 2. Nuevo compuesto fluorado como agente de resolución

INTRODUCTION AND AIMS

INTRODUCTION AND AIMS

The notion of chirality was introduced by Louis Pasteur one hundred fifty years ago[1] with the experiment in which he manually separated both enantiomers of a salt of tartaric acid from wine. He affirmed that the individual molecules were "*dissymmetric*". Chirality nowadays is defined as the property of an object of non-superimposability on its mirror image. Pair of compounds (crystals or molecules) that are mirror images of each other but cannot be superimposed onto each other are defined as enantiomers (Figure 1.).

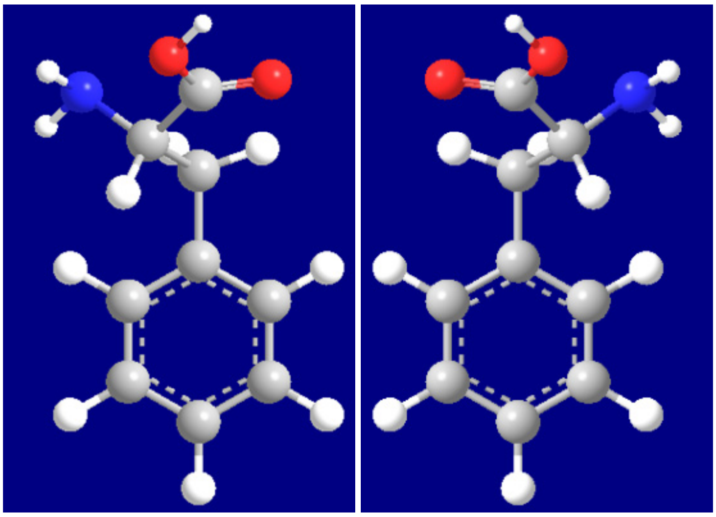


Figure 1. Chiral molecules. Non-superimposable mirror images

Molecular chirality plays an important role in many areas of chemistry, biochemistry and physics. For example the biological activity and chemical properties of one enantiomer of a chiral molecule may be very different from that of the opposite enantiomer.[2] The majority of important molecules in nature (proteins and their constituents – amino acids – and the nucleic acids and their constituents – ribose and deoxyribose sugars) are chiral. Nucleic acids hold the

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[1] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds* **1994**, 1267.
[2] Parker, D. *Chem. Rev.* **1991**, *91*, 1441-57.

information necessary for proteins to be synthesized. Not surprisingly, the biological activity of the two enantiomers might differ as proteins control most of the biological processes.

The necessity in the development of efficient methods for the preparation of enantiomerically pure compounds results from the increased requirement of high optical purity in many different fields. Resolution via formation of diastereomers, chromatographic separation of enantiomers, enzymatic resolution, kinetic resolution, asymmetric synthesis and asymmetric catalysis have all been widely used for the synthesis of enantiomerically pure compounds.[3]

Asymmetric catalysis constitutes the most elegant strategy for the preparation of enantiomerically pure compounds. In this strategy, the chirality of one molecule of catalyst is transferred to many molecules of the chiral product, by virtue of the continuous catalyst regeneration. This represents a great advantage with respect to other synthetic methods such as chemical resolution or asymmetric synthesis, which suffer from severe drawbacks (maximal yield up to 50% or the requirement of stoichiometric amounts of chiral strating materials). Furthermore, the catalytic event improve several aspects related to the sustainability of the process, such as efficient use of raw materials, atom economy, environmental impact and saving in energy.

The key step in most catalytic asymmetric processes involves the assembly of the substrate and the reagent(s), usually around a chiral metal - complex (ligand accelerated catalysis), or specifically around an enantiopure chiral molecule (organocatalysis). In the catalytic process, non-covalent interactions are responsible for the reversible assembly of substrates and reagents around the chiral catalyst. In such catalytic systems, the metal - complex (or chiral

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[3] Sheldon, R. A. *Chirotechnology: Industrial Synthesis of Optically Active Compounds* **1993**.

molecule) provide a low energy reaction pathway to the products (see Figure 2.). Furthermore, the chiral ligand is responsible for enantioselection as it creates an asymmetric environment around the active site and ultimately allows the preferential recognition of an enantiotopic atom, group or face from the substrate.

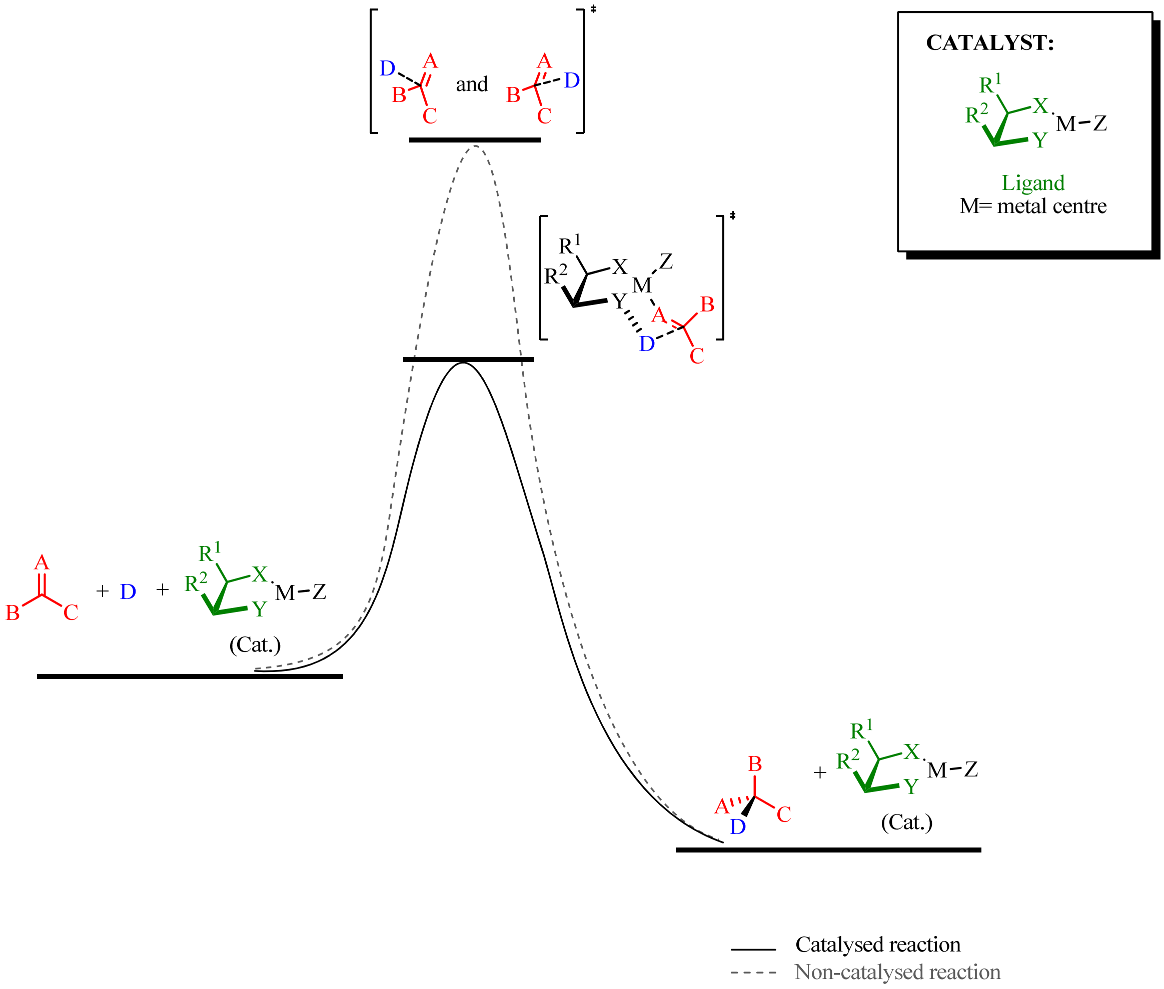

Figure 2. Asymmetric catalytic reaction

In developing improved asymmetric catalysts, many classes of chiral ligands have been designed, synthesised and tested in almost every synthetic transformation amenable to catalysis. In this way, almost every conceivable type of molecular chirality has been envisaged.[4] Significant effort in this field has focussed on ligand design and trial-and-error optimization cycles, but at the time, serendipity has also played its role. Two factors have contributed to the remarkable progress in the field. First and foremost, the use of ligands derived from enantiopure non-natural starting materials has broadened the structural diversity of available catalysts. Secondly, the modular nature of the ligands has facilitated the rapid and systematic optimization of the ligand structure. To achieve highly efficient and enantioselective catalysis of asymmetric reactions, the tuning of the catalyst to make a perfect match among the ligand, the metallic ion (if present) and substrate(s), is the key issue: by using a modular catalyst design, the structural features responsible for asymmetric induction can simply be modified and adjusted. This strategy has been commonly used by many groups working in the field,[5] including us.[6] A modular design of ligands, versatile synthetic strategies and the computational analysis of the diastereomeric

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[4] a) Noyori, R. *"Asymmetric Catalysis in Organic Synthesis"* **1994**; b) Ojima, I. *"Catalytic Asymmetric Synthesis"* **2000**; c) Jacobsen, E. N.; Pfaltz.A.; Yamamoto, H. E.; Vol. *"Comprehensive Asymmetric Catalysis I-III"* **1999**.

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transition states[6c] has allowed the development of very efficient catalytic systems for many asymmetric transformations.[5, 6]

The concept of C_2 symmetry in ligand design was introduced by Dang and Kagan in 1971 with the famous diphosphine, DIOP.[7] C_2 symmetric ligands (Figure I.3.) generally facilitate the understanding of the reaction because of the lower number of metal complex catalyst substrate arrangements which are formed, compared to nonsymmetrical ligands. Since this initial report many other examples have been described. Tartrate derivatives,[8] bisoxazolines (BOX),[9] C_2-diphosphines (DIPAMP,[4a] DIOP,[10] Chiraphos,[11] BDPP,[12] BINAP,[13] and DUPHOS[14]), BINOL,[15] TADDOL,[16] Britzinger's ligands,[17] PHAL[18] and SALEN ligands[19] have been developed and incorporated into the "asymmetric tool-box" of the synthetic community.

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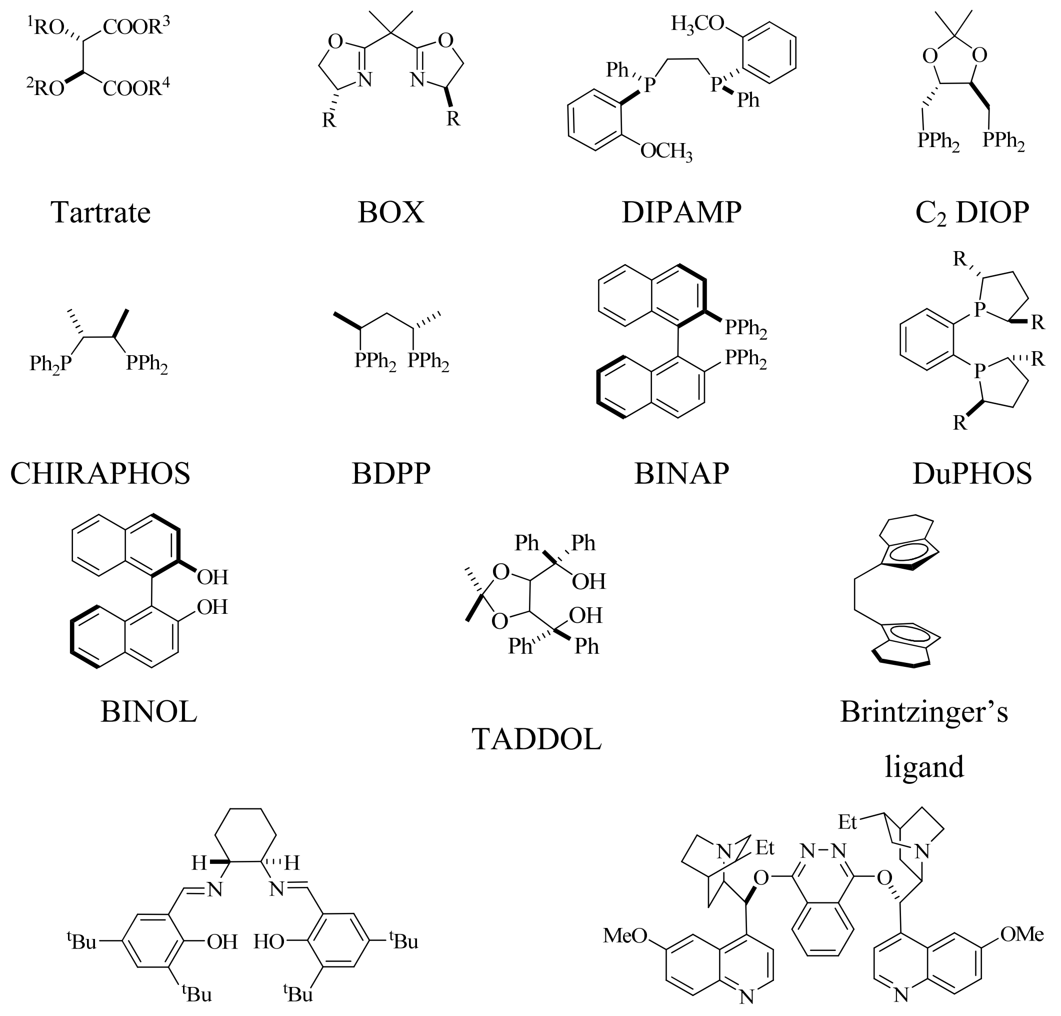

Tartrate BOX DIPAMP C$_2$ DIOP

CHIRAPHOS BDPP BINAP DuPHOS

BINOL TADDOL Brintzinger's ligand

Salen (DHQD)$_2$PHAL

Figure 3. C$_2$ ligands

On the other hand, C$_1$ asymmetric ligands can often induce higher enantioselectivities due to the steric and electronic differentiation of the coordinating units. One example of desymmetrisation is the DIOP ligand in which one diphenylphosphino unit was replaced by a bis[4-(dimethylamino)phenyl]phosphino group.[20] The results obtained using the C$_1$ DIOP in olefin asymmetric hydrogenation were better than the ones for the C$_2$ analogue.

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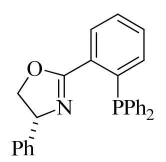
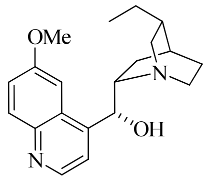
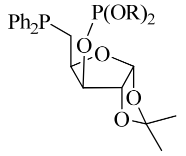
PHOX,[21] chinchona alkaloids,[22] sugar derivatives[23] are some examples of C_1 bidentate ligands that have been used in asymmetric catalysis and have found applications in many transformations.



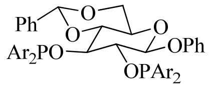
PHOX



Chinchona alkaloid



Phosphine-phosphite sugar derivatives



Phosphite sugar derivatives

Figure 4. C_1 ligands

A reduced group of ligands, the so called ¨Privileged Chiral Catalysts¨,[24] have gained prominence through their ability to effect a wide variety of unrelated transformations under very high enantiocontrol and high yield. These privileged ligands are structurally diverse for a number of reasons: the asymmetry (or dissymmetry) is either conferred by a stereogenic centre or chiral axis; some posses a two-fold axis of symmetry; some can consist of a number of covalently linked molecular fragments (modules), each of which can be functionalized individually, whereas other privileged ligands are structurally more simple.

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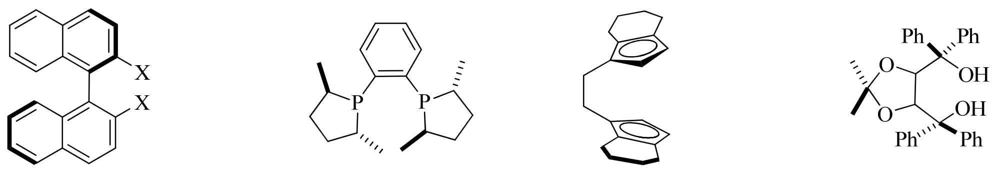
[24] The term ¨Privileged Chiral Catalysts¨ has been coined by E. Jacobsen (Science **2003**, 299, 1691) to indicate certain classes of enantioselective catalysts which are highly stereoselective over a wide range of mechanistically unrelated transformations. Chiral salens, BINOL, BINAP, DuPhos, bisoxazolines, phosphinooxazolines, tartrate ligands, cinchona alkaloids, Britzinger´s ligand or TADOLLates are the most relevant examples of this class of chiral catalysts.

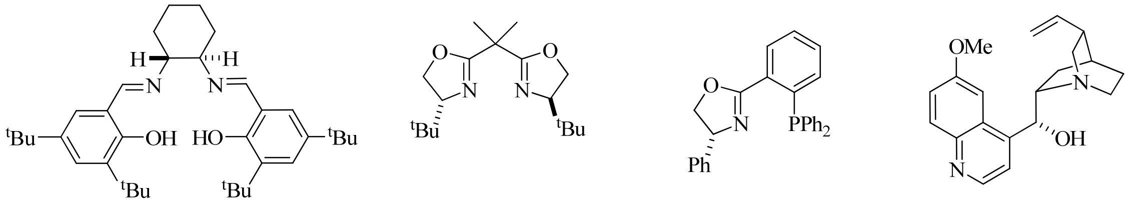


X=OH, BINOL
X=PPh$_2$, BINAP

MeDuPhos

Brintzinger's ligand

TADDOL



Salen

bisoxazoline (BOX)

phosphinooxazoline (PHOX)

Chinchona alkaloid derivative

Figure 5. Privileged structures

PHOX, which belong to C_1 class of bidentate ligands, can be regarded as privileged structures and have been used successfully in great number of asymmetric catalytic processes.

The first examples of PHOX ligands[21] were described simultaneously by Pfaltz, Helmchen and Williams in 1993 with very good results in the asymmetric alkylation reaction. PHOX ligands have progressively found applications in many other asymmetric transformations. In the next table we present some of the existing applications of the initial PHOX ligands in asymmetric catalysis: desymmetrization of meso-*N*-sulfonylaziridines,[25] asymmetric Grignard cross-coupling reactions,[26] monofunctionalization of cyclic anhydrides,[27] asymmetric cyclization of *ω*-formyl-1,3-diene and hydroxy allylic carbonates,[28] asymmetric

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cyclohexenylation,[29] alkylative ring-opening,[30] hydrosilylation of ketones,[31] ring-expanding allylation,[32] hydrogenation of olefins,[33] cyclopropanation,[34] decarboxylative protonation,[35] anhydride alkylation,[36] decarboxylative coupling with allyl electrophiles,[37] allylation of fluorinated silyl enols ethers,[38] alkylation of secondary nitroalkanes,[39] Diels-Alder reactions,[40] Heck reactions,[41] domino Heck reactions,[42] aza-Claisen rearrangements,[43] Michael reactions,[44] allylic fluorobis(phenylsulfonyl)methylation,[45] Tsuji allylation,[46] benzoylation of alcohols,[47] ring-opening of meso bicyclic hydrazines,[48] and allylic amination reactions.[49]

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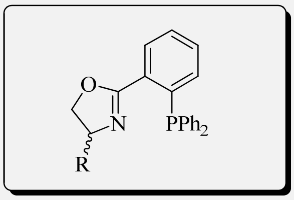
Table 1. PHOX ligands in the asymmetric catalysis



1[21]

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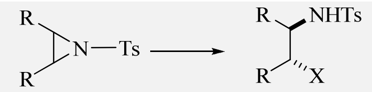
1	
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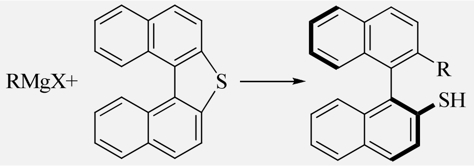
2	
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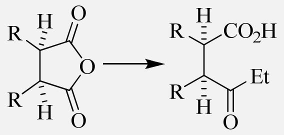
3	
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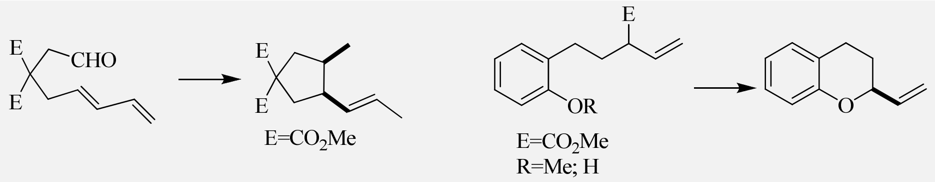
4	
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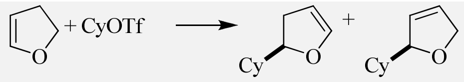
5	
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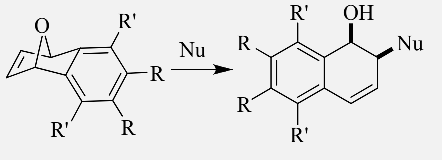
6	 R, R'=H, alkyl, OCH_3
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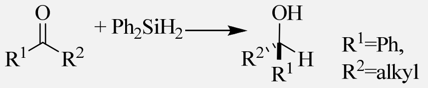
7	
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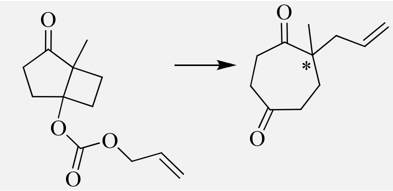
Table 1. PHOX ligands in the asymmetric catalysis	
8	
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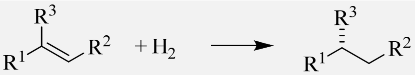
9	
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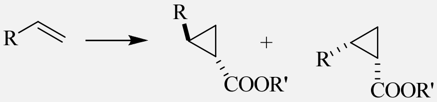
10	
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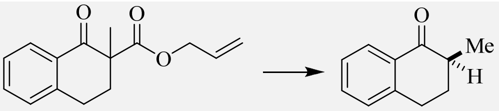
11	
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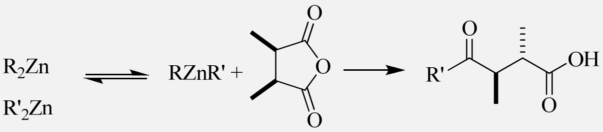
12	
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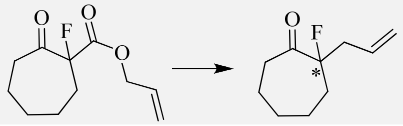
13	
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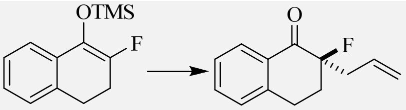
14	
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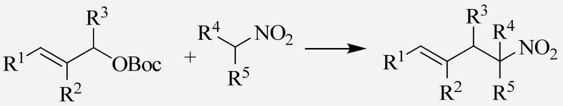
15	
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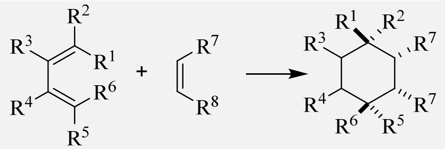
16	
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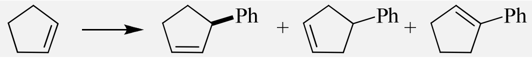
17	
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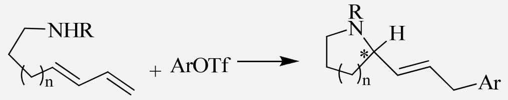
18	 n = 1, 2
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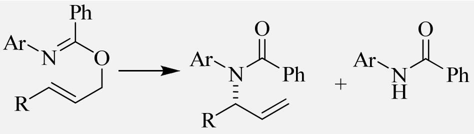
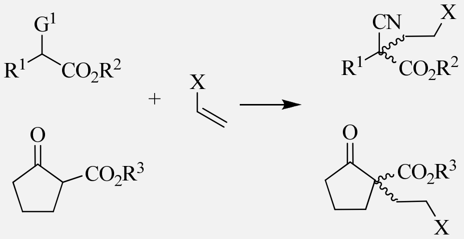
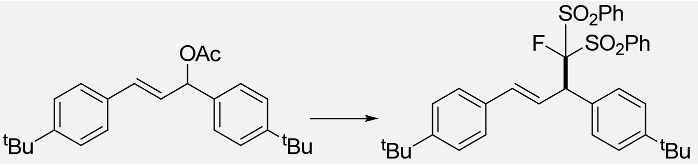
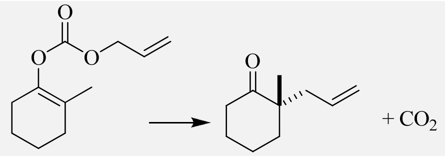
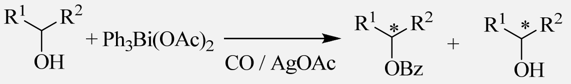
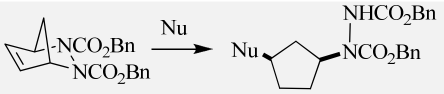
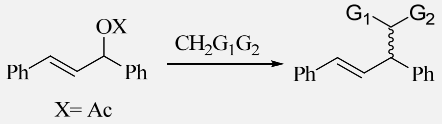
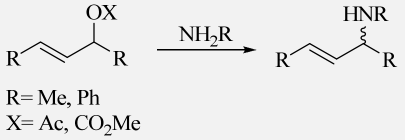
19	 R=alkyl
	Aza-Claisen rearrangement[43]
20	 R^1=H, alkyl R^2, R^3 =alkyl G^1=CN X=O, COOMe, CHO
	Michael reaction[44]
21	
	Allylic fluorobis(phenylsulfonyl)methylation[45]
22	
	Tsuji allylation[46]
23	
	Carbonylative benzoylation of alcohols[47]
24	
	Ring-opening of meso bicyclic hydrazines[48]

Table 1. PHOX ligands in the asymmetric catalysis

25	
	Allylic alkylation[21a]
26	
	Allylic amination[49]

Synthetic, yet enantiopure amino alcohols **3** arising from Sharpless epoxides **2** present several elements of structural diversity and have been developed by our group as very efficient mediators for the asymmetric addition of diethylzinc onto carbonyl compounds and imines,[50] ruthenium catalyzed enantioselective reduction of ketones by hydrogen transfer.[51] Their derived oxazaborolidines, **4** have been used in the enantioselective borane reduction of prochiral ketones,[52] the derived bisoxazolines, **5** in the asymmetric allylic alkylation[6a] and the Schiff bases **6** in the addition of cyanide to carbonyl groups.[53] The ligands developed by our group, that have been used as asymmetric catalysts in the previous transformations, have been summarized in Figure I.6. It should be mentioned at this point, that the modular nature of the ligands has allowed the tuning of the performance of the catalytic system by modifying free input parameters of the ligand (R^1, R^2 and R^3). The systematic variation of the substituents in **2** or their derivatives **3-6**, allowed us to develop catalytic systems with improved catalytic properties with respect to the ones already described for the studied processes.

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[50] a) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309-6318; b) Jimeno, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 777-780; c) Fontes, M.; Verdaguer, X.; Sola, L.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532-2543; d) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773-8776; e) Sola, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078-7082.

[51] Pasto, M.; Riera, A.; Pericas, M. A. *Eur. J. Org. Chem.* **2002**, 2337-2341.

[52] Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902-7911.

[53] Rodriguez, B.; Pasto, M.; Jimeno, C.; Pericas, M. A. *Tetrahedron: Asymmetry* **2006**, *17*, 151-160.

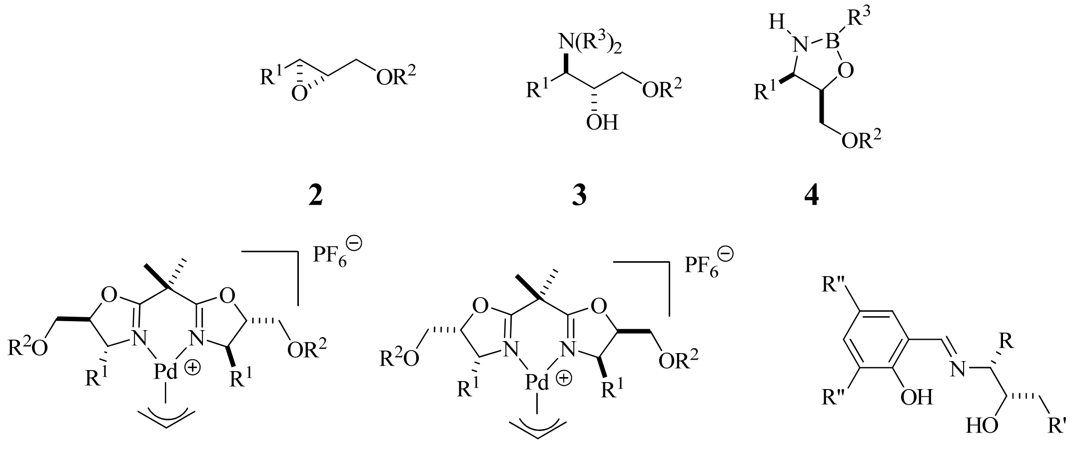
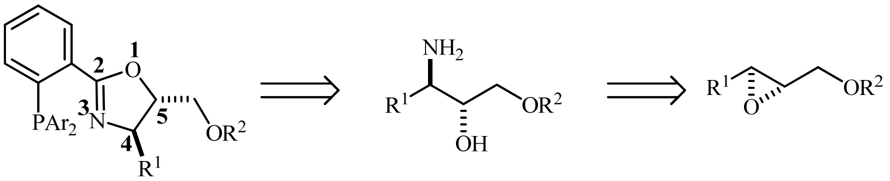


Figure 6. Enantiopure amino alcohols and chiral derivative ligands

Amino alcohols **3** (with R^3=H) are very interesting antecedents of asymmetric catalysts such as PHOX, whose catalytic properties have been summarized in Table I.1. This kind of chiral compounds can be prepared through the following synthetic strategy (Scheme I.1).



Scheme 1. Synthesis of PHOX from Sharpless epoxy ethers

In an analogous way to the previous asymmetric catalysts developed by the group, the PHOX ligands would be highly modular. A modular design is key in our approach, as it allows the optimization and the tuning of the catalytic properties as a function of free input parameters (modules or fragments). Furthermore, they would incorporate a R^2OCH_2 substituent at C5 in a *trans*-

arrangement. Examples of *trans*-disubstituted PHOX are scarce in the literature.[54]

It should be mentioned, that the present work is the continuation on the research on this topic started by C. Puigjaner, who developed the synthetic strategy for PHOX from Sharpless epoxy ethers and carried out preliminary catalytic studies in the allylic alkylation.

Consequently, the objectives of the present PhD thesis are as follow:

1- Preparation of a highly modular family of palladium phosphinooxazoline complexes. Optimization of critical aspects in the already existing synthesis.

2- Evaluation of the catalytic activity of the new Pd-PHOX complexes in the asymmetric allylic alkylation reaction.

3- Evaluation of the catalytic activity of the new Pd-PHOX complexes in the asymmetric allylic amination reaction.

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[54] a) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486-5487; b) Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J Organomet Chem* **1999**, *572*, 163-168; c) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis-Stuttgart* **2005**, 1431-1436.

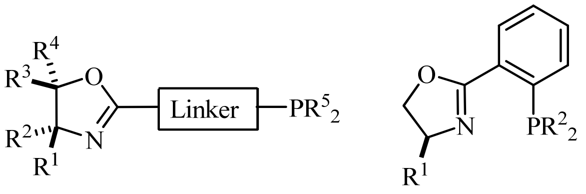
CHAPTER I

MODULAR PHOSPHINOOXAZOLINES FOR ASYMMETRIC CATALYSIS

MODULAR PHOSPHINOOXAZOLINES FOR ASYMMETRIC CATALYSIS

1. INTRODUCTION

Phosphinooxazolines(PHOX) **9** and **10** belong to a non C_2 symmetric class of ligands which combine the characteristics of a “soft” phosphorus donor group with π-acceptor properties and a “hard” nitrogen σ-donor group (Figure I.1.).[1] The oxazoline and phosphorus groups are separated by a linker which corresponded, in the seminal examples described by Pfaltz,[2] Helmchen[3] and Williams,[4] to a 1,2-disubstituted benzene ring, **10**.



9 **10**

Figure I.1. Phosphinooxazoline ligands

Following the initial studies on PHOX ligands, a great variety of backbones have been developed and studied in many catalyzed asymmetric processes. The modular

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[1] a) Frost, C. G.; Howart, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089-122;Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422;Williams, J. M. J. *Synlett* **1996**, 705-710;Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741-742;Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336-345;McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151-4202;Pfaltz, A.; Drury, W. J., III *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5723-5726.

[2] von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1993**, *32*, 566-8.

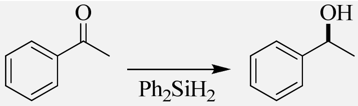
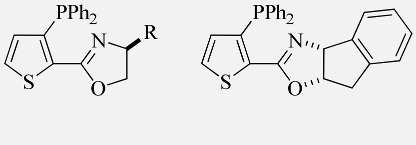
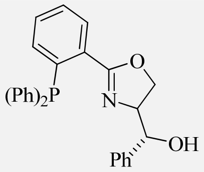
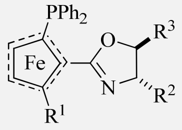
[3] Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769-1772.

[4] Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149-3150.

construction of the phosphinooxazoline ligands allowed extensive and independent variation of the phosphine part, the oxazoline ring and the backbone, thus being possible the optimization of the ligand structure for particular reactions.

Examples of such structural diversity in reported PHOX ligands together with their application in different catalytic asymmetric reactions are collected in Table I.1. Phosphinooxazoline ligands have been applied in: hydrosilylation reactions (entry 1 in Table I.1.), Diels Alder reactions (entry 2 in Table I.1.), enantioselective hydrogenation (entry 3 in Table I.1.), Heck reactions (entry 4 in Table I.1.) and cycloadition reactions (entry 5 in Table I.1.). Examples of PHOX ligands used successfully in the allylic alkylation and amination reactions will be presented in detail in chapters II and III.

Table I.1. PHOX and other related *P,N*-ligands in asymmetric catalysis

Entry	Enantioselective hydrosilylation reaction		
1			
	PHOX ligands		
	 **11, 12**[5]	 **13**[6]	 **14**[7]

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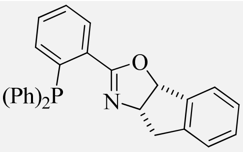
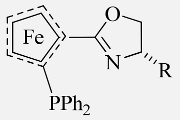
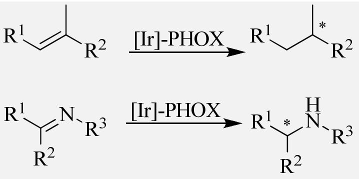
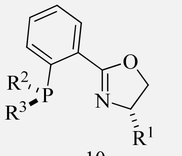
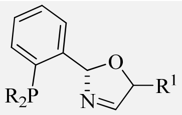
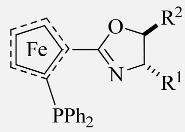
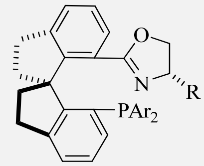
[5] Coyne, A. G.; Guiry, P. J. *Tetrahedron Lett.* **2007**, *48*, 747-750.

[6] Frolander, A.; Moberg, C. *Org. Lett.* **2007**, *9*, 1371-1374.

[7] a) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486-5487;Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.*

Table I.1. PHOX and other related *P,N*-ligands in asymmetric catalysis

2	**Asymmetric Diels Alder reaction**
	
	PHOX ligands
	 **15**[8]  **16**[9]
3	**Enantioselective hydrogenation of C=C and C=N bonds**
	
	PHOX and other related P-N ligands
	 **17**[10]  **18**[11]  **19**[12]  **20**[13]

2001, 2360-2361;Takei, I.; Nishibayashi, Y.; Arikawa, Y.; Uemura, S.; Hidai, M. *Organometallics* **1999**, 18, 2271-2274.

[8] a) Carmona, D.; Cativiela, C.; Elipe, S.; Lahoz, F. J.; Lamata, M. P.; Pilar, M.; de Viu, L. R.; Oro, L. A.; Vega, C.; Viguri, F. *Chem. Commun.* **1997**, 2351-2352;Carmona, D.; Vega, C.; Garcia, N.; Lahoz, F. J.; Elipe, S.; Oro, L. A.; Lamata, M. P.; Viguri, F.; Borao, R. *Organometallics* **2006**, *25*, 1592-1606.

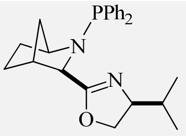
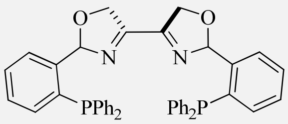
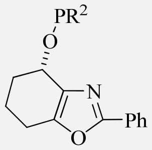
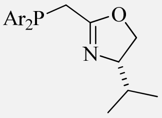
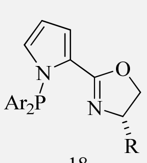
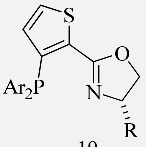
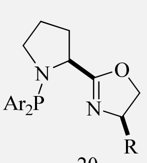
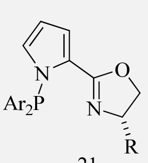
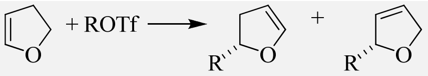
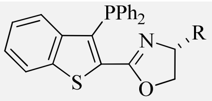
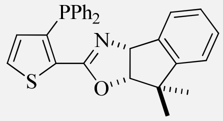
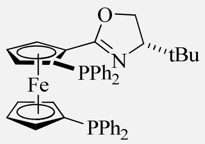
[9] a) Carmona, D.; Medrano, R.; Dobrinovich, I. T.; Lahoz, F. J.; Ferrer, J.; Oro, L. A. *J. Organomet. Chem.* **2006**, *691*, 5560-5566;Adams, H.; Bawa, R. A.; McMillan, K. G.; Jones, S. *Tetrahedron: Asymmetry* **2007**, *18*, 1003-1012.

[10] a) Naud, F.; Malan, C.; Spindler, F.; Ruggeberg, C.; Schmidt, A. T.; Blaser, H. U. *Adv. Synth. Catal.* **2006**, *348*, 47-50;Valla, C.; Pfaltz, A. *Chimica Oggi-Chemistry Today* **2004**, *22*, 4-7;Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmerman, N. *Chirality* **2000**, *12*, 442-449;Solinas, M.; Pfaltz, A.; Cozzi, P. G.; Leitner, W. *J. Amer. Chem. Soc.* **2004**, *126*, 16142-16147;McIntyre, S.; Hormann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282-288.

[11] Liu, D.; Tang, W. J.; Zhang, X. *Org. Lett.* **2004**, *6*, 513-516.

[12] Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1999**, *572*, 163-168.

Table I.1. PHOX and other related *P,N*-ligands in asymmetric catalysis

	 **21**[14]	 **22**[15]	 **23**[16]	 **24**[17]
	 **25**[18]	 **26**[19]	 **27**[20]	 **28**[21]
4	**Heck reaction**			
				
	Modified PHOX			
	 **29**[22]	 **30**[23]	 **31**[24]	

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[13] Zhu, S. F.; Xie, J. B.; Zhang, Y. Z.; Li, S.; Zhou, Q. L. *J. Amer. Chem. Soc.* **2006**, *128*, 12886-12891.

[14] Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825-3827.

[15] a) Lee, S. G.; Jung, H. R.; Kim, K. M.; Song, C. E.; Cho, C. G. *Bull. Korean Chem. Soc.* **2003**, *24*, 1407-1409;Lu, S. M.; Han, X. W.; Zhou, Y. G. *Adv. Synth. Catal.* **2004**, *346*, 909-912;Tellers, D. M.; Bio, M.; Song, Z. J.; McWilliams, J. C.; Sun, Y. K. *Tetrahedron: Asymmetry* **2006**, *17*, 550-553;Li, X. S.; Li, Q.; Wu, X. H.; Gao, Y. H.; Xu, D. C.; Kong, L. C. *Tetrahedron: Asymmetry* **2007**, *18*, 629-634.

[16] Kallstrom, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Amer. Chem. Soc.* **2004**, *126*, 14308-14309.

[17] Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8274-8276.

[18] Cozzi, P. G.; Zimmermann, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal.* **2001**, *343*, 450-454.

[19] Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833-836.

[20] Xu, G. P.; Gilbertson, S. R. *Tetrahedron Lett.* **2003**, *44*, 953-955.

[21] Hou, D. R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206-215.

[22] a) Kilroy, T. G.; Cozzi, P. G.; End, N.; Guiry, P. J. *Synthesis-Stuttgart* **2004**, 1879-1888;Fitzpatrick, M. O.; Coyne, A. G.; Guiry, P. J. *Synlett* **2006**, 3150-3154.

[23] Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205-2210.

<table>
<tr><th colspan="3">Table I.1. PHOX and other related <i>P,N</i>-ligands in asymmetric catalysis</th></tr>
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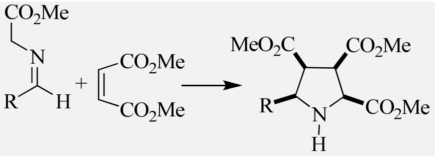
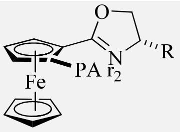
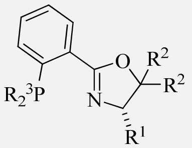
<tr><td rowspan="3"></td><td colspan="2"> </td></tr>
<tr><td colspan="2">PHOX ligands</td></tr>
<tr><td>
32[25]</td><td>
33[26]</td></tr>
</table>

Other interesting applications of the PHOX ligands which have not been so well studied in catalysis are presented in the next table: coupling of alkynes to enynes (entry 1 in Table I.2.),[27] asymmetric aza-Claisen rearrangement (entry 2 in Table I.2.),[28] insertion of α–diazocompounds into *NH* bonds (entry 3 in Table I.2.),[29] asymmetric hydroformylation (entry 4 in Table I.2.),[30] Kinugasa reaction (entry 5 in Table I.2.),[31] reduction of ketones with alcohols (entry 6 in Table I.2.),[32] and transfer hydrogenation of ketones (entry 7 in Table I.2.).[33]

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[24] Tu, T.; Hou, X. L.; Dai, L. X. *Org. Lett.* **2003**, *5*, 3651-3653.

[25] a) Yan, X. X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X. L.; Wu, Y. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1979-1983;Zeng, W.; Zhou, Y. G. *Org. Lett.* **2005**, *7*, 5055-5058.

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[31] Coyne, A. G.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, *18*, 199-207.

[32] a) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 3819-3822; b) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291-2293.

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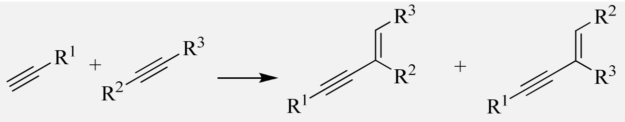
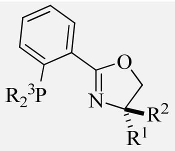
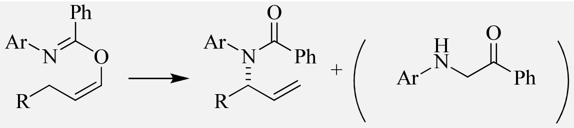
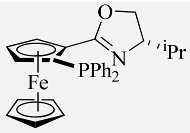
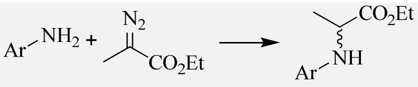
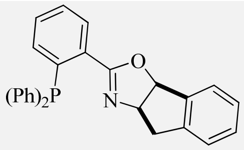
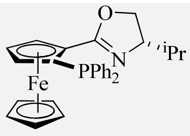
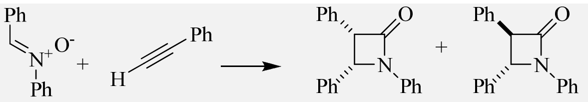
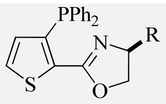
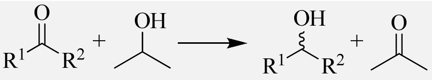
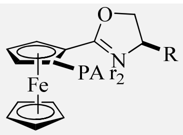
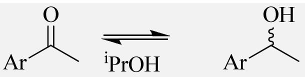
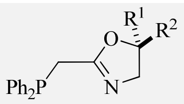
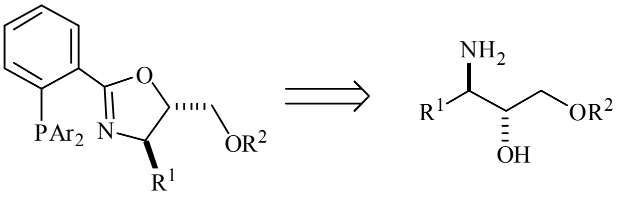
Table I.2. PHOX ligands in different asymmetric reactions

Entry	Reaction	PHOX ligand
1		
	Coupling of alkynes to enynes	**34**[27]
2		
	Asymmetric aza-Claisen rearrangement	**35**[28]
3		
	Insertion of α diazocompounds into N-H bonds	**36**[29]
4		
	Asymmetric hydroformylation	**37**[30]
5		
	Kinugasa reaction	**38**[31]
6		
	Reduction of ketones with alcohols	**39**[32]
7		
	Transfer hydrogenation of ketones	**40**[33]

Taking advantage of the group expertise in the synthesis of ligands derived from amino alcohols, we planned to develop a new family of modular phosphinooxazolines derived from enantiomerically pure amino alcohols **7** (R^2 = H) (Figure I.2.) and to carry out the study of their catalytic properties in asymmetric transformations of interest.[34]



8 **7**

Figure I.2. Synthesis of a new family of PHOX ligands

The modular nature of the designed ligands is key in our strategy (see Figure I.3.). By using a modular catalyst design, the structural features responsible for improving asymmetric induction can be simply modified and adjusted.

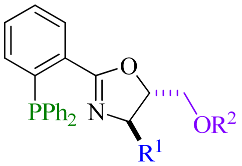


Figure I.3. Modularity in PHOX ligands.

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[34] Preliminary research on this topic was carried out by C. Puigjaner during her PhD tesis (UB 2000).

Whereas known phosphinooxazoline libraries incorporate modifications at the phosphorous atom or at the substituent of the carbon atom next to nitrogen, the study of the effects of the substituents at C-5 of the oxazoline moiety (such as the R^2OCH_2 group in **8**) remains unexplored. Besides its primary effect on catalytic activity and on enantioselectivity, the alkoxymethyl substituent in **8** offers the additional interest of allowing the heterogeneisation of the phosphinooxazoline ligand onto polymer supports. From this perspective, the optimization of the R^2OCH_2 moiety in **8** is of great importance: On one hand, the primary hydroxyl group of these structures is the obvious point for polymer anchoring with minimal perturbation of the reaction site.[35] On the other hand, the optimal OR^2 group will dictate the optimal nature for the resin onto which **8** can be anchored.

In this chapter the synthesis of the family of PHOX ligands together with the corresponding palladium complexes and their complete characterization, is described.

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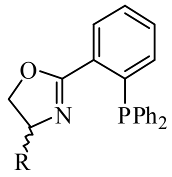
[35] a) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309-6318;Fraile Jose, M.; Mayoral Jose, A.; Serrano, J.; Pericas Miquel, A.; Sola, L.; Castellnou, D. *Org Lett*, *5*, 4333-5;Pericas, M. A.; Castellnou, D.; Rodriguez, I.; Riera, A.; Sola, L. *Adv. Synth. Catal.* **2003**, *345*, 1305-1313;Castellnou, D.; Fontes, M.; Jimeno, C.; Font, D.; Sola, L.; Verdaguer, X.; Pericas, M. A. *Tetrahedron* **2005**, *61*, 12111-12120;Castellnou, D.; Sola, L.; Jimeno, C.; Fraile, J. M.; Mayoral, J. A.; Riera, A.; Pericas, M. A. *J. Org. Chem.* **2005**, *70*, 433-438;Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653-4655;Bastero, A.; Font, D.; Pericas, M. A. *J. Org. Chem.* **2007**, *72*, 2460-2468;Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2007**, *9*, 1943-1946.

2. RESULTS AND DISCUSSION

2.1- Synthesis of the phosphinooxazolines 55, or their precedents 48

2.1.1. Antecedents for the preparation of the phosphinooxazoline moiety from an amino alcohol.



1

Figure I.4. Phosphinooxazoline ligand

As mentioned earlier, 2-(2-phosphinophenyl)ozaxolines (PHOX) **1** are well known in the literature. Phenyloxazolines **42** are key intermediates for the preparation of PHOX[36a] as they can be easily converted into the final compounds **45** by substitution of the halogenated atom by a nucleophilic trivalent phosphorous reagent or by metallation followed by phosphorylation (it will be discussed later, Scheme I.3). As far as the preparation of the required 2-phenyloxazolines **42** is concerned, they can be obtained through different routes. The first one involves the treatment of the corresponding amino alcohol with a 2-halobenzoic acid or its derivative, such as a nitrile or an amidate. 2-Phenyloxazolines (X= F, Br, H) **42** are obtained in this way in a one pot process (Scheme I.1.).

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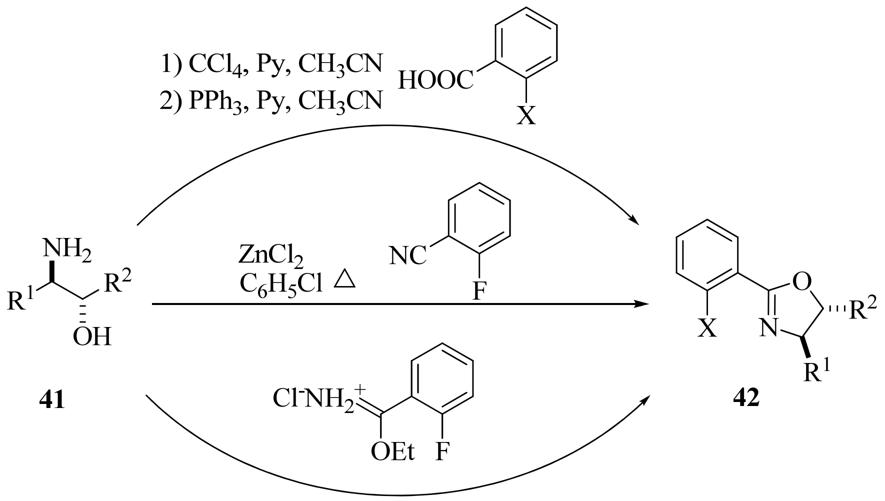
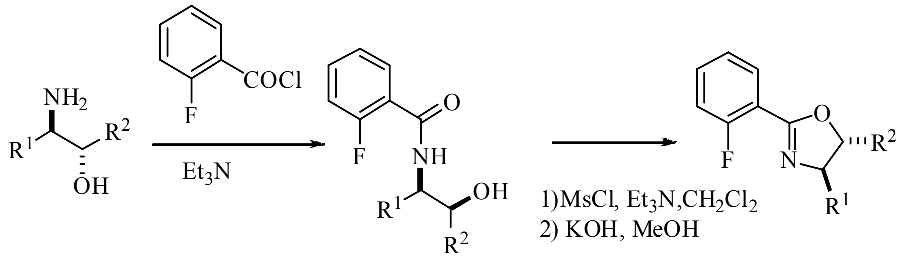
[36] a) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; et al. *Tetrahedron* **1996**, *52*, 7547-7583;Overman, L. E.; Owen, C. E.; Zipp, G. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 3884-3887;Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421-6429.



Scheme I.1. Synthesis route for 2-phenyloxazolines

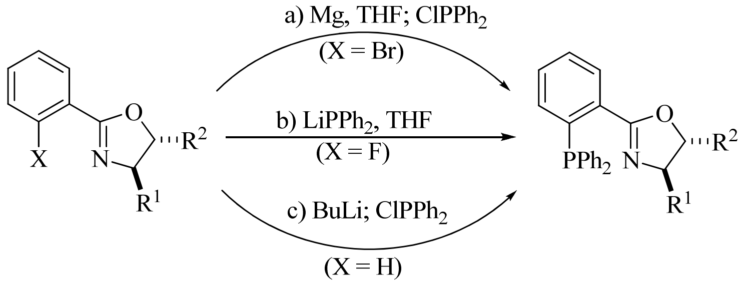
Another method, mainly used in the synthesis of *trans*-bisoxazolines **5**, consists, first, in the *N*-acylation of the amino alcohol followed by the activation of the secondary hydroxyl group as a leaving group for a S_N2 reaction. The cyclization step and subsequent formation of the oxazoline ring can subsequently be achieved in basic media. This method, which involves *N*-acylation, *OH*-activation and cyclization (Scheme I.2.), yields the target 2-(2-halophenyl)oxazolines **44** in higher yields than the ones obtained with the one-pot procedures already mentioned. Most interestingly, the cyclization should take place with inversion of configuration at the carbon that bears the hydroxyl group. In this way, *trans*-disubstituted oxazolines should be obtained when the starting amino alcohol has an *anti*-arrangement of the amino and hydroxyl substituents, as it is shown in Scheme I.2.



41 **43** **44**

Scheme I.2. Alternative synthesis route for 2-phenyloxazolines

The phosphino group could then be introduced in the last step of the synthetic sequence with three different strategies. The first strategy (path a in Scheme I.3.) consists in the magnesiation of an haloderivative (X=Br) followed by phosphorylation with an electrophilic phosphorous reagent ($ClPPh_2$).[36a] The second possible approach (path b in Scheme I.3.) consists in aromatic nucleophilic substitution of the fluoride group (X = F) by a nucleophilic phosphorous reagent ($LiPPh_2$).[36a] In the last strategy, (path c in Scheme I.3.) directed metallation of the *ortho* position of the aromatic ring to the oxazoline moiety followed by phosphorylation with an electrophilic phosphorous reagent ($ClPPh_2$) should render the target phosphinooxazolines.[36b,c]

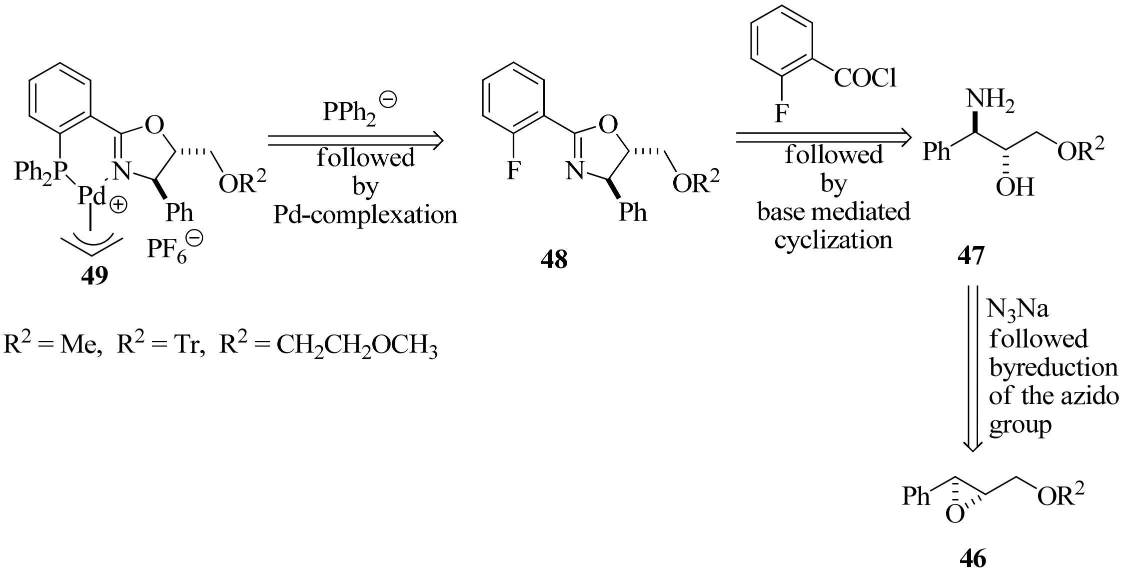


42 **45**

Scheme I.3. Introduction of the phosphino group

2.1.2. Synthesis of a family of phosphinooxazolines

In the preliminary work carried out by C. Puigjaner, the synthesis of the family of PHOX derived from Sharpless epoxides was envisaged following the synthetic sequence depicted in Scheme I.4.[37]



Scheme I.4. Synthetic sequence for Pd-PHOX complexes derived from Sharpless epoxides

Enantiopure Sharpless epoxy ethers are readily available.[38] Epoxide ring-opening with azide followed by reduction of the intermediate azido alcohols, rendered amino alcohols **47**. The already mentioned protocol (see Scheme I.2.) which consisted in acylation followed by base mediated cyclization and nucleophilic displacement of

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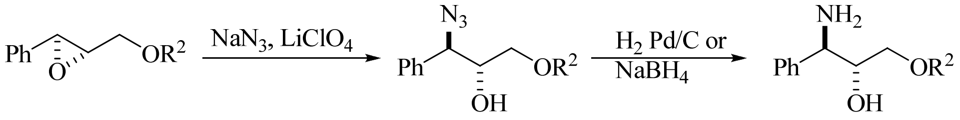
[37] Compounds 49 (R^1=Me, Tr, CH$_2$CH$_2$OCH$_3$) were described and preliminary catalytic studies on the allylic alkylation were carried out in the PhD tesis of C. Puigjaner.

[38] Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970-4982.

the fluoride group by PPh_2 rendered PHOX derivatives. The treatment of these compounds with an appropriated Pd precursor lead to the isolation of Pd-PHOX complexes **49** in good yields.

The regioselective and stereospecific ring-opening of the corresponding epoxides could be achieved by using sodium azide in a 5M $LiClO_4$ solution (Crotti's methodology[39]). Reduction of the azido alcohols **50** with either $NaBH_4$ or H_2 using palladium on charcoal as catalyst rendered the enantiopure amino alcohol in high yields (Scheme I.5.).



46 **50** **47**

Scheme I.5. Epoxide ring-opening with NaN_3 and reduction of the azido group to amine

Given that sodium azide is a hazardous reagent, we considered the possibility to develop alternative synthetic strategies to avoid this reagent. In this way, the direct aminolysis of Sharpless epoxy ethers appeared to be an attractive alternative.

By aminolysis of the epoxy ethers under pressure either under microwave irradiation[40, 41] or by simple thermal activation,[41] the enantiopure amino alcohols,

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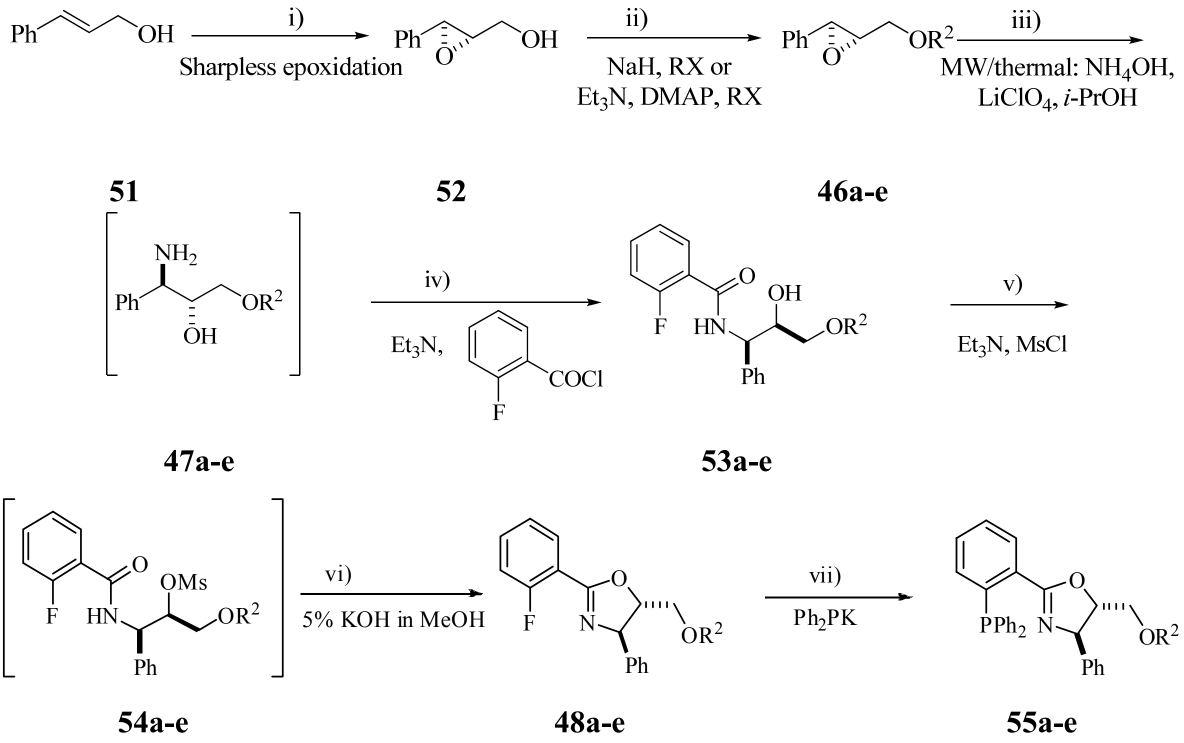
[39] a) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 7043-8; b) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939-42.

[40] a) Rodriguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericas, M. A. *Org. Lett.* **2005**, *7*, 3829-3832;Sabitha, G.; Subba Reddy, B. V.; Abraham, S.; Yadav, J. S. *Green Chemistry* **1999**, *1*, 251-252;Lindstrom, U. M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* **1999**, *40*, 9273-9276;Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731-734;Olofsson, B.; Somfai, P. *J. Org.*

47a-e (Scheme I.6., step iii) could be prepared. With microwave activation, the ring-opening proceeded satisfactorily just by dissolving **46a** (R=Me), **46b** (R=CH_2Ph) and **46e** (R=$(CH_2)_2OMe$) in 25% aqueous ammonia (50 eq.) and irradiating the corresponding solution for 8 min. at 125 ºC. Epoxy ethers **46c, d, f** and **46g**, which bear bulkier R groups, were not soluble in aqueous ammonia and a co-solvent (*i*-PrOH) was required to facilitate the reaction. In those latter cases, 1 eq. of lithium perchlorate was also added to the reaction mixture in order to accelerate the ring-opening reaction. Full conversion was achieved in this manner after not more than 20 min. It is worth noting that, under thermal conditions, these reactions required 5 to 7 hours for complete conversion (entries 4, 6 and 7 Table I.3.). Independently of the ring-opening method which was used, all the reactions took place stereospecifically and with high regiocontrol (Scheme I.6., step iii).

Chem. **2002**, *67*, 8574-8583;Favretto, L.; Nugent, W. A.; Licini, G. *Tetrahedron Lett.* **2002**, *43*, 2581-2584;Charrada, B.; Hedhli, A.; Baklouti, A. *Tetrahedron Lett.* **2000**, *41*, 7347-7349.

[41] Pasto, M.; Rodriguez, B.; Riera, A.; Pericas, M. A. *Tetrahedron Lett.* **2003**, *44*, 8369-8372.



a R^2= Me, **b** R^2 = CH_2Ph, **c** R^2 = $CHPh_2$, **d** R^2 = CPh_3, **e** R^2 = $(CH_2)_2OCH_3$

Scheme I.6. Synthesis of the 2-(2-diphenylphosphinophenyl)oxazolines **55a-e**

Amino alcohols **47a-e** were not further purified at this stage and were *N*-acylated under standard conditions with 2-fluorobenzoyl chloride in the presence of an auxiliary base (step iv in Scheme I.6.). The acylated products **53a-e** were purified and characterized. The overall yields (referred to the ring-opening and benzoylation steps) range from 53% to 80% and have been summarized in Table I.3.

Table I.3. Ring-opening and acylation of the epoxy ethers **46a-e**

Entry	**Epoxy ether**	**Aminolysis Conditions***	**2-Fluoro Benzamide**	**Overall yield** (%)
1	**46a**, R^2=Me	MW:125 ºC, 8 min.	**53a**	53
2	**46b**, R^2=CH_2Ph	MW:125 ºC, 8 min.	**53b**	69
3	**46c**, R^2=$CHPh_2$	MW:125 ºC, *i*-PrOH, 8 min.	**53c**	61
4	**46c**, R^2= $CHPh_2$	T:100 ºC, *i*-PrOH, 5 h, 1 eq. $LiClO_4$	**53c**	80
5	**46d,** R^2= CPh_3	MW:130 ºC, *i*-PrOH, 20 min, 1 eq. $LiClO_4$	**53d**	67
6	**46d,** R^2= CPh_3	T:100 ºC, *i*-PrOH, 5 h, 1 eq. $LiClO_4$	**53d**	60
7	**46e,** R^2=$(CH_2)_2OMe$	MW: 125 ºC, 8 min	**53e**	59

*MW: Microwave irradiation conditions; T: Thermal conditions.

Hydroxy benzamides **53a-e** were converted into the 2-(2-halophenyl) oxazolines in a two-step sequence,[42] involving activation of the free hydroxyl group in **54a-e** as a mesylate (methanesulfonyl chloride and triethylamine as auxiliary base; step v in Scheme I.6.) followed by base-induced cyclization (5% KOH/MeOH; step vi in Scheme I.6.). The overall activation-cyclization sequence took place in a straightforward way and good overall yields for the two steps were observed in all the cases (68-80%, Table I.4.). Due to the limited stability of the mesylates **54a-e**, these compounds were not stored and the cyclization was carried out within few hours after their preparation.

---

[42] Pericas, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gomez, M.; Jimenez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164-4178.

Table I.4. Preparation of the fluorooxazolines **48a-e** and phosphinooxazolines **55a-e**

Entry	Hydroxy amide	Overall yield steps v and vi	Yield of step vii	Final *P, N*-ligand
1	**53a** R^2= Me	76	93	**55a**
2	**53b** R^2= CH_2Ph	68	97	**55b**
3	**53c** R^2= $CHPh_2$	70	62	**55c**
4	**53d** R^2= CPh_3	80	76	**55d**
5	**53e** R^2=$(CH_2)_2OMe$	68	85	**55e**

The *trans* stereochemistry in the oxazoline ring arises from the fact that the cyclization step takes place with inversion of configuration at C-2, where the hydroxyl substituent had been previously activated as the mesylate. The relative *trans* stereochemistry of the chiral centres in the oxazoline ring could be confirmed by means of a NOESY experiment on **48b**, where a cross peak indicating NOE between the C*H*-N and the CH_2 units could be observed (the NOE cross peak is marked with a green circle).

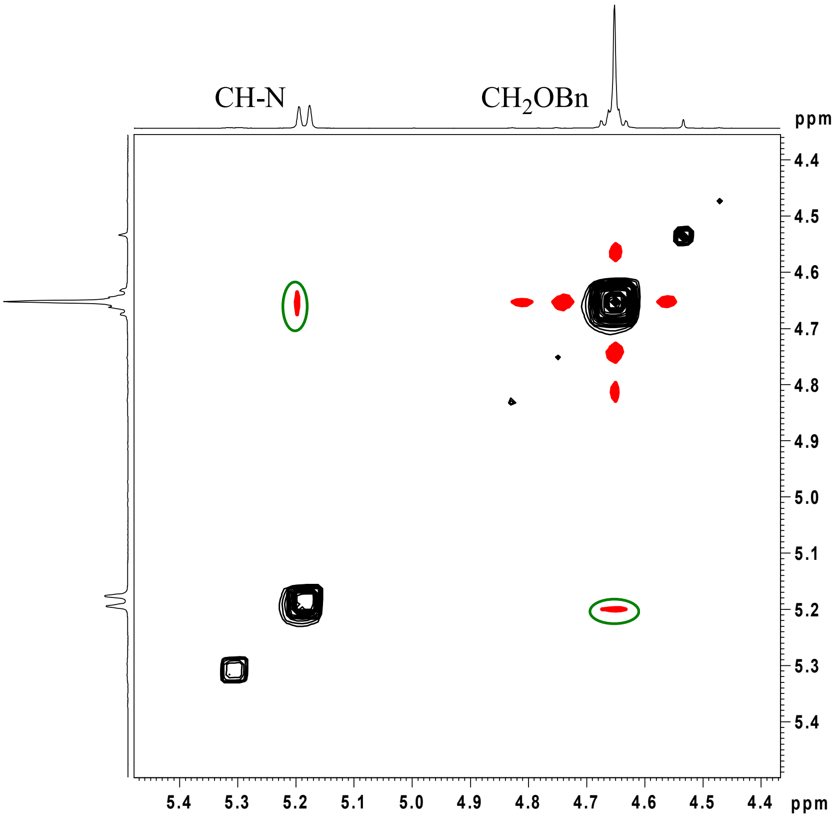
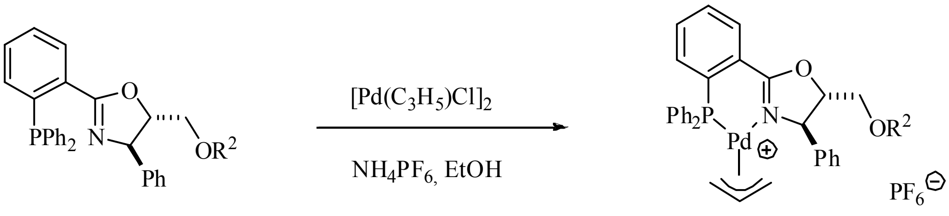


Figure I.5. NOESY spectra of oxazoline **48b, (R^2=Bz)**

The nucleophilic displacement of fluoride group with potassium diarylphosphide proceeded straightforwardly in THF at -20ºC. Quenching of the reaction mixture with sodium sulphate decahydrate followed by a short filtration through deoxygenated silica gel rendered pure phosphinooxazolines. The ^{31}P-NMR spectra confirmed the formation of the PHOX species by the presence of a singlet around -2 ppm. Good yields were obtained following this synthetic sequence (62-97% yield).

2.1.3. Synthesis of [Pd(η^3-allyl)(PHOX)]PF_6 complexes

The palladium phosphinooxazoline complexes were prepared from phosphinooxazolines **55** and commercial allyl palladium dimer $[Pd(C_3H_5)Cl]_2$ in the presence of ammonium hexafluorophosphate in ethanol, following the methodology described for the preparation of bisoxazoline palladium complexes.[42,43] The palladium complexes could be isolated from the reaction media by crystallization at low temperature (4ºC) in good yields (Table I.5.). The allylic compounds were obtained as monometallic complexes of general formula [Pd(η^3-allyl)(**L**)]PF_6 (Scheme I.7.).



55a-e

49a-e

Scheme I.7. Synthesis of Pd(η^3-allyl)(PHOX)]PF_6 complexes

To conclude with, it should be recalled that we have widened the Pd-PHOX library in order to be able to study more in depth the influence of the alkoxy substituent over the catalytic activity of the complex and the mechanistical issues in the allylic alkylation and amination reactions (chapters II and III).

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[43] a) von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rueegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265-84; b)Gomez, M.; Jansat, S.; Muller, G.; Maestro, M. A.; Saavedra, J. M.; Font-Bardia, M.; Solans, X. *J. Chem. Soc., Dalton Trans.* **2001**, 1432-1439.

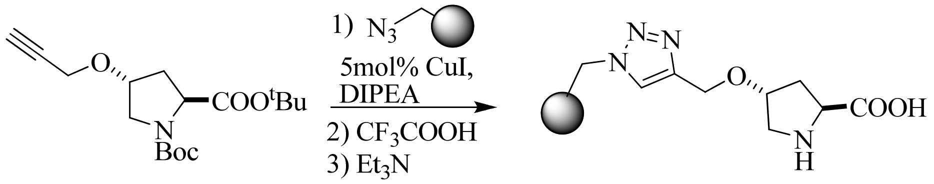
Table I.5. Synthesis yields for the palladium complexes

Pd-complex	**%yield**
49a, R^2= Me	76
49b, R^2= CH_2Ph	65
49c, R^2= $CHPh_2$	64
49d, R^2= CPh_3	63
49e, R^2=$(CH_2)_2OMe$	63

2.2. Synthesis of precursors of heterogenised phosphinooxazolines

The immobilization of chiral catalysts onto solid supports is a well known strategy to prepare chiral ligands with improved efficiency, handling and process control properties. Furthermore, immobilized catalysts can be more easily separated and reused than their homogeneous counterparts.[44]

Not surprisingly, many research groups are active in this field and a wide variety of organic and inorganic supports have been studied. Pericàs and co-workers have recently developed a strategy to anchor chiral ligands onto several polymer supports via click chemistry[45] (see scheme below for one example).



Scheme I.8. Strategy to anchor chiral ligands onto polymer supports

As a project that does not fully fall within the scope of the present PhD thesis, it was envisaged to develop anchoring strategies for the PHOX ligands described in this work onto polymer supports using click chemistry. The anchoring strategy is depicted in Scheme I.9.

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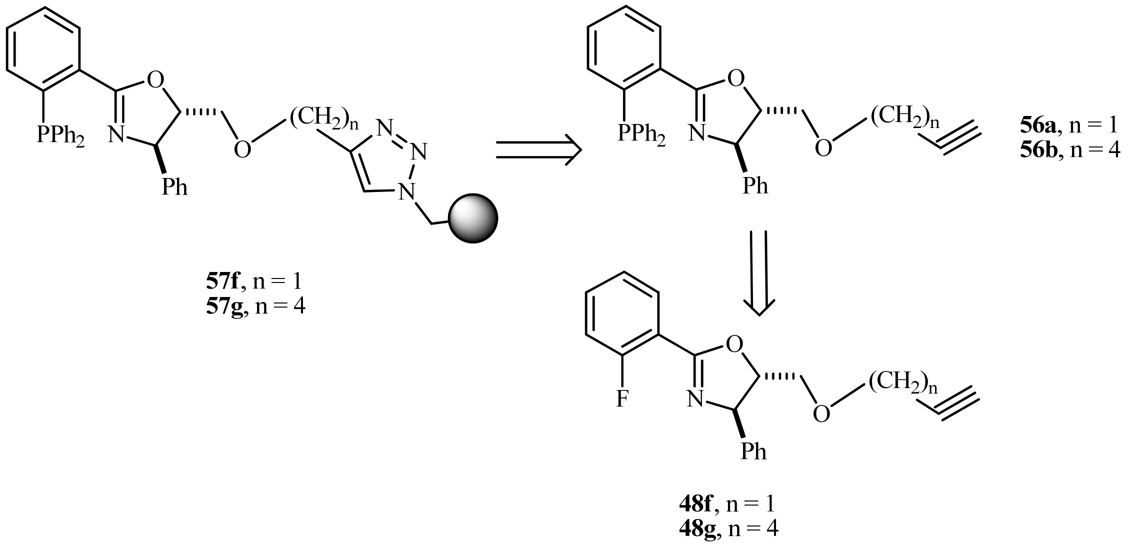
[44] De Vos, D. E.; Vankelecom, I. F. J., Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling* **2000**.

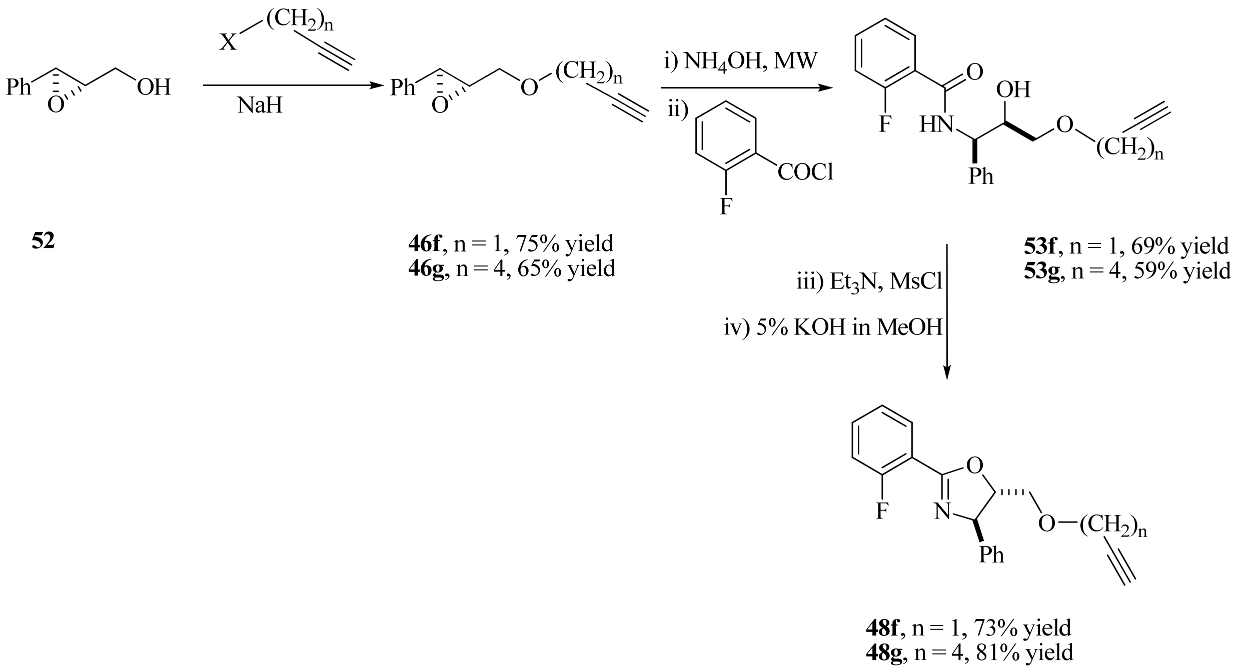
[45] a) Bastero, A.; Font, D.; Pericas, M. A. *J. Org. Chem.* **2007**, *72*, 2460-2468;Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653-4655;Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2007**, *9*, 1943-1946;Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2007**, *9*, 3717-3720;Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2008**, *10*, 337-340.

ISBN:978-84-691-8862-0/DL:T-1275-2008



Scheme I.9. Anchoring of the PHOX ligands onto polymer supports

The required 2-(2-halophenyl) oxazolines **48f** and **48g** could be easily synthesized with our synthetic strategy in good yields (see scheme I.10).



52

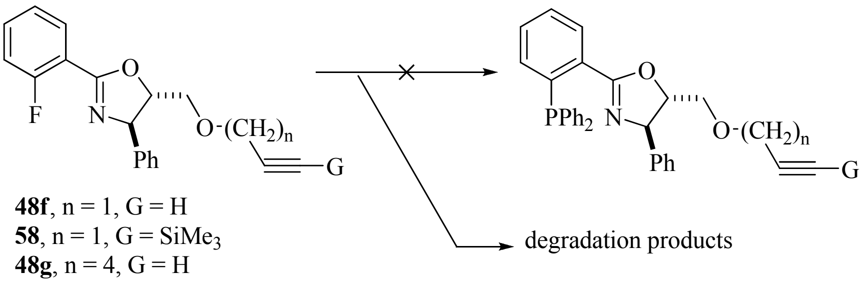
46f, n = 1, 75% yield
46g, n = 4, 65% yield

53f, n = 1, 69% yield
53g, n = 4, 59% yield

48f, n = 1, 73% yield
48g, n = 4, 81% yield

Scheme. I.10. Synthesis of the 2-(2-halophenyl)oxazolines **48f** and **48g**

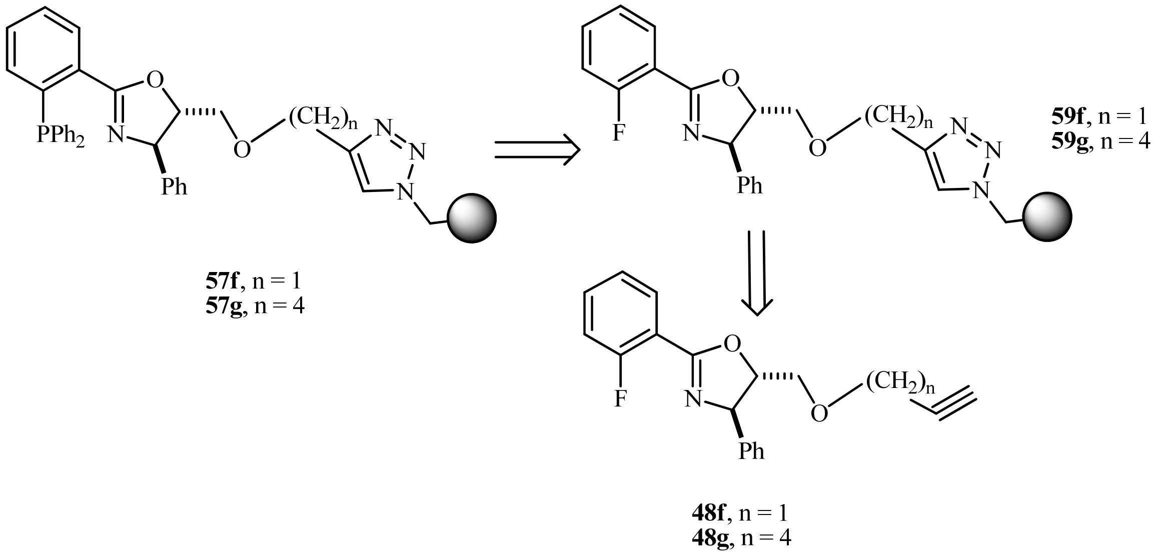
Unfortunately, the nucleophilic displacement of the fluoride by phosphorous nucleophilic reagent (KPPh$_2$) failed under all reaction conditions tested, even in the case of TMS-protected derivatives. In all cases, only degradation products could be isolated (Scheme. I.11.).



48f, n = 1, G = H
58, n = 1, G = SiMe$_3$
48g, n = 4, G = H

Scheme. I.11. Nucleophilic displacement of the fluoride by KPPh$_2$

As a consequence, the synthetic strategy was changed and it was decided to anchor first the fluorooxazolines onto the polymer support and to carry out the displacement of the fluoride group by $KPPh_2$ onto the immobilized fluorooxazoline **48** with solid phase synthetic techniques (Scheme. I.12.).



Scheme. I.12. Different anchoring approach

This chemistry is already underway within the PhD thesis of Rocío Marcos at our institute.

In order to be able to compare the catalytic activity of polymer bound PHOX and their homogeneous counterparts, it was decide to prepare **49f**. Furthermore, with this compound in hand, it should be possible to study the contribution of the polymer backbone and the triazole ring to the outcome of the asymmetric transformations.

The synthetic strategy to prepare monomeric analogues of polymer bound PHOX ligands is shown in the Scheme. I.13. Fluorooxazoline **48** was obtained according to the standard procedure described in this work (see Scheme. I.10.). The formation of the *N*- benzylated triazole could be easily achieved in one step under microwave irradiation conditions in the presence of an *in situ* generated Cu(I) catalyst (step i in Scheme. I.13.) in high yield (81%).[46, 45b]

Nucleophilic displacement of the fluoride group by potassium diphenylphosphide rendered **61** in 73% yield (step ii in Scheme. I.13.). Palladium complex, **49f** was prepared from phosphinooxazolines **61** and commercial allyl palladium dimer $[Pd(C_3H_5)Cl]_2$ in the presence of ammonium hexafluorophosphate in ethanol, following the general methodology described for the preparation of bisoxazoline palladium complexes.[42,43] Palladium complex **49f** was isolated from the reaction media by crystallization at low temperature (4ºC) in 79% yield (step iii, Scheme. I.13.).

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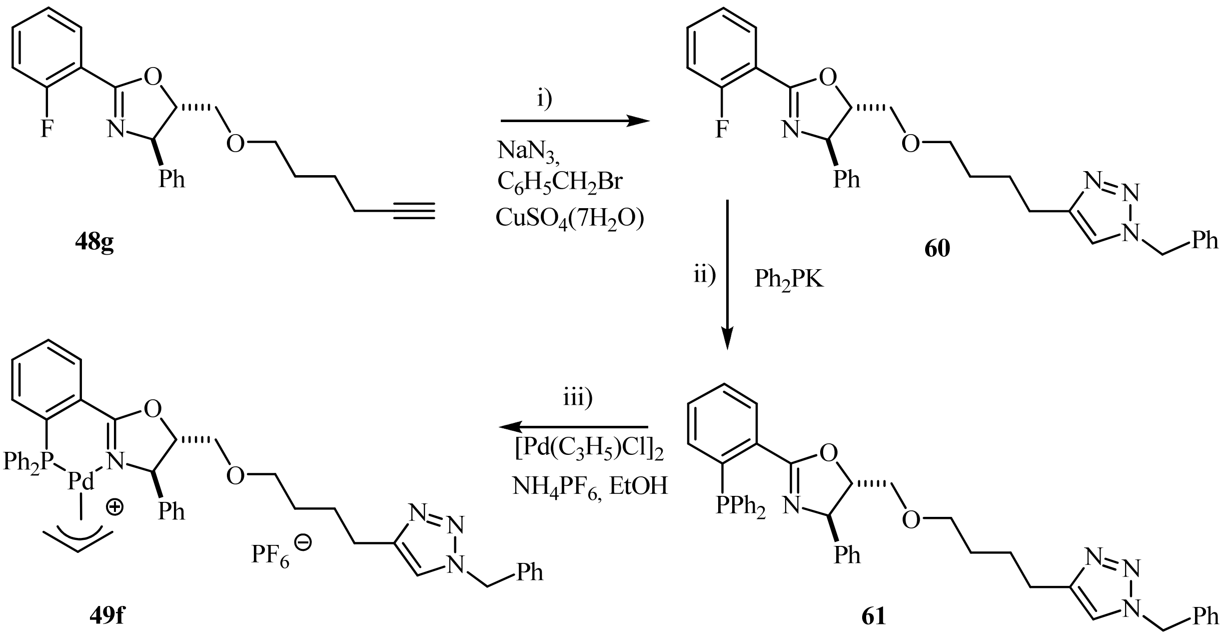
[46] Padwa, A.; Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry, Vol. 1* **1984**.



Scheme. **I.13.** Synthesis path of **49f** from the fluorooxazoline **48g**

2.3. Characterization of the [Pd(η^3-allyl)(PHOX)]PF_6 complexes

[Pd(η^3-allyl)(PHOX)]PF_6 complexes were fully characterized by the usual techniques. ESI mass spectra in its positive detection mode exhibited, in all cases, the peak at highest ratio for the [Pd(η^3-allyl)(**L**)] fragment.

NMR spectroscopy has been very useful to determine the structure of these complexes. In the first place, their cationic nature was demonstrated by the observation of a signal in ^{31}P-NMR at around -140 ppm corresponding to the PF_6 counteranion. Secondly, the coordination of the palladium centre with the phosphorous donor group was demonstrated by a downfield shift (ca. 30 ppm, see Table I.6.) in the ^{31}P-NMR between the complexed and the free ligand.

As far as the structure of **49a-f** in solution is concerned, it is well known that palladium η^3-allyl complexes are normally observed as two isomeric species which interconvert through a fluxional process of the allyl group.[47] In the case of an asymmetric palladium complex such as **49a-f**, an *endo* and an *exo* isomers are possible: the central C-atom of the allyl group points towards the phenyl substituent of the oxazoline ring (position 3) in the case of the *exo* isomer and towards the opposite direction in the case of the *endo* isomer.[48] The interconversion of the *endo* and *exo P,N*-palladium η^3-C_3H_5[47b,d, 49] and allylic substituted[47c,48, 50] species is a well

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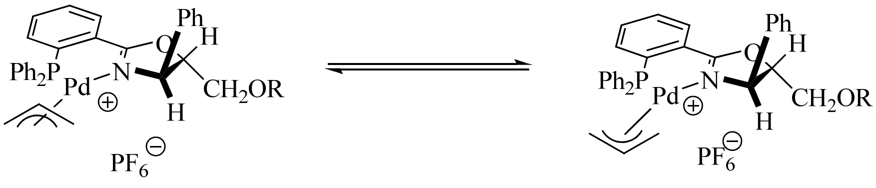
[47] a) Pregosin, P. S.; Salzmann, R.; Togni, A. *Organometallics* **1995**, *14*, 842-847;Herrmann, J.; Pregosin, P. S.; Salzmann, R.; Albinati, A. *Organometallics* **1995**, *14*, 3311-3318;Barbaro, P.; Pregosin, P. S.; Salzmann, R.; Albinati, A.; Kunz, R. W. *Organometallics* **1995**, *14*, 5160-5170;Breutel, C.; Pregosin, P. S.; Salzmann, R.; Togni, A. *J. Amer. Chem. Soc.* **1994**, *116*, 4067-4068;Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523-6.

[48] Baltzer, N.; Macko, L.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **1996**, *79*, 803-812.

[49] Schaffner, S.; Macko, L.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1997**, *80*, 463-471.

studied process which involves, in most of the cases, a η^3-η^1 isomerization, subsequent rotation of the sp^3-sp^2 bond of the allyl moiety in the palladium sigma complex followed by a final coordination of the olefin to the palladium centre.



49-*exo*

49-*endo*

Scheme. **I.14.** *Exo-endo* dynamic equilibrium

COSY and NOESY experiments together with reported NMR data allowed the complete assignation of the NMR signals for the two isomers *endo* and *exo* **49a-f**. For example, the cross peaks of the COSY experiment led to the assignation of the allylic protons of each isomer (Figure I.6.). The proton of the central carbon that appears as a well defined signal in the ^{1}H-NMR spectra gives cross peaks with the other four non equivalent terminal protons of the allyl moiety making possible a good differentiation of the *endo* and *exo* isomers.

---

[50] a) Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *155*, 35-68;Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Amer. Chem. Soc.* **1996**, *118*, 1031-7;Malet, R.; MorenoManas, M.; Pajuelo, F.; Parella, T.; Pleixats, R. *Magn. Reson. Chem.* **1997**, *35*, 227-236;Liu, S. Y.; Muller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv Chim Acta* **2000**, *83*, 1256-1267;Kollmar, M.; Goldfuss, B.; Reggelin, M.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2001**, *7*, 4913-4927;Dotta, P.; Kumar, P. G. A.; Pregosin, P. S. *Magn. Reson. Chem.* **2002**, *40*, 653-658.

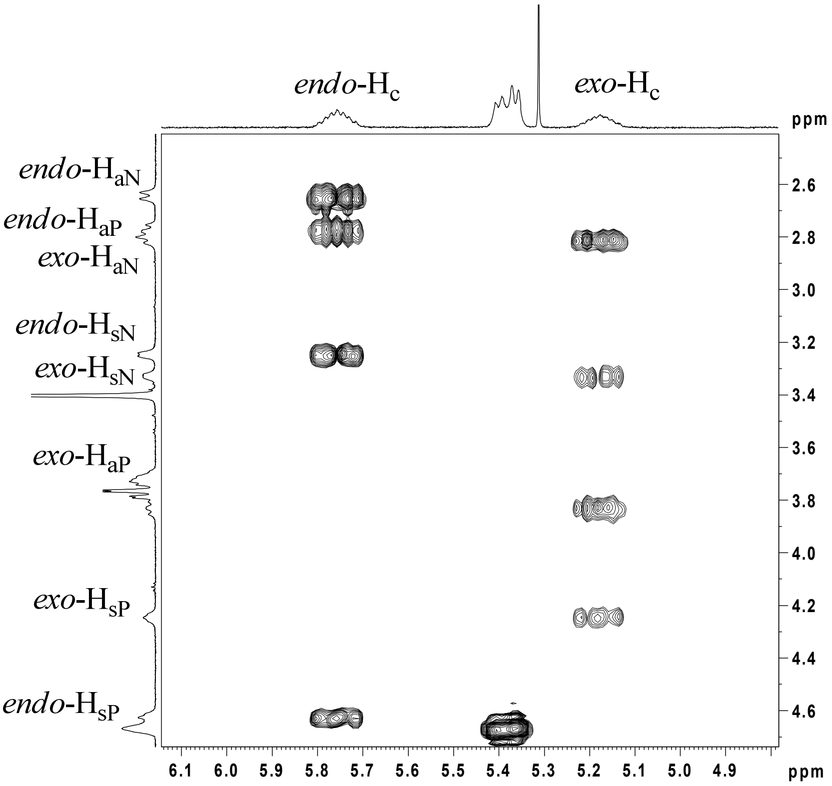


Figure I.6. COSY of **49a** complex. Central allylic protons of both isomers *endo/exo*

The NOESY experiments gave us worthy information in relation with the spatial orientation of the Pd-PHOX substituents in the complexes **49a-f** and helped with the signal assignation. The relevant NMR spectroscopic data is summarized in Table I.6.

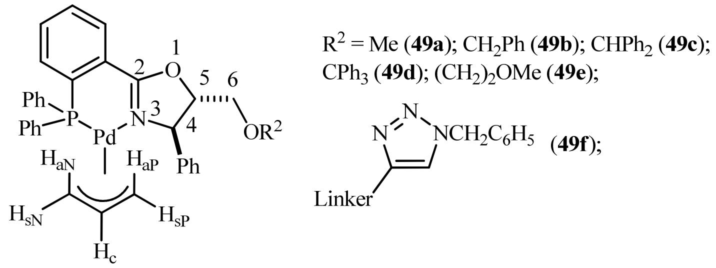


Table I.6. Selected NMR (^{1}H-, ^{31}P and ^{13}C-NMR) data for complexes **49a-f**^{a}

		49a	**49b**	**49c**	**49d**	**49e**	**49f**^{e}
PHOX moiety	**H-C$_5$**	4.63(bs, 2H)	4.59(m,3H)	4.65 (m, 2H)	4.48(bs, 2H)	4.70 (m, 2H)	4.69 (m, 2H)
	H-C$_4$	5.34 (d, 7.5, 1H)$^{+}$	5.27 (d, 7.4, 1H)$^{+}$	5.24 (d, 7.5, 1H)$^{+}$	5.07 (d, 7.5, 2H)	5.36 (bs, 2H)	5.3 (d, 7.0, 2H)
		5.38 (d, 7.5, 1H)*	5.29 (d, 7.4, 1H)*	5.27 (d, 7.5, 1H)*			
	H-C$_6$	3.83(m, 5H)	3.76(m, 5H)	3.86 (dd, 11.1, 3.6, 2H)	3.49(m, 4H)	3.89 (dd, 11.5, 3.5, 2H)	3.82 (dd, 11.5, 3.5, 2H)

Table I.6. Selected NMR (^{1}H-, ^{31}P and ^{13}C-NMR) data for complexes **49a-f**^{a}

	C_P^{b}	79.2 ($^2J_{CP}$= 29)$^+$ 80.9 ($^2J_{CP}$= 30)*	79.1 ($^2J_{CP}$= 29)$^+$ 81.4 ($^2J_{CP}$= 29)*	78.8 ($^2J_{CP}$= 30)$^+$ 81.0 ($^2J_{CP}$= 30)*	d	d	d
	C_N^{b}	57.2 $^+$ 56.2 *	57.5 $^+$ 56.1*	57.7 $^+$ 56.0*	58.5$^+$ d*	58.5$^+$ d	d
	P	24.5$^+$, 25.0* (-2.9)^c	24.5$^+$, 25.1* (-2.9)^c	24.4$^+$, 25.1* (-2.8)^c	24.6$^+$, 25.1* (-2.8)^c	24.4$^+$, 25.1* (-2.8)^c	24.5$^+$, 25.1* (-3.0)^c
Allyl moiety	**H_c**	5.73 (tt, 13.0, 7.0, 1H)$^+$ 5.15 (tt, 13.3, 6.7, 1H)*	5.66 (tt, 13.2, 7.2, 1H)$^+$ 5.08 (tt, 13.5, 7.1, 1H)*	3.78 (dd, 11.5, 5.6, 2H) 5.62 (tt, 13.6, 8.0, 1H)$^+$ 5.09 (tt, 13.5, 7.6, 1H)*	5.38 (bs, 1H)$^+$ 5.65 (bs, 1H)*	3.86 (dd, 11.5, 5.5, 2H) 5.71 (bs, 1H)$^+$ 5.15 (bs, 1H)*	3.70 (dd, 11.5, 3.5, 2H) 5.70 (bs, 1H)$^+$ d

Table I.6. Selected NMR (^{1}H-, ^{31}P and ^{13}C-NMR) data for complexes **49a-f**[a]

	H$_{sP}$	4.60 (bs, 1H)$^{+}$	4.59(m, 3H)$^{+}$	4.48 (bs, 1H)$^{+}$	4.33 (bs, 1H)$^{+}$	4.60 (bs, 1H)$^{+}$	d
		4.22 (bs, 1H)*	4.19 (t, 7.0, 1H)*	4.29 (bs, 1H)*	4.03 (bs, 1H)*	4.19 (bs, 1H)*	d
	H$_{sN}$	3.22 (d, 6.3, 1H)$^{+}$	3.16 (d, 6.5, 1H)$^{+}$	3.15 (d, 6.3, 1H)$^{+}$	2.95 (bs, 1H)$^{+}$	3.24 (bs, 1H)$^{+}$	d
		3.31 (d, 6.3, 1H)*	3.26 (d, 6.7, 1H)*	3.29 (d, 6.3, 1H)*	3.26 (bs, 1H)*		d
	H$_{aP}$	2.74 (d, 11, 1H)$^{+}$	2.6 (d, 12, 1H)$^{+}$	2.67 (d, 11, 1H)$^{+}$	2.65 (bs, 3H)$^{+}$	2.74 (bs, 1H)$^{+}$	d
		3.83 (m, 5H)*	3.76(m, 5H)*	3.62 (dd, 12.5, 10.0, 1H)*	3.65 (bs, 1H)*	2.74 (bs, 1H)*	d
	H$_{aN}$	2.61 (d, 12.5, 1H)$^{+}$	2.57 (d, 12.6, 1H)$^{+}$	2.61 (t, 11Hz, 1H)$^{+}$	2.65 (bs, 3H)$^{+*}$	2.65 (bs, 1H)$^{+}$	d

Table I.6. Selected NMR (^{1}H-, ^{31}P and ^{13}C-NMR) data for complexes **49a-f**[a]

		2.78 (t, 12, 1H)*	2.70 (d, 10.1, 1H)*	2.71 (t,11Hz, 1H)			[d]

[a] The suprascript + refers to the *endo* isomer and * to the *exo* one.

[b] Allylic carbon *trans* to the phosphorous centre in **49a-f**

[c] ^{31}P-NMR chemical shifts of the free phosphino oxazolines **55a-e** and **61**

[d] This carbons are observed as a hump

[e] Probably due to the equilibrium exchange the allylic signals (protons and carbons) could not be well identified; are observed as hump.

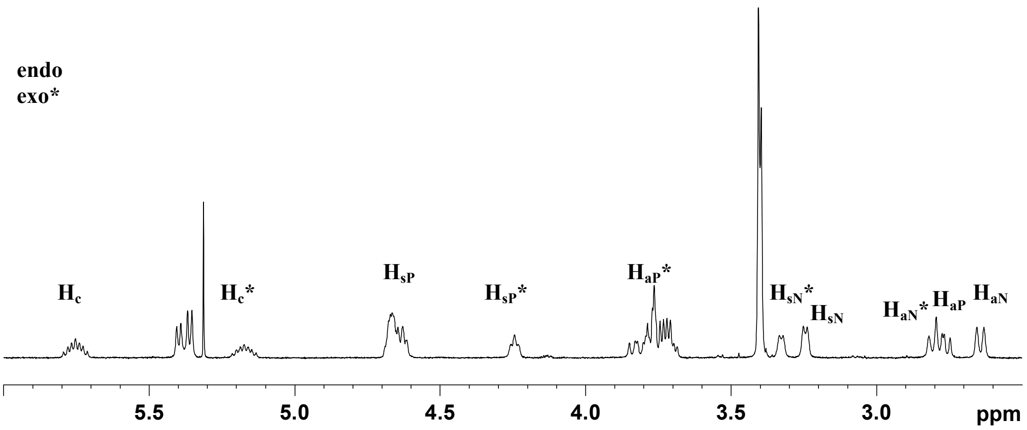
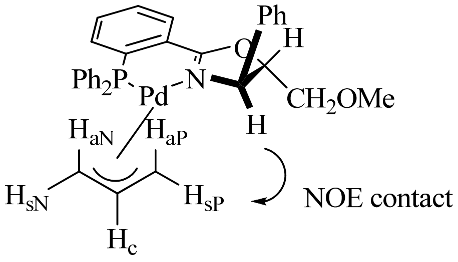


Figure I.7. Complete assignment of allylic protons of *endo* and *exo* isomers of the **49a** complex

The lack of symmetry of complexes **49** is clearly reflected in the signals of the allyl moiety as two set of signals for the *anti* (H_a) and for the *syn* (H_s) protons that are observed for almost all the studied PHOX palladium complexes. Furthermore, the *endo*- and the *exo*-complexes **49** are in a slow exchange regime in the NMR time scale at room temperature. Each *syn* and/or *anti* proton for each of the allyl *endo* and *exo* isomers could be observed for the complexes **49a-e**. The allyl region in the ^{1}H-NMR spectrum of palladium complex **49a** together with the assignment of the different signals of the allyl group has been depicted in Figure I.7. The major isomer has been assigned to the *endo* form as it is described in the literature that the ^{1}H-NMR signal of the central allylic proton in the *endo* isomer is deshielded with respect to the same signal in the *exo* isomer.[48] Furthermore, a NOESY experiment for **49a** revealed a NOE interaction between the allylic H_{sP} proton and the CH-N proton of the major isomer (Figure I.8.), which corroborates the previous assumption that the major isomer corresponds to the *endo*-complex. As far as the other palladium complexes **49b-f** are concerned, one of the two possible isomers consistently predominates and the major ones have been assigned to the *endo* form by means of the same arguments as for **49a**. As far as the other signals in ^{31}P-, ^{13}C-for both kind of palladium complexes are concerned, the signals of the phosphino groups of the **49a-f,** in ^{31}P-NMR can be observed one signal for each diastereomer and the signals of the allylic carbons *trans* to phosphorous for complexes **49a-e** as two sets for each of the allyl *endo*- and *exo*- complexes (see Table I.6.).



49a-*endo*

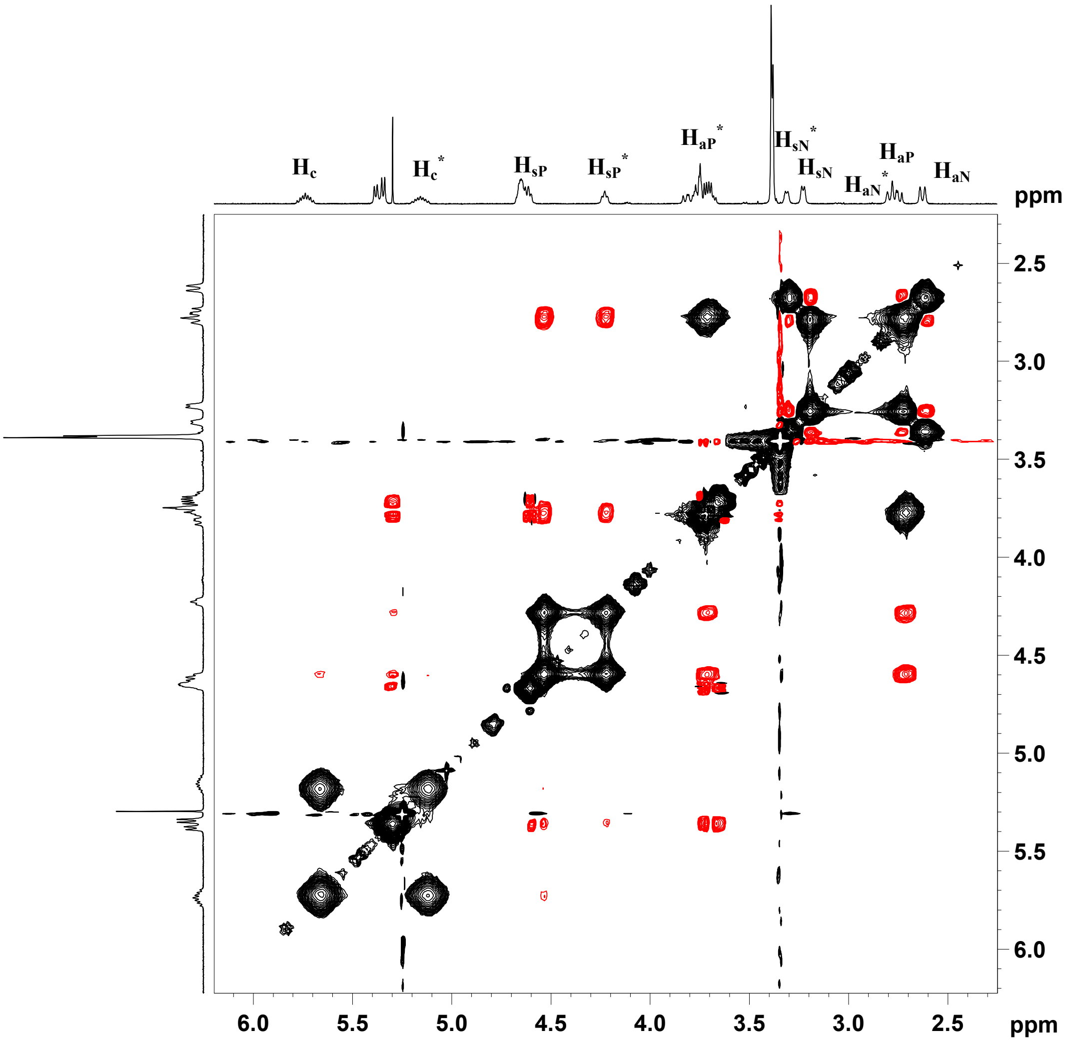


Figure I.8. Allylic region in the phase-sensitive NOESY of palladium complex **49a** at rt. (The suprascript * refers to the *exo*-isomer)

The analysis of the phase-sensitive NOESY spectra of the *endo*- and *exo*-mixture of complexes **49a**, and more concretely the exchange peaks of the allylic protons (see Figure I.8.), gave information about the fluxional process through which the two complexes are interconverting at room temperature. The NOESY spectrum was also recorded at -40ºC and the two spectra were completely superimposable. An exchange signal (opposite colour to the diagonal peaks in the NOESY spectra of Figure I.8.) between the *syn* proton *trans* to nitrogen (H_{sN}) of the *exo* isomer and the *anti*-proton *trans* to nitrogen (H_{aN}) of the *endo* isomer was observed. Analogous exchange signals were observed for the following pairs: *endo* H_{sN} with *exo* H_{aN}; *endo* H_{sP} with *exo* H_{sP} and *endo* H_{aP} with *exo* H_{aP} (See Figure I.8.). Analogous exchange peaks were observed for the *endo*- *exo*- complex mixtures **49b-d**. These observations are in agreement with a π–σ–π isomerization process which has been reported for referable systems.[47a,c,48,50c-f,51] The phosphorous and the nitrogen groups have different coordinative properties and the π–acceptor properties of the phosphorous group towards palladium confers a weaker character to the Pd-C bond *trans* to the phosphorous substituent. This has been demonstrated by a longer Pd-C bond distance for the terminal allylic C *tran*s to phosphorous as single crystal X-ray diffraction measurements in **49a** have revealed (Table I.7.).[52] In this way, the *endo-exo* conversion through a π–σ–π mechanism begins with the opening of the Pd-C bond *trans* to P and is followed by a rotation of the Pd-C sigma-bond and subsequent palladium-allyl bond formation. The equivalences between the allylic protons from the *endo* and *exo* complexes through this fluxional process have been summarized in Figure I.9. and are in agreement with what has been reported in the

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[51] Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214.

[52] This weaker Pd-C bond character of one of the two terminal allyl carbons was also observed in the η^3-1,3-diphenylallyl-bis(oxazoline) palladium complexes previously reported by us too, but steric hindrance between the bisoxazoline moiety and the allyl group accounted for this observation in our previous case.

literature.[47d] It should be recalled at this point that an analogous *endo-exo* conversion through a π–σ–π mechanism starting with the opening of the Pd-C bond *trans* to N can be basically excluded as the expected exchange peaks between the allylic protons for such a process (see Figure I.9.) are not observed in the NOESY spectrum.

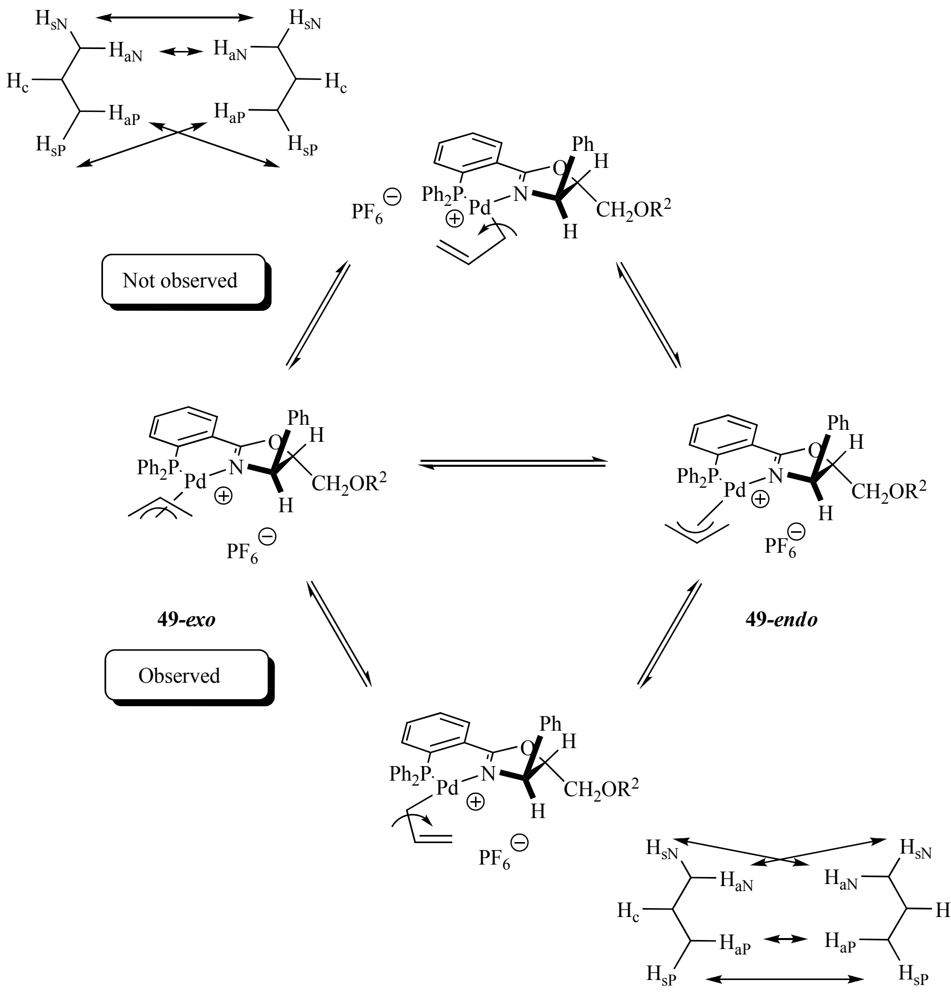


Figure I.9. Dynamic equilibrium through π-σ-π isomerization

The structure of the palladium complex **49a** in the solid state could be determined by X-Ray crystallography as single crystals could be grown in methanol.

Selected bond-distances for the allyl moiety in complex **49a** have been summarized in Table I.7. The allylic ligand of **49a** was found to be disordered and refined with only one position for one terminal allylic carbon (C30, see Figure I.10.) and two positions for the other terminal (C32) and the central (C31) allylic carbon atoms. Refining the occupancy factors afforded an *endo/exo* ratio of 58:42. The *endo/exo* ratio could be measured in solution by integration of the central allylic proton signals and it was found to be 65:35 being the *endo* isomer the more abundant in solution too.

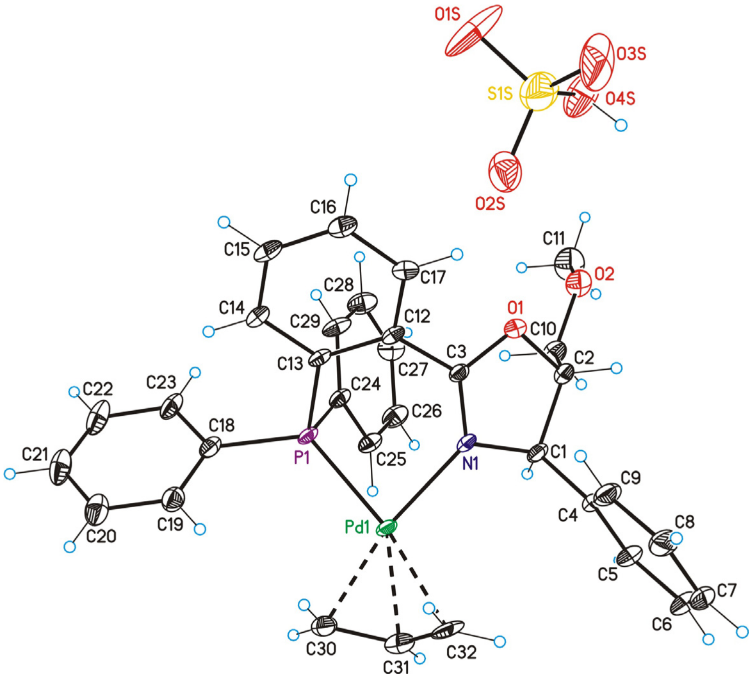


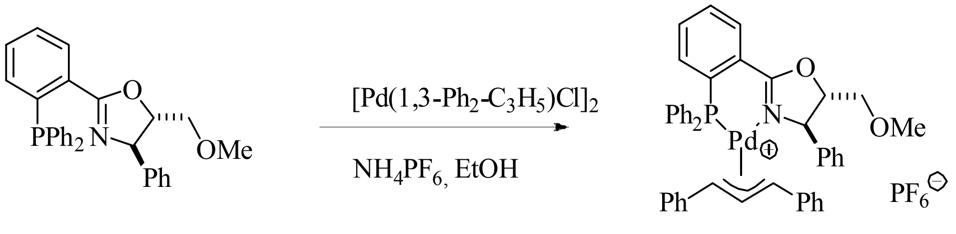
Figure I.10.X-Ray structure of the *endo* form of complex **49a**

Table I.7. Bond lengths [Å] for **49a**

Pd(1)-N(1)	2.109(3)
Pd(1)-C(30)	2.125(4)
Pd(1)-C(31)	2.137(7)
Pd(1)-C(31')	2.206(8)
Pd(1)-C(32)	2.217(7)
Pd(1)-C(32')	2.225(8)
Pd(1)-P(1)	2.2892(8)

The coordination geometry is a distorted square-planar complex and the four coordination sites are occupied by the phosphorous, nitrogen and terminal allylic carbon atoms. The Pd-C bond to the terminal allylic C-atom *trans* to the P-atom is significantly longer (2.217 Å for the *endo* isomer and 2.225 Å for the *exo* one) than that to the C-atom trans to the N-atom (2.137 Å for both the *endo* and *exo* isomers). The weaker character of the Pd-C bond *trans* to the P-atom has its importance in the dynamic processes which are going on as it has been discussed before and in reactivity of this complexes towards the allylic alkylation and amination reaction. The X-Ray structure of the complex has been depicted in Figure I.10.

The model substrate normally employed for the evaluation of the catalytic activity of the PHOX ligands in the substitution reaction is the 3-acetoxy-1,3-diphenyl-1-propene. The Pd-catalyzed enantioselective nucleophilic substitution starts from the racemic substrate and proceed via a symmetrical [Pd(η^3-(1,3-Ph$_2$-C$_3$H$_3$)PHOX] complex. Thus the study of the structure and the determination of the ratio of the possible isomers of the complex **49a** might divulge interesting information respect to the allylic substitution mechanism. As will be explained more detailed in the mechanistic section of the chapter II the Pd(I)-1,3-disubstituted allyl complexes can give rise to several isomers depending on the stereochemical relationship between the substituents of the allyl group and the central hydrogen: *syn-syn*, *syn-anti*, *anti-syn*, *anti-anti.*[3,50a-f] For this reason, the diphenylallyl palladium complex **62**, was prepared from the appropriate PHOX ligand, **55a** following the same general procedure[42,43] as for the complexes **49a-f** but employing the palladium dimer [Pd(1,3-Ph_2-C_3H_3)Cl]$_2$ instead.



55a **62**

Scheme. **I.15.** Synthesis of the phosphinooxazoline-palladium complex **62**

The *exo* and the *endo* forms of complex **62** were assigned by comparison with NMR signals (proton, carbon and phosphorous) of similar complexes described in the literature. As it was normally observed for 1,3-diphenyl allyl PHOX complexes, in the complex **62** the *exo* form predominates. The isomers *syn-anti* and *anti-syn* were detected in minor proportion by ^{31}P-NMR (for more details see chapter II).[53]

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[53] The ^{31}P-NMR spectra of the complex **62** showed six signals at 81.7, 40.5, 34.9, 27.8, 24.7, and 23.1 ppm with relative intensities 0.09:0.06:0.05:0.26:0.1:10.00.

3. EXPERIMENTAL PROCEDURES

3.1. General Remarks

All compounds were prepared under Argon atmosphere using standard vacuum-line and Schlenk techniques. Tetrahydrofuran, dichloromethane, acetonitrile, dimethylformamide and hexane were dried and deoxygenated by using a Solvent Purification System (SPS). Ethylacetate and ethanol were deoxygenated with two freeze-thaw cycles.

All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Compounds **52 a-e** and **61** were filtered through a short SiO_2, pad which was previously deoxygenated with Argon, immediately before being converted into the palladium complexes **47**.

The experiments under microwave irradiation were carried out in a CEM discover microwave reactor (the temperature is automatically controlled by a non-contact infrared sensor that monitors and controls the temperature conditions of the reaction vessel).

NMR spectra were recorded on Bruker Avance 400 and 500 Ultrashield spectrometers in $CDCl_3$ unless otherwise cited. ^{1}H-NMR and ^{13}C-NMR chemical shifts are quoted in ppm relative to TMS whereas ^{31}P-NMR chemical shifts are quoted in ppm relative to 85% phosphoric acid in water. IR spectra were recorded on a Bruker Tensor 27 spectrometer in Fourier transform mode. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 spectropolarimeter. Enantiomeric excesses were determined by HPLC on Agilent 1100 Series chromatograph with a UV detector, by GC on a Agilent Technologies 6890N gas chromatograph with a FID detector, and by ^{1}H-NMR using Eu(hcf)$_3$ as a chiral shift reagent. Elemental analyses were carried out by the *"Unidade de Análise Elemental"* from the *"Universidade de Santiago de Compostela"* in an Eager 200 microanalyzer.

Crystal structure determination was carried out using a Bruker-Nonius diffractometer equipped with a APPEX 2 4K CCD area detector, a FR591 rotating anode with Mo$_{K\alpha}$ radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = 100 K). Fullsphere data was collected using omega and phi scans. Apex2 V. 1.0-22 (Bruker-Nonius 2004) was used for the data collection, Saint + Version 6.22 (Bruker-Nonius 2001) for the data reduction and SADABS V. 2.10 (2003) for the absorption correction. Crystal structure solution was achieved using direct methods as implemented in SHELXTL Version 6.10 (Sheldrick, Universtität Göttingen (Germany), 2000). Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL Version 6.10 (Sheldrick, Universtität Göttingen (Germany), 2000. All non hydrogen atoms were refined including anisotropic displacement parameters.

$[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ was purchased from Alpha Aesar and $KPPh_2$ from Aldrich and were used without any further purification. $[Pd(\eta^3\text{-}PhCHCHCHPh)(\mu\text{-}Cl)]_2$ was synthesized following general described methodologies.[54]

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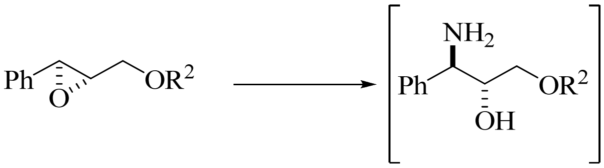
[54] Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Amer. Chem. Soc.* **1989**, *111*, 6301-11.

3.2. General procedures

The synthesis and characterization of the phenylglycidol and its *O*-protected derivatives excepting **46f** and **46g**, have been described in the literature.[38] The amino alcohols have been reported previously,[55] excepting for **47f** and **47g**.

P1. Microwave assisted epoxide ring opening with aqueous ammonia. Synthesis of amino alcohols 47a-e.



46a-e **47a-e**

The corresponding epoxide (1.0 mmol), 30% aqueous NH_3 (50.0 mmol), $LiClO_4$ (1.0 mmol) and of *iso*-propanol (5.0 mL) if required, were irradiated at 125 ºC for the period of time from 8 to 40 minutes. The mixture was left to reach room temperature and the solvent was removed *in vacuo*. The crude was dissolved in CH_2Cl_2 (5.0 mL) and washed with water (3 x 5.0 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The corresponding amino alcohols **47a-e** were used in the next step without further purification.

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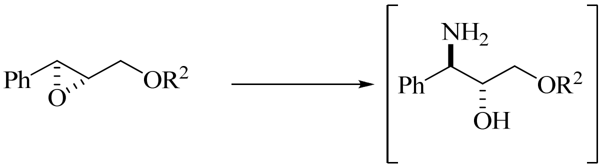
[55] Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902-7911.

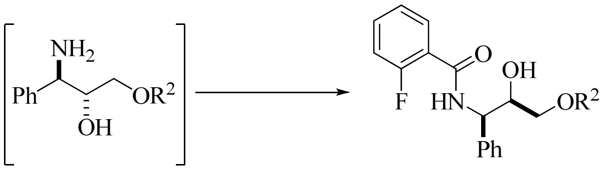
P2. Epoxide ring opening with aqueous ammonia. Thermal Conditions. Synthesis of amino alcohols 47 d, f, g.



46d, f, g **47 d, f, g**

The corresponding epoxide (1.0 mmol), 30% aq. NH_3 (50.0 mmol), $LiClO_4$ (1 mmol) and *iso*-propanol (5.0 mL) if required, were heated in a sealed pressure at 100 ºC for the period of time from 1.5 to 7 hours. The mixture was left to reach room temperature and the solvent was removed under reduced pressure. The crude was dissolved in CH_2Cl_2 (5.0 mL) and washed with water (3 x 5.0 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure. The corresponding amino alcohols **47 d, f, g** were used in the next step without further purification.

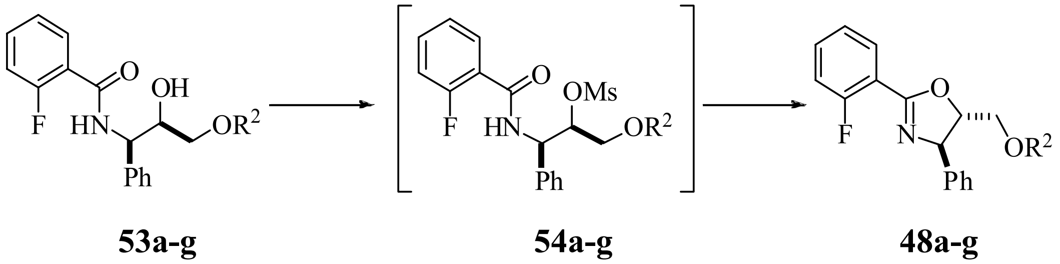
P3. Synthesis of (2-fluoro)phenyl hydroxy amides 53a-g.



47a-g **53a-g**

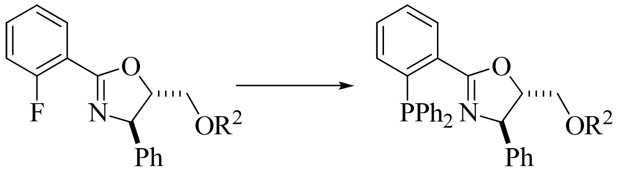
Et_3N (1.95 mmol) was added under Ar to a solution of the corresponding amino alcohol **47a-g** (1.0 mmol) in dry THF (1.5 mL) and the mixture was cooled at 0 ºC. A solution of 2-fluorobenzoyl chloride (0.95 mmol) in dry THF (1.3 mL) was slowly added to the previous solution. The mixture was left to reach room temperature and further stirred for two hours. The solvents were removed *in vacuum*. The crude was dissolved in CH_2Cl_2 (5.0 mL) and washed with brine (3 x 5.0 mL). The organic phase was dried over anhydrous Na_2SO_4, the drying agent was filtered off and the solvent removed under reduced pressure. The raw material was purified by chromatography over SiO_2 eluting with a mixture of hexanes/AcOEt of increasing polarity: from 100:0 to 60:40.

P4. Synthesis of (2-fluoro)phenyl oxazolines 48a-g.



Methanesulfonyl chloride (1.1 mmol) was slowly added under Argon to a solution of compounds **53a-g** (1.0 mmol) and Et_3N (2.2 mmol) in CH_2Cl_2 (8.2 mL) at 0ºC. The mixture was left to reach room temperature and further stirred for two hours. The mixture was washed with a saturated aqueous solution of NH_4Cl (9.0 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 6.0 mL). All organic phases were washed with brine (5.0 mL), dried over anhydrous Na_2SO_4. The drying agent was filtered off and solvent removed under reduced pressure. This raw material was added to a 5% solution of KOH in MeOH (9.0 mL, 2.0 mmol), and the mixture was stirred 15 hours at room temperature. The reaction was quenched with water (5.0 mL) and extracted with CH_2Cl_2 (3 x 5.0 mL). The organic phases were dried over anhydrous Na_2SO_4. The drying agent was filtered off and solvent removed under reduced pressure. The purification of the products **48a-g** was carried out by flash column chromatography.

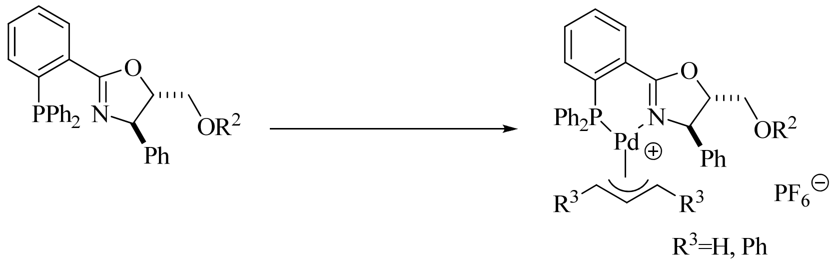
P5. Synthesis of the phosphinooxazoline ligands 55a-e.



48a-e **55a-e**

A THF solution of Ph_2PK (1.45 mmol, 2.8 mL of 0.5 M) was slowly added under Argon at -78 ºC via cannula to an oven dried schlenk flask which contained the corresponding fluorooxazoline **48a-e** (1.0 mmol) in THF (2.0 mL). The temperature was allowed to reach -20 ºC and the reaction mixture was further stirred for 2 hours at this temperature. Then allowed to reach room temperature, further stirred for 12 hours at this temperature, quenched with Na_2SO_4 $10H_2O$ in order to hydrolyze the excess of diphosphine, and filtered through a short SiO_2 pad and eluting with CH_2Cl_2. The residue after removing the solvents was further purified by column chromatography over SiO_2 under Argon. SiO_2 and the solvents which were involved in the chromatographic purifications were previously deoxygenated either by flushing or bubbling Argon. Compounds **55a-e** were not fully characterized (only ^{1}H- and ^{31}P-NMR were recorded, see characterization section) and were immediately transformed into the corresponding palladium complexes **49a-e**.

P6. Synthesis of the phosphinooxazoline allyl-palladium complexes 49a-f and 62



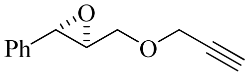
55a-e

49a-e (R^3=H)
62 (R^3=Ph)

A solution of compound **55a-e** (1.0 mmol) in deoxygenated ethanol (2.0 mL) was added via cannula to a schlenk flask which contained a solution of allyl-palladium precursor in ethanol (5.0 mL) ($[Pd(C_3H_5)Cl]_2$ for complexes **49a-e** and $[Pd(C_3H_3)(C_6H_5)_2Cl]_2$ for complex **62** (0.53 mmol). The reaction mixture was stirred 1 hour under Argon at room temperature, then NH_4PF_6 (1.02 mmol) was added. The resulting solution was further stirred for 14 hours and allowed to stand at -20 ºC for several hours. The Palladium complexes precipitated were filtered off, washed with cold ethanol (3.0 mL) and dried *in vacuum*.

3.3. Synthesis and characterization

3.3.S1. Synthesis of (*2S, 3S*)-2-phenyl-3-((prop-2-ynyloxy)methyl)oxirane, 46f



The synthesis of the *O*-protected derivative, **46f** was performed following reported methods.[38] A solution of 2, 3-cinnamyl-epoxialcohol (1.4 g, 9.3 mmol) in anhydrous DMF (10.0 mL) was added under Argon to a suspension of sodium hydride (0.45 g, 11.19 mmol) in dry DMF (10.0 mL) previously cooled at -20 ºC. The reaction mixture was stirred for 20 minutes. To the reaction mixture propargyl bromide (1.5 mL, 14.0 mmol) was then added drop wise. The reaction mixture was stirred at -20 ºC for one hour, then allowed to reach room temperature and stirred for 16 hours. The reaction was quenched with methanol (4.0 mL) and brine (10.0 mL). The layer was extracted with dichloromethane (3 x 20.0 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure. The title compound was obtained (1.32 g) after column chromatography through SiO_2 (hexanes/AcOEt 100:0/80:20) as a pale yellow oil in a 75% yield.

$[\alpha]^{23}_{D}$= -49.02 (c = 1.1 in $CHCl_3$);

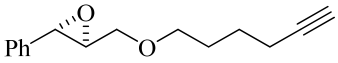
IR (film)ν: 3285, 2854, 1461, 1100, 879, 699 cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 7.36-7.25 (m, 5H, Ph), 4.29-4.20 (m, 2H), 3.90 (dd, *J* = 11.5 Hz, *J* = 3.0 Hz, 1H, C*H*HO), 3.81 (d, *J* = 2.3 Hz, 1H, C*H*Ph), 3.68 (dd, *J* = 11.5 Hz, *J* = 5 Hz, 1H, CH*H*O), 3.24-3.21 (m, 1H, C*H*CH_2), 2.47-2.46 (m, 1H, *H*CCCH_2);

^{13}C-NMR (100.6 MHz, $CDCl_3$)δ: 136.7 (*C*, Ph), 128.5 (*C*H, Ph), 128.3 (*C*H, Ph), 125.7 (*C*H, Ph), 79.2 (*C*CH), 75.0 (C*C*H), 69.4 (*C*H_2O), 60.7 (*C*H_2CCH), 58.6 (*C*HCHO), 55.9 (CH*C*HO);

HRMS (ESI+ve) calcd for $C_{12}H_{12}O_2Na$ (M+Na): 211.0735, found 211.0731.

3.3.S2. Synthesis of (*2S,3S*)-2-((hex-5-ynyloxy)methyl)-3-phenyloxirane, 46g



The synthesis of the *O*-protected derivative of the phenylglycidol, **46g** was performed following described literature methods.[40] A solution of 2, 3-cinnamyl-epoxyalcohol (1.5 g, 9.9 mmol) in anhydrous DMF (10.0 mL) was added under Argon to a suspension of sodium hydride (0.47 g, 11.7 mmol) in dry DMF (15.0 mL) previously cooled at -20 ºC. The reaction mixture was stirred for 20 minutes. To the reaction mixture 6-chloro-1-hexyne (1.6 mL, 13.0 mmols) was added drop wise. The reaction mixture was stirred at -20 ºC for 3 hour. Then allowed to reach room temperature and stirred for 24 hours. The reaction was quenched with methanol (10.0 mL) and brine (20.0 mL). The layer was extracted with dichloromethane (3 x 20.0 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed at reduced pressure. The title compound was obtained (1.5 g) after column chromatography through SiO_2 (hexanes/AcOEt 100:0/80:20) as a pale yellow oil in a 65% yield.

$[\alpha]^{23}_{D}$= -148.58 (c = 1.3 in $CHCl_3$);

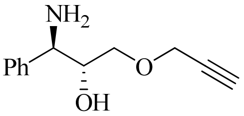
IR (film)ν: 3293, 2921, 1459, 1259, 1112, 880, 750 cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 7.35-7.25 (m, 5H, Ph), 3.81-3.76 (m, 2H, C*H₂*), 3.59-3.50 (m, 3H, C*H₂*, OC*H*), 3.20-3.17 (m, 1H, C*H*-O), 2.22 (td, 2H, *J* = 7.1 Hz, *J* = 2.7 Hz, C*H₂*CCH), 1.95 (t, 1H, *J* = 2.7 Hz, CC*H*), 1.76-1.67 (m, 2H, C*H₂*), 1.65-1.58 (m, 2H, C*H₂*);

^{13}C-NMR (100.6 MHz, $CDCl_3$)δ: 136.9 (*C*, Ph), 128.5 (*C*H, Ph), 128.2 (*C*H, Ph), 125.7 (*C*H, Ph), 84.2 (*C*CH), 71.07 (*C*H_2O), 70.6 (*C*H_2O), 68.5 (C*C*H), 61.2 (*C*HCHO), 55.9 (CH*C*HO), 28.7 (*C*H_2), 25.1 (*C*H_2), 18.2 (*C*H_2);

HRMS (TOF MS ES+) calcd for $C_{15}H_{18}O_2Na$ (M+Na): 253.1204, found 253.1198.

3.3.S3. Synthesis of (*1R,2R*)-1-amino-1-phenyl-3-(prop-2-ynyloxy)propan-2-ol, 47f



The synthesis of the amino alcohol **47f** was performed following general thermal ring opening procedure, **P2** employing the corresponding epoxide. The epoxide, **46f** (0.30 g, 1.60 mmol), 30% aq. NH_3 (5 mL, 79.70 mmol), $LiClO_4$ (0.17 g, 1.60 mmol) and *iso*-propanol (3.00 mL) reacted at 110 ºC for 6h. The mixture was left to reach room temperature and the solvent was removed under reduced pressure. The raw material was dissolved in CH_2Cl_2 (5 mL) and washed with water (3 x 5 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure. The corresponding amino alcohol was used in the next step without further purification. In order to characterize properly the compound **47f** was performed column chromatography purification, silica, hexanes/ethyl acetate 100:0 to 50:50. The final product was obtained in >99% yield as pale-yellow viscous oil.

$[\alpha]^{23}_{D}$= -33.3 (c = 0.9 in $CHCl_3$);

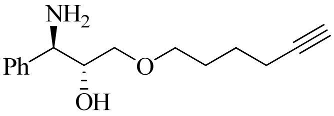
IR (film)ν: 3337, 3277, 2852, 1601, 1494, 1453, 1071, 763, 701 cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.20 (m, 5H, Ph), 4.12-4.10 (m, 3H, C*H*NH_2, CHOHC*H*$_2$), 3.95 (ddd, *J* = 5.1 Hz, *J* = 5.1 Hz, *J* = 5.1 Hz, 1H, C*H*OH), 3.48-3.46 (m, 2H, OC*H*$_2$CCH), 2.44 (bs, 2H,O*H*, N*H*$_2$), 2.41-2.40 (m, 1H,CH_2CC*H*).

^{13}C-NMR (100.6 MHz, $CDCl_3$)δ: 141.7 (*C*, Ph), 128.4 (*C*H, Ph), 127.5 (*C*H, Ph), 127.2 (*C*H, Ph), 79.4 (*C*CH), 74.8 (C*C*H), 73.5(*C*HCOH), 71.1 (*C*H_2O), 58.6 (*C*H_2CCH), 57.8 (*C*HCNH_2);

HRMS (ESI+ve) calcd for $C_{12}H_{16}NO_2$(M+H): 206.1181, found 206.1178.

3.3.S4. Synthesis of (*1R,2R*)-1-amino-3-(hex-5-ynyloxy)-1-phenylpropan-2-ol, 47g



The synthesis of the amino alcohol **47g** was performed following general thermal ring opening procedure, **P2** employing the corresponding epoxide (1.4 g, 6.08 mmol), 30% aq. NH_3 (19.3 mL, 3.04 mmol), $LiClO_4$ (0.68 g, 6.08 mmol) and *iso*-propanol (7.0 mL). The mixture was heated in a sealed pressure tube at 100 ºC for 7h. The mixture was left to reach room temperature and the solvent was removed under reduced pressure. The raw material was dissolved in CH_2Cl_2 (7.0 mL) and washed with water (3 x 7.0 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure. In order to characterize properly the compound was performed column chromatography purification, silica, hexanes/ethyl acetate 100:0 to 50:50. The final product was obtained in 90% yield as yellow viscous oil.

$[\alpha]^{23}_{D}$= -68.75 (c = 1.0 in $CHCl_3$);

IR(film)ν : 3287, 2865, 1668, 1454, 1114, 704, 632 cm^{-1};

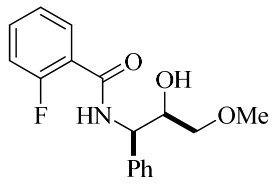
^{1}H-NMR (400 MHz, $CDCl_3$)δ: 7.36-7.20 (m, 5H, Ph), 4.13 (d, 1H, *J* = 5.0 Hz, C*H*NH_2), 3.95 (ddd, *J* = 5.0 Hz, *J* = 5.0 Hz, *J* = 5.0 Hz, 1H, C*H*-OH), 3.40-3.28 (m, 4H, C*H₂*OCH_2), 2.19 (td, 2H, *J* = 7.1 Hz, *J* = 2.6 Hz, C*H₂*CCH), 1.94 (t, 1H, *J* = 2.7 Hz, CC*H*), 1.69-1.62 (m, 2H, C*H₂*), 1.69-1.52 (m, 2H, C*H₂*);

^{13}C-NMR (100.6 MHz, $CDCl_3$)δ: 141.0 (*C*, Ph), 128.5 (*C*H, Ph), 127.6 (*C*H, Ph), 127.2 (*C*H, Ph), 84.2 (*C*CH), 73.0 (*C*HOH), 71.7 (*C*H_2O), 70.9 (O*C*H_2), 68.6 (C*C*H), 57.8 (*C*HNH_2), 28.5 (*C*H_2), 25.1 (*C*H_2), 18.2 (*C*H_2);

HRMS (TOF MS ES+) calcd for $C_{15}H_{22}NO_2$(M+H): 248.1651, found 248.1658.

3.3.S5. A. Synthesis of (2-fluoro)phenyl hydroxylamides

3.3.S5. A1. *Synthesis of 2-fluoro-N-((1R,2R)-2-hydroxy-3-methoxy-1-phenylpropyl)benzamide,* ***53a****.*



Employing general method **P3** was added 2-fluorobenzoyl chloride (0.11 mL, 0.95 mmols) and Et_3N (0.27 mL 1.95 mmols) dissolved in anhydrous THF (1.3 mL) over a solution amino alcohol **47a** (0.18 g, 1.0 mmol) in anhydrous THF (1.5 mL). The final product **53a** was isolated as white foam, 0.18 g in 60% yield.

$[\alpha]_D^{23}$ = + 32.9 (c = 0.74, $CHCl_3$).

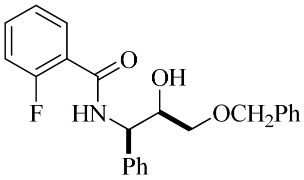
IR(film) ν: 3330, 2900, 1635, 1530, 1481, 1451, 1098, 751, 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 8.22 (bs, 1H, N*H*), 8.06 (dt, *J* = 7.9 Hz, *J* = 1.9 Hz, 1H, Ph), 7.48-7.10 (m, 8H, Ph), 5.45 (ddd, *J* = 8.4 Hz, *J* = 4.6 Hz, *J* = 2.3 Hz, 1H, C*H*N), 4.13-4.09 (m, 1H, C*H*OH), 3.42 (dd, *J* = 9.8 Hz, *J* = 3.6 Hz, 1H, C*H*H), 3.36 (s, 3H, C*H₃*O), 3.26 (dd, *J* = 9.8 Hz, *J* = 5.0 Hz, 1H, CH*H*), 2.81 (d, *J* = 6.6 Hz, 1H, O*H*);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 162.9 (d, $J_{C\text{-}F}$ = 2.9 Hz, *C*=O), 160.7 (d, $J_{C\text{-}F}$ = 246.0 Hz, *C*F), 138.6 (*C*, Ph), 133.2 (d, $J_{C\text{-}F}$ = 9.5 Hz, *C*H, Ph), 132.1 (d, $J_{C\text{-}F}$ = 2.0 Hz, *C*H, Ph), 128.6 (*C*H, Ph), 127.6 (*C*H, Ph), 127.1 (*C*H, Ph), 124.7 (d, $J_{C\text{-}F}$ = 3.6 Hz, *C*H, Ph), 121.0 (d, $J_{C\text{-}F}$ = 11.0 Hz, *C*, Ph), 115.9 (d, $J_{C\text{-}F}$ = 24.5 Hz, *C*H, Ph), 73.4 (*C*H_2), 72.0 (*C*HOH), 59.1 (*C*H_3O), 57.1 (*C*HNH);

HRMS(ESI+ve): Calcd. for: $C_{17}H_{18}NO_3NaF$ (M+Na): 326.1168, Found: 326.1165.

3.3.S5. A2. *Synthesis of N-((1R,2R)-3-(benzyloxy)-2-hydroxy-1-phenylpropyl)-2-fluorobenzamide,* ***53b***



Employing general method **P3** was added 2-fluorobenzoyl (0.11 mL, 0.95 mmols) chloride and Et_3N (0.27 mL, 1.95 mmols) dissolved in anhydrous THF (1.3 mL) over a solution of amino alcohol **47b** (0.26 g, 1.0 mmol) in anhydrous THF (2 mL). The final product was isolated as white foam, 0.25 g in 65% yield.

$[\alpha]_D^{23}$ = + 35.19 (c = 0.86, $CHCl_3$).

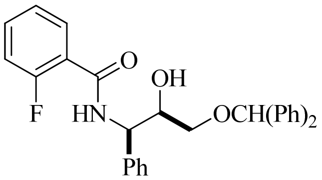
IR(film) ν: 3344, 3029, 1634, 1529, 1484, 1451, 1065, 749 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.08 (bs, 1H, N*H*), 7.97 (dt, *J* = 8.0 Hz, *J* = 1.9 Hz, 1H, Ph), 7.41-6.98 (m, 13H, Ph), 5.38 (ddd, *J* = 8.3 Hz, *J* = 4.5 Hz, *J* = 2.1 Hz, 1H, C*H*N), 4.48-4.40 (cs, 2H, C*H₂*Ph), 4.09-4.06 (m, 1H, C*H*-OH), 3.44 (dd, *J* = 9.6 Hz, *J* = 3.5 Hz, 1H, C*H*H), 3.28 (dd, *J* = 9.8 Hz, *J* = 4.9 Hz, 1H, CH*H*);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 163.0 (d, J_{C-F} = 2.9 Hz, *C*=O), 160.7 (d, J_{C-F} = 249.5 Hz, *C*F, Ph), 138.4 (*C*, Ph), 137.3 (*C*, Ph), 133.2 (d, J_{C-F} = 9.6 Hz, *C*H, Ph), 132.1 (d, J_{C-F} = 2.2 Hz, *C*H, Ph), 128.6 (*C*H, Ph), 128.5 (*C*H, Ph), 128.1 (*C*H, Ph), 127.9 (*C*H, Ph), 127.6 (*C*H, Ph), 127.3 (*C*H, Ph), 124.7 (d, J_{C-F} = 2.9 Hz, *C*H, Ph), 121.2 (d, J_{C-F} = 11.0 Hz, *C*, Ph), 116.0 (d, J_{C-F} = 24.0 Hz, *C*H, Ph), 73.7 (*C*H_2(Ph)), 72.1 (*C*HOH), 71.00 (*C*H_2(CHOH)), 57.0 (*C*HNH);

HRMS(ESI+ve): Calcd. for: $C_{23}H_{23}NO_3F$ (M+H): 380.166, Found: 380.1659.

3.3.S5. A.3. *Synthesis of N-((1R,2R)-3-(benzhydryloxy)-2-hydroxy-1-phenylpropyl)-2-fluorobenzamide,* ***53c***



Employing general method **P3** was added 2-fluorobenzoyl (0.11 mL, 0.95 mmols) chloride and Et_3N (0.27 mL, 1.95 mmols) dissolved in anhydrous THF (1.6 mL) over a solution of amino alcohol **47c** (0.33 g, 1.0 mmol) in 2.5 mL of anhydrous THF. The final product was isolated as white foam, 0.34 g in 75% yield.

$[\alpha]_D^{23}$ = + 17.4 (c = 1.09, $CHCl_3$).

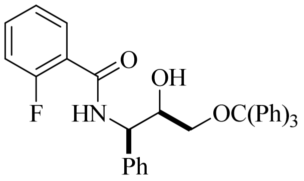
IR(film) ν: 3390, 3028, 1644, 1519, 1483, 1450, 1094, 749 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00-7.92 (m, 1H, N*H*, 1H, Ph), 7.44-6.98 (m, 18H, Ph), 5.46-5.42 (m,1H, C*H*N), 5.27 (s,1H, C*H*Ph_2), 4.20 (ddd, *J* = 4.6 Hz, *J* = 4.6 Hz, *J* = 4.6 Hz, 1H, C*H*OH), 3.46 (dd, *J* = 10.1 Hz, *J* = 4.46 Hz, 1H, C*H*H), 3.33 (dd, *J* = 9.9 Hz, *J* = 5.1 Hz, 1H, CH*H*);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 163.0 (d, $J_{C\text{-}F}$ = 2.8 Hz, *C*=O), 160.4 (d, $J_{C\text{-}F}$ = 248.7 Hz, *C*F, Ph), 141.3 (*C*, Ph), 141.2 (*C*, Ph), 138.1 (*C*, Ph), 133.0 (d, $J_{C\text{-}F}$ = 9.9 Hz, *C*H, Ph), 131.7 (d, $J_{C\text{-}F}$ = 2.0 Hz, *C*H, Ph), 128.4 (*C*H, Ph), 128.3 (*C*H, Ph), 127.5 (*C*H, Ph), 127.4 (*C*H, Ph), 127.3 (*C*H, Ph), 126.9 (*C*H, Ph), 126.8 (*C*H, Ph), 124.5 (d, $J_{C\text{-}F}$ = 3.0 Hz, *C*H, Ph), 121.2 (d, $J_{C\text{-}F}$ = 11.6 Hz, C, Ph), 115.8 (d, $J_{C\text{-}F}$ = 24.5 Hz, *C*H, Ph), 84.5 (*C*H$(Ph)_2$), 72.1 (*C*HOH), 70.1 (*C*H_2(CHOH)), 56.5 (*C*HNH);

HRMS(ESI+ve): Calcd. for: $C_{29}H_{26}NO_3FNa$ (M+Na): 478.1794, Found: 478.1794.

3.3.S5. A.4. Synthesis of 2-fluoro-N-((1R,2R)-2-hydroxy-1-phenyl-3-(trityloxy)propyl)benzamide, ***53d***



Employing general method **P3** was added 2-fluorobenzoyl chloride (0.11 mL, 0.95 mmols) and Et_3N (0.27 mL, 1.95 mmols) dissolved in anhydrous THF (1.6 mL) over a solution of amino alcohol **47d** (0.408 g, 1.0 mmol) in anhydrous THF (3.0 mL). The final product was isolated as a white foam, 0.34 g in 64%yield.

$[\alpha]_D^{23}$ = + 21.76 (c=0.99, $CHCl_3$).

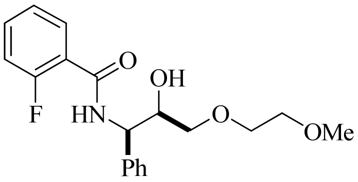
IR(film) ν: 3350, 3059, 1647, 1533, 1480, 1423, 1076, 753 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (dt, *J* = 8.0 Hz, *J* = 1.8 Hz, 1H, Ph), 7.79 (bs, 1H, N*H*), 7.47-7.02 (m, 23H, Ph), 5.42 (ddd, *J* = 8.1Hz, *J* = 2.2 Hz 1H, C*H*-N), 4.18 (m, 1H, C*H*-OH), 3.12 (dd, *J* = 9.6 Hz, *J* = 5 Hz, 1H, C*H*H), 3.06 (dd, *J* = 9.7 Hz, *J* = 5.1 Hz, 1H, CH*H*), 2.44 (d, *J* = 6.8 Hz, 1H, O*H*);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 162.9 (d, $J_{C\text{-}F}$ = 2.9 Hz, *C*=O), 160.6 (d, $J_{C\text{-}F}$ = 248.1 Hz, *C*-F, Ph), 143.4 (*C*, Ph), 137.7 (*C*, Ph), 133.2 (d, $J_{C\text{-}F}$ = 9.9 Hz, *C*H, Ph), 132.0 (d, $J_{C\text{-}F}$ = 2.0 Hz, *C*H, Ph), 128.5 (*C*H, Ph), 128.4 (*C*H, Ph), 127.9 (*C*H, Ph), 127.6 (*C*H, Ph), 127.5 (*C*H, Ph), 127.1 (*C*H, Ph), 124.7 (d, $J_{C\text{-}F}$ = 3.6 Hz, *C*H, Ph), 121.4 (d, $J_{C\text{-}F}$ = 11.6 Hz, *C*, Ph), 115.9 (d, $J_{C\text{-}F}$ = 23.8 Hz, *C*H, Ph), 87.3 (*C*$(Ph)_3$), 72.6 (*C*HOH), 64.3 (*C*H_2(CHOH)), 56.5 (*C*HNH);

HRMS(ESI+ve): Calcd. for: $C_{35}H_{30}NO_3FNa$ (M+Na): 554.2107, Found: 554.2123.

3.3.S5. A.5. *. Synthesis of 2-fluoro-N-((1R,2R)-2-hydroxy-3-(2-methoxyethoxy)-1-phenylpropyl)benzamide,* ***53e***



Employing general method **P3** was added 2-fluorobenzoyl chloride (0.3 mL, 2.54 mmol) and Et_3N (0.726 mL, 5.2 mmol) dissolved in anhydrous THF (7.0 mL) over a solution of amino alcohol **47e** (0.6 g, 2.66 mmol) in anhydrous THF (15.0 mL). The final product was isolated as white foam, 0.93 g in quantitative yield.

$[\alpha]_D^{23}$ = -23.34 (c=1, $CHCl_3$).

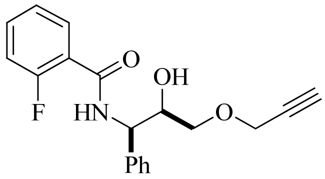
IR (film) ν: 3398, 1661, 1615, 1526, 1482, 1455, 1100, 758, 702 cm^{-1}.

^{1}H-RMN (200 MHz, $CDCl_3$) δ: 8.18 (bs, 1H, NH), 8.03 (dt, *J* = 7.9 Hz, *J* = 1.8 Hz, 1H, Ph), 7.45-7.15 (m, 8H, Ph), 5.44 (ddd, *J* = 8.0 Hz, *J* = 4.4 Hz, *J* = 2.2 Hz, 1H, C*H*N), 4.14-4.11 (m, 1H, C*H*OH), 3.6-3.50 (m, 6H, C*H₂*), 3.31 (s, 3H, C*H₃*O);

^{13}C-RMN (50 MHz, $CDCl_3$)δ: 163.0 (*C*=O), 160.5 (d, $J_{C\text{-}F}$ = 242 Hz, *C*F, Ph), 138.6 (*C*, Ph), 133.0 (d, $J_{C\text{-}F}$ = 9.2 Hz, *C*H, Ph), 132.0 (d, $J_{C\text{-}F}$ = 2.3 Hz, *C*H, Ph), 128.4 (*C*H, Ph), 127.5 (*C*H, Ph), 127.2 (*C*H, Ph), 124.6 (d, $J_{C\text{-}F}$ = 3.2 Hz, *C*H, Ph), 121.3 (d, $J_{C\text{-}F}$ = 11.3 Hz, *C*, Ph), 115.8 (d, $J_{C\text{-}F}$ = 24.2 Hz, *C*H, Ph), 72.4 (*C*H_2), 72.1 (*C*HOH), 71.7 (*C*H_2), 70.8 (*C*H_2), 58.8 (*C*H_3O), 56.9 (*C*HNH);

MS (CI, NH_3) *m/e*: 365 (M^+ + 18, 6%), 348 (M^+ + 1, 100%).

3.3.S5. A.6.. Synthesis of 2-fluoro- N-((1R,2R)- 2-hydroxy-1-phenyl-3-(prop-2-ynyloxy)propyl)benzamide, ***53f*****.**



Employing general method **P3** was added 2-fluorobenzoyl chloride (0.63 mL, 5.26 mmol) in anhydrous THF (15.0 mL) and Et_3N (1.59 mL, 11.4 mmol) over a solution of the corresponding amino alcohol (1.2 g, 5.85 mmol) in anhydrous THF (35.0 mL). The final product **53f** was isolated as white foam, 1.32 g in 69%yield.

$[\alpha]^{23}_D$= +46.09 (c = 0.8 in $CHCl_3$);

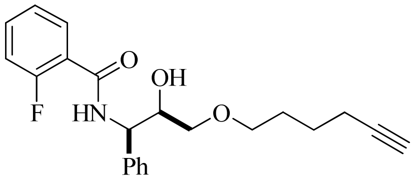
IR (film) ν: 3316, 3266, 3032, 2941, 1636, 1613, 1527, 1481, 1452, 1099, 752, 702cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.11 (bs, 1H, N*H*), 8.06 (ddd , *J* = 7.8 Hz, *J* = 1.9 Hz, 1H, Ph), 7.49-7.10 (m, 8H, Ph), 5.48-5.44 (m, 1H, C*H*OH), 4.19-4.14 (m, 3H, C*H*NH, C*H₂*O), 3.59 (dd, *J* = 9.6 Hz, *J* = 3.6Hz, 1H, C*H*HCC), 3.41 (dd, *J* = 9.8 Hz, *J* = 5.1Hz, 1H, CH*H*CC), 2.67 (d, *J* = 6.35 Hz, 1H, O*H*), 2.43-2.41 (m, 1H, CC*H*);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 162.8 (d, J_{C-F} = 3.5 Hz, *C*=O), 160.9 (d, J_{C-F} = 248.0 Hz, *C*F), 138.3 (*C*, Ph), 133.2 (d, J_{C-F} = 9.3 Hz, *C*H, Ph), 132.2 (d, J_{C-F} = 2.1 Hz, *C*H, Ph), 128.6 (*C*H, Ph), 127.7 (*C*H, Ph), 127.3 (*C*H, Ph), 124.7 (d, J_{C-F} = 3.2 Hz, *C*H, Ph), 120.9 (d, J_{C-F} = 11.0 Hz, *C*H, Ph), 115.9 (d, J_{C-F} = 24.8 Hz, *C*H, Ph), 78.8 (*C*CH), 75.1 (C*C*H), 72.0 (*C*HOH), 70.8 (*C*H_2O), 58.6 (*C*H_2CCH), 56.8 (*C*HNH);

HRMS (ESI+ve) calcd for $C_{19}H_{18}FNO_3Na$ (M+Na): 350.1168, found 350.1153.

3.3.S5. A7. Synthesis of 2-fluoro-N-((1R,2R)-3-(hex-5-ynyloxy)-2-hydroxy-1-phenylpropyl)benzamide, ***53g***



Employing general method **P3** was added 2-fluorobenzoyl chloride (0.6 mL, 4.9 mmols) and Et_3N (1.5 mL, 10.7 mmols) dissolved in anhydrous THF (15.0 mL) over a solution of amino alcohol (1.36 g, 5.5 mmol) in anhydrous THF (40.0 mL). The final product was isolated as white foam, 1.32 g in 65%yield.

$[\alpha]^{23}_{D}$= +32.79 (c = 1.1 $CHCl_3$);

IR(film) ν: 3316, 3266, 3032, 2941, 1636, 1613, 1527, 1481, 1452, 1099, 752, 702 cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.35- 8.30 (m, 1H, N*H*), 7.95 (dt , *J* = 7.9 Hz, *J* = 1.9 Hz, 1H, Ph), 7.39-7.02 (m, 8H, Ph), 5.49-5.476 (m, 1H, C*H*OH), 4.99-4.06 (m, 1H, C*H*NH), 3.38-3.22 (m, 4H, CH_2OCH_2) 2.17 (td, 2H, *J* = 7.1 Hz, *J* = 2.7 Hz, CH_2CCH), 1.95 (t, 1H, *J* = 2.7Hz, CC*H*) 1.69-1.64 (m, 2H, CH_2), 1.58-1.52 (m, 2H, CH_2);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 163.0 (d, J_{C-F} = 3.0 Hz, *C*=O), 160.4 (d, J_{C-F} = 248.2 Hz, *C*F), 138.8 (*C*, Ph), 133.15 (d, J_{C-F} = 9.3 Hz, *C*H, Ph), 131.8 (d, J_{C-F} = 2.0 Hz, *C*H, Ph), 128.4 (*C*H, Ph), 127.4 (*C*H, Ph), 127.2 (*C*H, Ph), 124.6 (d, J_{C-F} = 3.3 Hz, *C*H, Ph), 121.2 (d, J_{C-F} = 12.0 Hz, *C*H, Ph), 115.9 (d, J_{C-F} = 24.3 Hz, *C*H, Ph), 84.1 (*C*CH), 71.7(*C*HOH), 71.6 (CH_2O), 71.0 (OCH_2), 68.7 (C*C*H), 57.1 (*C*HNH), 28.4 (CH_2), 25 (CH_2), 18.2 (CH_2).

HRMS (TOF MS ES+) calcd for $C_{22}H_{24}FNO_3Na$ (M+Na): 392.1650, found 392.1638.

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MODULAR PHOSPHINOOXAZOLINES: SYNTHESIS AND EVALUATION IN ALLYLIC SUBSTITUTIONS
Dana Madeleine Popa
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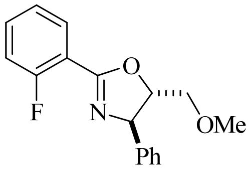
3.3.S6. B . Synthesis of the fluorooxazolines

3.3.S6. B1. *Synthesis of (4R,5S)-2-(2-fluorophenyl)-5-(methoxymethyl)-4-phenyl-4,5-dihydrooxazole,* ***48a***



Employing general method **P4** were employed fluorophenyl-hydroxylamide(0.30 g, 1 mmol), Et_3N (0.3 mL, 2.2 mmols), and methanesulfonyl-chloride (0.085 mL, 1.1 mmols) dissolved in anhydrous dichloromethane (8.2 mL). The mesylated product was obtained as yellow-orange oil, with total conversion and used without further purification in the next step. The mesylated product (0.38g, 1.0 mmol) was treated with a solution of KOH (8.7 mL, 6.2 mmols) in methanol, 5% weight. The final product was obtained as a transparent oil, 0.23 g in 82% yield.

$[\alpha]_D^{23}$ = + 47.6 (c=0.68 in $CHCl_3$)

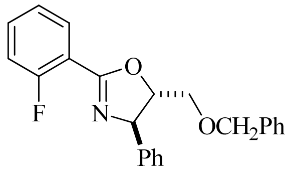
IR(film) ν: 1646, 1492, 1454, 1054, 750 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 8.04 (dt, J = 7.7 Hz, J = 1.95 Hz, 1H, Ph), 7.38-7.03 (m, 8H, Ph), 5.04 (d, J = 7.4 Hz, 1H, C*H*N), 4.50 (ddd, J = 7.6 Hz, J = 4.7 Hz, J = 4.7 Hz, 1H, C*H*O), 3.61-3.59 (m, 2H, CH_2), 3.35 (s, 3H, CH_3O);

^{13}C-RMN (100.6 MHz, $CDCl_3$)δ: 161.2 (d, J_{C-F} = 258.2 Hz, *C*-F, Ph), 160.7 (d, J_{C-F} = 5.8 Hz, *C*=N), 141.7 (*C*, Ph), 132.9 (d, J_{C-F} = 8.3 Hz, *C*H, Ph), 131.2 (d, J_{C-F} = 1.1 Hz, *C*H, Ph), 128.6 (*C*H, Ph), 127.5 (*C*H, Ph), 126.5 (*C*H, Ph), 123.8 (d, J_{C-F} = 3.7 Hz, *C*H, Ph), 116.6 (d, J_{C-F} = 21.7 Hz, *C*H, Ph), 115.8 (d, J_{C-F}= 10.3 Hz, *C*, Ph), 85.5 (*C*HO), 73.4 (CH_2), 72.2 (*C*HN), 59.4 (CH_3O);

HRMS(ESI+ve): Calcd. for: $C_{17}H_{17}NO_2F$ (M+H): 286.1243, Found: 286.1245.

3.3.S6. B2**. Synthesis of (4R,5S)-5-(benzyloxymethyl)-2-(2-fluorophenyl)-4-phenyl-4,5-dihydrooxazole, **48b



Employing general method **P4** was used fluorophenyl-hydroxylamide(0.38 g, 1.0 mmol), Et_3N (0.30 mL, 2.2 mmols), and methanesulfonyl-chloride (0.085 mL, 1.1 mmols) dissolved in anhydrous dichoromethane (8.2 mL). The mesylated product was obtained as yellow oil, with total conversion and used without further purification in the next step. Were employed mesylated product (0.46 g, 1 mmol) with a solution of KOH (8.7 mL, 6.2 mmols) in methanol, 5% weight. The final product was obtained as transparent oil, 0.25 g in 69% yield.

$[\alpha]_D^{23}$ = + 52.27 (c = 0.53 $CHCl_3$)

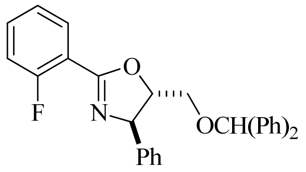
IR(film) ν: 1647, 1493, 1454, 1085, 797 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 7.98 (dt, *J* = 7.5 Hz, *J* = 2 Hz, 1H, Ph), 7.49-7.14 (m, 13H, Ph), 5.18 (d, *J* = 7.2 Hz, 1H, C*H*N), 4.67-4.62 (m, 3H,OCH_2Ph; C*H*O), 3.80-3.70 (m, 2H, C H_2O);

^{13}C-RMN (100.6 MHz, CD Cl_3)δ: 161.2 (d, $J_{C\text{-}F}$ = 257.7 Hz, *C*F, Ph), 160.8 (d, $J_{C\text{-}F}$ = 5.4 Hz, *C*=N), 141.8 (*C*, Ph), 137.7 (*C*, Ph), 132.9 (d, $J_{C\text{-}F}$ = 8.3 Hz, *C*H, Ph), 131.2 (*C*H, Ph), 128.6 (*C*H, Ph), 128.3 (*C*H, Ph), 127.7 (*C*H, Ph), 127.6 (*C*H, Ph), 127.5 (*C*H, Ph), 126.60 (*C*H, Ph), 123.8 (d, $J_{C\text{-}F}$ = 3.9 Hz, *C*H, Ph), 116.6 (d, $J_{C\text{-}F}$ = 21.9 Hz, *C*H, Ph), 115.8 (d, $J_{C\text{-}F}$= 10.3 Hz, *C*, Ph), 85.6 (*C*HO), 73.3 (*C*H_2Ph), 72.3 (*C*HN), 70.6 (O*C*H_2O);

HRMS(ESI+ve): Calcd. for: $C_{23}H_{21}NO_2F$ (M+H): 362.1556, Found: 362.1555.

3.3.S6. B3*. Synthesis of (4R,5S)-5-(benzhydryloxymethyl)-2-(2-fluorophenyl)-4-phenyl-4,5-dihydrooxazole,****48c***



Employing general method **P4** was used fluorophenyl-hydroxylamide(0.46 g, 1.0 mmol) , Et_3N (0.3 mL, 2.2 mmols), and methanesulfonyl-chloride (0.085 mL, 1.1 mmols) dissolved in anhydrous dichloromethane (9.0 mL). The mesylated product was obtained as yellow oil, with total conversion and used without further purification in the next step. Were employed mesylated product (0.53 g, 1.0 mmol) with a solution of KOH (8.7 mL, 6.2 mmols) in methanol, 5% weight. The final product was obtained as transparent oil, 0.33 g in 74% yield.

$[\alpha]_D^{23} = + 52.4$ (c=0.96 $CHCl_3$).

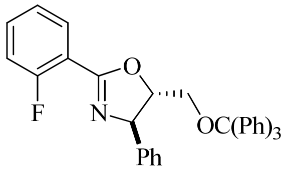
IR(film) ν: 1655, 1489, 1452, 1051, 738 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 7.96 (dt, J = 7.4 Hz, J = 1.8 Hz, 1H, Ph), 7.50-7.14 (m, 18H, Ph), 5.48 (s, 1H, C*H*$(Ph)_2$), 5.25 (d, J = 7.0 Hz, 1H, C*H*N), 4.70 (ddd, J = 6.9 Hz, J = 4.7 Hz, J = 4.7 Hz, 1H, C*H*O), 3.82-3.74 (m, 2H, CH_2);

^{13}C-RMN (100.6 MHz, $CDCl_3$)δ: 161.3 (d, J_{C-F} = 259.1 Hz, *C*F, Ph), 160.8 (d, J_{C-F} = 4.8 Hz, *C*=N), 141.9 (*C*, Ph), 141.7 (*C*, Ph), 141.7 (*C*, Ph), 133.0 (d, J_{C-F} = 9.4 Hz, *C*H, Ph), 131.3 (*C*H, Ph), 128.6 (*C*H, Ph), 128.4 (*C*H, Ph), 128.3 (*C*H, Ph), 127.6 (*C*H, Ph), 127.56 (*C*H, Ph), 127.5 (*C*H, Ph), 126.9 (*C*H, Ph), 126.9 (*C*H, Ph), 126.7 (*C*H, Ph), 123.9 (d, J_{C-F} = 4.6 Hz, *C*H, Ph), 116.6 (d, J_{C-F} = 21.6 Hz, *C*H, Ph), 116.0 (d, J_{C-F}= 10.4 Hz, *C* , Ph), 85.6 (*C*HO), 84.0 (*C*H$(Ph)_2$), 72.5 (*C*HN), 69.6 (CH_2);

HRMS(ESI+ve): Calcd. for $C_{29}H_{25}NO_2F$ (M+H): 438.1878 Found: 438.1869

3.3.S6. B4**. Synthesis of (4R,5S)-2-(2-fluorophenyl)-4-phenyl-5-(trityloxymethyl)-4,5-dihydrooxazole,**48d



Employing general method **P4** was used fluorophenyl-hydroxylamide(0.53 g, 1.0 mmol), Et_3N (0.3 mL, 2.2 mmols), and methanesulfonyl-chloride (0.085 mL, 1.1 mmols) dissolved in anhydrous dichloromethane (10.0 mL). The mesylated product was obtained as yellow oil, with total conversion and used without further purification in the next step. Were employed (0.6 g, 1.0 mmol) of mesylated product with a solution of KOH (8.7 mL, 6.2 mmols) in methanol, 5% weight. The final product was obtained as white foam, 0.41 g in 80% yield.

$[\alpha]_D^{23}$ = + 58.27 (c=1.0 $CHCl_3$).

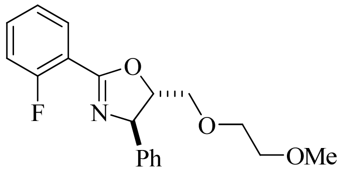
IR(film) ν: 1644, 1607, 1489, 1449, 1031, 739 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.04 (dt, *J* = 7.5 Hz, *J* = 1.7 Hz, 1H, Ph), 7.52-7.17 (m, 23H, Ph), 5.18 (d, *J* = 7.1 Hz, 1H, C*H*N), 4.63 (ddd, *J* = 7.0 Hz, *J* = 4.8 Hz, *J* = 4.8 Hz, 1H, C*H*-O), 3.47 (dd, *J* = 10.1 Hz, *J* = 4.1 Hz, 1H, C*H*H), 3.39 (dd, *J* = 10.3 Hz, *J* = 4.8 Hz, 1H, CH*H*);

^{13}C-RMN (100.6 MHz, $CDCl_3$) δ: 161.6 (d, $J_{C\text{-}F}$ = 259.8 Hz, *C*F, Ph), 160.9 (d, $J_{C\text{-}F}$ = 5.1 Hz, *C*=N), 143.6 (*C*, Ph), 142.0 (*C*, Ph), 133.0 (d, $J_{C\text{-}F}$ = 8.5 Hz, *C*H, Ph), 131.3 (*C*H, Ph), 128.7 (*C*H, Ph), 128.6 (*C*H, Ph), 127.8 (*C*H, Ph), 127.5 (*C*H, Ph), 127.1 (*C*H, Ph), 126.6 (*C*H, Ph), 123.9 (d, $J_{C\text{-}F}$ = 3.6 Hz, *C*H, Ph), 116.7 (d, $J_{C\text{-}F}$ = 22.10 Hz, *C*H, Ph), 116.0 (d, $J_{C\text{-}F}$= 10.4 Hz, *C*, Ph), 86.7 (*C*HO), 85.7 (*C*$(Ph)_3$), 72.4 (*C*HN), 64.7 (*C*H_2);

HRMS(ESI+ve): Calcd. for: $C_{35}H_{29}NO_2F$ (M+H): 514.2182, Found: 514.2186.

3.3.S6. B5**. Synthesis of (4R,5S)-2-(2-fluorophenyl)-5-((2-methoxyethoxy)methyl)-4-phenyl-4,5-dihydrooxazole, **48e



Employing general method **P4** was used fluorophenyl-hydroxylamide(0.8 g, 2.3 mmol), Et_3N (0.7 mL 5.0 mmol) and methanesulfonyl-chloride (0.19 mL, 2.5 mmol) dissolved in anhydrous dichloromethane (20.0 mL). The mesylated product was obtained as yellow oil, with total conversion and used without further purification in the next step. The row material was added to 5% solution of KOH in MeOH (20.0 mL, 14.1 mmols) and the mixture was stirred 15 h at room temperature. The final product was purified by column chromatography though silica eluting with hexane/ ethyl acetate of increasing polarity from 100:0 to 85:15. The final product, was obtained as pale yellow oil (0.5 g) in 69% yield.

$[\alpha]_D^{23}$ = + 47.47 (c = 2 en $CHCl_3$).

IR (film) ν: 2881, 1648, 1615, 1457, 1111, 1055, 1030, 747, 700 cm^{-1}.

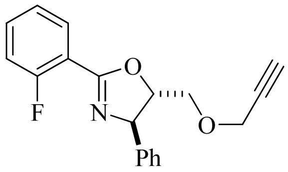
^{1}H-RMN (200 MHz, $CDCl_3$) δ: 7.98 (dt, J = 7.6 Hz, J = 1.7 Hz, 1H, Ph), 7.50-7.10 (m, 8H, Ph), 5.15 (d, J = 7.2 Hz, 1H, C*H*N), 4.65 (ddd, J = 7.3 Hz, J = 4.9 Hz, J = 4.9 Hz, 1H, C*H*-O), 3.85-3.72 and 3.60-3.55 (m, 6H, CH_3), 3.83 (s, 3H, CH_3O);

^{13}C-RMN (50 MHz, $CDCl_3$) δ: 161.2 (d, $J_{C\text{-}F}$ = 257 Hz, *C*F, Ph), 160.8 (*C*=N), 141.8 (*C*, Ph), 133.0 (d, $J_{C\text{-}F}$ = 8.6 Hz, *C*H, Ph), 131.2 (d, $J_{C\text{-}F}$ = 1.4 Hz, *C*H, Ph), 128.6 (*C*H, Ph), 127.6 (*C*H, Ph), 126.6 (*C*H, Ph), 123.9 (d, $J_{C\text{-}F}$ = 3.6 Hz, *C*H, Ph), 116.6 (d, $J_{C\text{-}F}$ = 21.8 Hz, *C*H, Ph), 115.9 (d, $J_{C\text{-}F}$ = 10.4 Hz, *C*, Ph), 85.8 (*C*HO), 72.4 (*C*HN), 72.3 (CH_2), 71.9 (CH_2), 71.1 (CH_3), 59.1 (CH_3O);

EM (FAB) *m/e*: 330 (M^++1, 100%).

HRMS (CI) Calcd.$C_{19}H_{20}NO_3F$ (M^+): 329.1427. Found: 329.1423

3.3.S6. B6**. Synthesis of (4R,5S)-2-(2-fluorophenyl)-4-phenyl-5-((prop-2-ynyloxy)methyl)-4,5-dihydrooxazole, **48f



Employing general method **P4** was used fluorophenyl-hydroxylamide (1.24 g, 3.8 mmol), Et_3N (1.2 mL, 8.3 mmol), and methanesulfonyl-chloride (0.33 mL, 4.17 mmols) dissolved in anhydrous dichloromethane (50.0 mL). The mesylated product was obtained as yellow oil, with total conversion and used without further purification in the next step. The row material was added to 5% solution of KOH in MeOH (36.0 mL, 23.2 mmol) and the mixture was stirred 15 h at room temperature. The final product was purified by column cromatography though silica eluting with hexane/ ethyl acetate of increasing polarity from 100:0 to 90:10. The final product was obtained as colourless oil (0.85 g) in 73% yield.

$[\alpha]^{23}_D$= + 52.0 (c = 1.2 in $CHCl_3$);

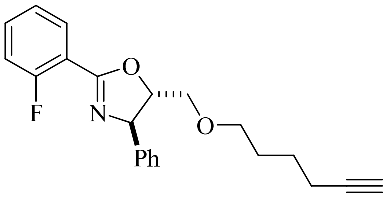
IR (film) ν: 3290, 2857, 1648, 1495, 1457, 1053, 766, 701cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 7.98 (ddd, *J* = 7.5 Hz, *J* = 1.8 Hz, *J* = 1.8 Hz, 1H, Ph), 7.5-7.14 (m, 8H, Ph), 5.18 (d, *J* = 7.3 Hz, 1H, C*H*N), 4.64 (ddd, *J* = 7.3, 4.7, 4.7 Hz, 1H, C*H*OH), 4.32-4.23 (cs, 2H, CH_2O), 3.89-3.83 (cs, 2H, CH_2CCH), 2.47-2.45 (m, 1H, CC*H*);

^{13}C-NMR (100.6 MHz, $CDCl_3$)δ: 161.1 (d, J_{C-F} = 258.5 Hz, *C*F, Ph), 160.8 (d, J_{C-F} = 5.4 Hz, *C*=N), 141.7 (*C*, Ph), 133.0 (d, J_{C-F} = 8.4 Hz, *C*H, Ph), 131.3 (d, J_{C-F} = 1.4 Hz, *C*H, Ph), 128.7 (*C*H, Ph), 127.6 (*C*H, Ph), 126.6 (*C*H, Ph), 123.9 (d, J_{C-F} = 3.8 Hz, *C*H, Ph), 116.6 (d, J_{C-F} = 21.0 Hz, *C*H, Ph), 115.8 (d, J_{C-F} = 10.2 Hz, *C*, Ph), 85.4 (*C*HO), 79.1 (*C*CH), 75.1 (C*C*H), 72.4 (*C*HN), 70.3 (*C*H_2O)**,** 58.7 (*C*H_2CCH);

HRMS (ESI+ve) calcd for $C_{19}H_{16}FNO_2Na$ (M+Na): 332.1063, found 332.1049.

3.3.S6. B7*. Synthesis of (4R,5S)-2-(2-fluorophenyl)-5-((hex-5-ynyloxy)methyl)-4-phenyl-4,5-dihydrooxazole,* ***48g***



Employing general method **P4** was used fluorophenyl-hydroxylamide (1.0 g, 2.7 mmol), Et_3N (0.83 mL, 5.95 mmols), and methanesulfonyl-chloride (0.23 mL, 2.7 mmols) dissolved in anhydrous dichloromethane (40.0 mL). The mesylated product was obtained as yellow oil, with total conversion and used without further purification in the next step. The row material was added to 5% solution of KOH in MeOH, (30.0 mL, 16.0 mmols) and the mixture was stirred 15 h at room temperature. The final product was purified by column cromatography though silica eluting with hexane/ ethyl acetate of increasing polarity from 100:0 to 85:15. The final product was obtained as pale yellow oil (0.7 g) in 81% yield.

$[\alpha]^{23}_{D}$= +47.15 (c = 1.14 $CHCl_3$);

IR (film) ν: 3300, 2863, 1648, 1613, 1495, 1457, 1111, 760 cm^{-1};

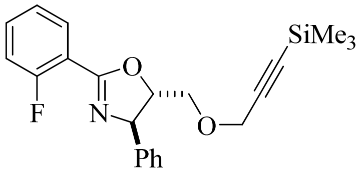
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (ddd, *J* = 7.5 Hz, *J* = 1.8 Hz, *J* = 1.8 Hz, 1H, Ph), 7.50-7.15 (m, 8H, Ph), 5.19 (d, *J* = 7.2 Hz, 1H, C*H*N), 4.64 (ddd, *J* = 7.4 Hz, *J* = 5 Hz, *J* = 5 Hz, 1H, C*H*O), 3.79-3.74 (m, 2H, CH_2O), 3.64-3.54 (m, 2H, OCH_2), 2.27 (td, 2H, *J* = 7.1 Hz, *J* = 2.7 Hz, CH_2CCH), 1.95 (t, 1H, *J*=2.7Hz, CC*H*),1.78-1.71 (m, 2H, CH_2),1.68-1.59 (m, 2H, CH_2);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 161.5 (d, $J_{C\text{-}F}$ = 260.0 Hz, *C*F, Ph), 160.9 (d, $J_{C\text{-}F}$ = 5.4 Hz, *C*=N), 141.9 (*C*, Ph), 133.0 (d, $J_{C\text{-}F}$ = 8.9 Hz, *C*H, Ph), 131.3 (d, $J_{C\text{-}F}$ = 1.5 Hz, *C*H, Ph), 128.7 (*C*H, Ph), 127.6 (*C*H, Ph), 126.7 (*C*H, Ph), 123.9 (d, $J_{C\text{-}F}$ = 4.0

Hz, *C*H, Ph), 116.7 (d, $J_{C\text{-}F}$ = 22.0 Hz, *C*H, Ph), 116.0 (d, $J_{C\text{-}F}$ = 11.0 Hz, *C*, Ph), 85.7 (*C*HO), 84.2 (*C*CH), 72.5 (C*C*H), 71.6 (*C*HN), 71.2 (*C*H_2O), 68.5 (O*C*H_2), 28.6 (*C*H_2), 25.1 (*C*H_2), 18.1 (*C*H_2);

HRMS (TOF MS ES+) calcd for $C_{22}H_{23}FNO_2$ (M+H): 352.1713, found 352.172.

3.3.S6. B8. *Synthesis of (4R,5S)-2-(2-fluorophenyl)-4-phenyl-5-((3-(trimethylsilyl)prop-2-ynyloxy)methyl)-4,5-dihydrooxazole,* ***58***



To a previously cooled at -78ºC solution of fluorooxazoline (0.05 g, 0.16 mmol) in 3.0 mL THF was added drop wise nBuLi, (0.11 mL, 0.17 mmols, 1.6 M in hexane). The temperature was raised to -40ºC over three hours and then cooled again at -78ºC. TMSCl (0.02 mL, 0.17 mmol), was added drop wise. The reaction evolves for 16 hours at -78ºC and then the temperature was raised to -20ºC over four hours time. The reaction was quenched by the addition of a saturated solution of 5.0 mL NH_4Cl. The aqueous layers were extracted with diethyl ether 3 X 5.0 mL. The organic phases were dried with anhydrous $MgSO_4$. The drying agent was filtered off and solvent removed under reduced pressure. The purification of the product was carried by flash column chromatography through SiO_2 eluting with a mixture of hexanes/AcOEt of increasing polarity: from 100:0 to 90:10. The final product (0.03 g) was obtained as colorless oil in a 57% yield.

$[\alpha]^{23}_{D}$= + 47.5 (c = 0.96 in $CHCl_3$);

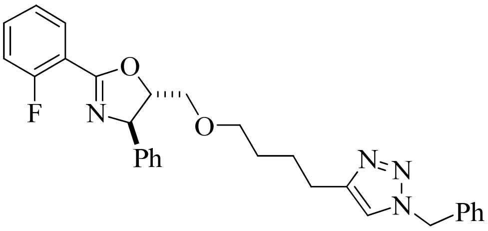
IR (film) ν: 3032, 2956, 1650, 1496, 1455, 1048, 760, 700;

^{1}H-NMR (400 MHz, $CDCl_3$)δ : 7.98 (ddd, *J* = 7.5, 1.9, 1.9 Hz, 1H, Ph), 7.5-7.15 (m, 8H, Ph), 5.19 (d, *J* = 7.3 Hz, 1H, C*H*N), 4.64 (ddd, *J* = 7.3, 4.7, 4.7 Hz, 1H, C*H*OH), 4.32-4.24 (cs, 2H, C*H*$_2$O), 3.89-3.82 (cs, 2H, C*H*$_2$CCH), 0.17 (s, 9H, Si(C*H*$_3$)$_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$)δ : 161.5 (d, $J_{C\text{-}F}$ = 257.8 Hz, *C*F, Ph), 160.9 (d, $J_{C\text{-}F}$ = 5.0 Hz, *C*=N), 141.8 (*C*, Ph), 133.1 (d, $J_{C\text{-}F}$ = 8.9 Hz, *C*H, Ph), 131.3 (d, $J_{C\text{-}F}$ = 1.4 Hz, *C*H, Ph), 128.7 (*C*H, Ph), 127.7 (*C*H, Ph), 126.7 (*C*H, Ph), 123.9 (d, $J_{C\text{-}F}$ = 3.8 Hz, *C*H, Ph), 116.7 (d, $J_{C\text{-}F}$ = 21.9 Hz, *C*H, Ph), 115.9 (d, $J_{C\text{-}F}$ = 10.7 Hz, *C*, Ph), 100.9 (H_2*C*C), 92.1 (C*C*Si(C*H*$_3$)$_3$), 85.6 (*C*H_2O), 72.4 (*C*HO), 70.2 (*C*HN), 59.5 (O*C*H_2CC), -0.1 (Si(*C*H_3)$_3$);

HRMS (ESI+ve) calcd for C_{22} H_{25} N O_2 Si F (M+H): 382.1639, found 382.1642.

3.3.S6. B9. Synthesis of (4R,5S)-5-((4-(1-benzyl-1H-1,2,3-triazol-4-yl)butoxy)methyl)-2-(2-fluorophenyl)-4-phenyl-4,5-dihydrooxazole, ***60***



Benzyl bromide (0.06 mL, 0.51 mmol) was added to a mixture of (4R,5S)-2-(2-fluorophenyl)-5-((hex-5-ynyloxy)methyl)-4-phenyl-4,5-dihydrooxazole (0.15 g, 0.42 mmol) copper (I) sulphate pentahydrate (0.002g, 0.0085 mmol), and sodium salt of L-ascorbic acid (0.017g, 0.0896 mmol), in *tert*-butanol and water 1:1 (1 mL) and the mixture was submitted to microwave irradiation (150W, 100ºC, 2 min ramp and 40 min hold time). The mixture was extracted with ethyl acetate (3x5.0 mL); the combined organic phase were dried (Na_2SO_4) and concentrated in vacuum. Purification by column chromatography on silicagel (hexane / ethyl acetate 8:2 to 2:8) afforded the product as yellow oil in 81% yield.

$[\alpha]^{23}_D$= + 27.31 (c = 1.1 $CHCl_3$);

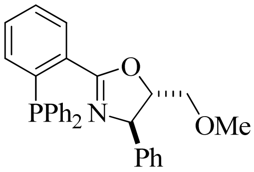
IR (film) ν: 2939, 2861, 1733, 1495, 1456, 1127, 700 cm^{-1};

UNIVERSITAT ROVIRA I VIRGILI
MODULAR PHOSPHINOOXAZOLINES: SYNTHESIS AND EVALUATION IN ALLYLIC SUBSTITUTIONS
Dana Madeleine Popa
ISBN:978-84-691-8862-0/DL:T-1275-2008

^{1}H-NMR (400 MHz, $CDCl_3$) δ :7.97 (ddd, *J* = 7.5 Hz, *J* = 1.9 Hz, *J* = 1.9 Hz, 1H, Ph), 7.49-7.12 (m, 13H, Ph, 1H, triazole), 5.47 (s, 2H, $CH_2C_6H_5$), 5.16 (d, *J* = 7.6 Hz, 1H, C*H*N), 4.60 (ddd, *J* = 7.4 Hz, *J* = 5.0 Hz, *J* = 5.0 Hz, 1H, C*H*OH), 3.75-3.71(m, 2H, CH_2O), 3.62-3.53 (m, 2H, OCH_2), 2. 72 (t, 2H, *J* = 7.7 Hz, CH_2-triazole), 1.78-1.70 (m, 2H, CH_2), 1.69-1.62 (m, 2H, CH_2);
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ :161.5 (d, $J_{C\text{-}F}$ = 260.0 Hz, *C*F, Ph), 160.9 (d, $J_{C\text{-}F}$ = 5.4 Hz, *C*=N), 148.5 (*C*, Ph), 141.9 (*C*, Ph), 135.0 (*C*H, Ph), 133.0 (d, $J_{C\text{-}F}$ = 8.9 Hz, *C*H, Ph), 131.3 (*C*, triazole), 129.0 (*C*H, Ph), 128.7 (*C*H, Ph), 128.6 (*C*H, Ph), 128.3 (*C*H, Ph), 127.9 (*C*H, Ph)), 127.6 (*C*H, Ph)), 126.7 (*C*H, Ph), 123.9 (d, $J_{C\text{-}F}$ = 4.0 Hz, *C*H, Ph), 120.6 (*C*H, triazole), 116.7 (d, $J_{C\text{-}F}$ = 22.0 Hz, *C*H, Ph), 116.0 (d, $J_{C\text{-}F}$ = 11 Hz, *C*, Ph), 85.7 (*C*HO), 72.4 (*C*HN), 71.6(CH_2O), 71.5(CH_2O), 53.9 ($CH_2C_6H_5$), 29.1 (CH_2), 25.9 (CH_2), 25.4 (CH_2);
HRMS (TOF MS ES+) calcd for $C_{29}H_{30}FN_4O_2$ (M+H): 485.2353, found 485.2343.

3.3.S7. C. Synthesis of phosphinooxazolines

<u>*3.3.S7. C1 .Synthesis of the (4R,5S)-2-(2-(diphenylphosphino)phenyl)-5-(methoxymethyl)-4-phenyl-4,5-dihydrooxazole,* ***55a***</u>

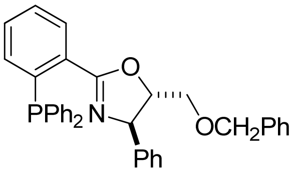


Following the general procedure **P5**, was used fluorooxazoline (0.28 g, 1.0 mmol) dissolved in anhydrous THF (2 mL) and $KP(Ph)_2$ 0.5 M in THF (2.8 mL, 1.45 mmols). The final product was obtained as white foam, 0.41 g in 93% yield.
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.96-7.93 (m, 1H, Ph), 7.31-7.17 (m, 13H, Ph), 7.11 (t, *J* = 3.4 Hz, 2H, Ph), 6.86-6.81 (m, 3H, Ph), 4.86 (d, *J* = 8.1 Hz, 1H, C*H*N), 4.29

(ddd, *J* = 8.1 Hz, *J* = 5.2 Hz, *J* = 5.2 Hz, 1H, C*H*O), 3.42-3.36 (m, 2H, CH_2), 3.29 (s, 3H, CH_3);

^{31}P-RMN (161.97 MHz, $CDCl_3$) δ: -2.9 (s, PPh_2);

3.3.S7. C2 Synthesis of the (4R,5S)-5-(benzyloxymethyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole, 55b

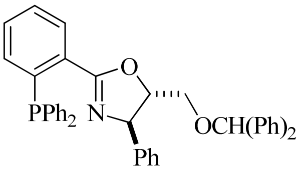


Following the general procedure **P5**, was used fluorooxazoline (0.36 g, 1.0 mmol) dissolved in anhydrous THF (2.0 mL) and $KP(Ph)_2$ 0.5 M in THF (2.8 mL, 1.45 mmols). The final product was obtained as white foam, 0.51 g in 97% yield.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.93-7.90 (m, 1H, Ph), 7.27-7.16 (m, 18H, Ph), 7.06 (t, *J* = 3.2 Hz, 2H, Ph), 6.86-6.80 (m, 3H, Ph), 4.89 (d, *J* = 7.8 Hz, 1H, C*H*N), 4.40 (s, 2H, OC*H*$_2$Ph), 4.30 (ddd, *J* = 8.6 Hz, *J* = 5.5 Hz, *J* = 5.5 Hz, 1H, C*H*O), 3.50-3.40 (m, 2H, C*H*$_2$O);

^{31}P-RMN (161.97 MHz, $CDCl_3$) δ: -2.9 (s, PPh_2);

3.3.S7. C3 Synthesis of the (4R,5S)-5-(benzhydryloxymethyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole, 55c

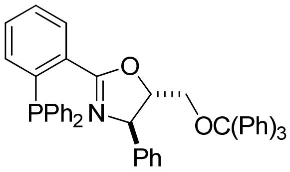


Following the general procedure **P5**, was used fluorooxazoline (0.44 g, 1.0 mmol) dissolved in dry THF (2.5 mL) and 0.5 M in THF (2.8 mL, 1.45 mmols) $KP(Ph)_2$. The final product was obtained as white foam, 0.37 g in 62% yield.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 8.03-7.98 (m, 1H, Ph), 7.35-7.10 (m, 25H, Ph), 6.88-6.83 (m, 3H, Ph), 5.32 (s, 1H, C*H*Ph_2), 5.01 (d, *J* = 7.0 Hz, 1H, C*H*N), 4.44 (ddd, *J* = 7.9 Hz, *J* = 5.0 Hz, *J* = 5.0 Hz, 1H, C*H*O), 3.53 (dd, *J* = 10.5 Hz, *J* = 5.2 Hz, 1H, C*H*HO), 3.47 (dd, *J* = 10.5 Hz, *J* = 4.9 Hz, 1H, CH*H*O);

^{31}P-RMN (161.97 MHz, $CDCl_3$) δ: -2.8 (s, P Ph_2);

*3.3.S7. **C4** Synthesis of the (4R,5S)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-5-(trityloxymethyl)-4,5-dihydrooxazole, **55d***

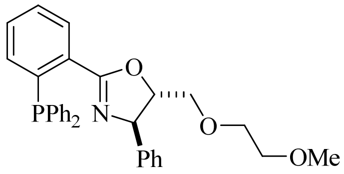


Following the general procedure **P5**, have been used fluorooxazoline (0.52 g, 1.0 mmol) dissolved in dry THF (3.0 mL) and $KP(Ph)_2$ 0.5 M in THF (2.8 mL, 1.45 mmols). The final product was obtained as white solid, 0.51 g in 76% yield.

^{1}H-RMN (400 MHz, $CDCl_3$) δ: 7.95 (ddd, *J* = 7.50 Hz, *J* = 3.7 Hz, *J* = 1.90 Hz, H, Ph), 7.40-7.00 (m, 33H, Ph), 5.10 (d, *J* = 6.8 Hz, 1H, C*H*N), 4.54 (ddd, *J* = 7.0 Hz, *J* = 4.8 Hz, *J* = 4.8 Hz, 1H, C*H*O), 3.40 (dd, *J* = 10.2 Hz, *J* = 4.0 Hz, 1H, C*H*HO), 3.31 (dd, *J* = 10.4 Hz, *J* = 4.8 Hz, 1H, CH*H*O);

^{31}P-RMN (161.97 MHz, $CDCl_3$) δ: -2.80 (s, PPh_2);

*3.3.S7. **C5** Synthesis of the (4R,5S)-2-(2-(diphenylphosphino)phenyl)-5-((2-methoxyethoxy)methyl)-4-phenyl-4,5-dihydrooxazole, **55e***

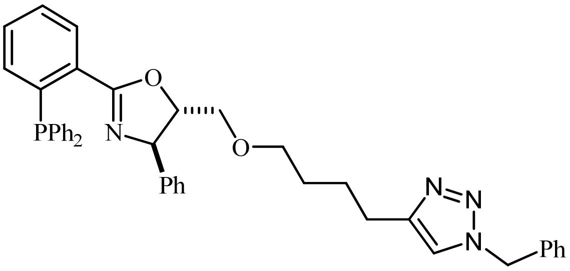


Following the general procedure **P5**, have been used fluorooxazoline (0.32 g, 1.0 mmol) dissolved in dry THF (3.0 mL) and $KP(Ph)_2$ 0.5 M in THF (2.8 mL, 1.45 mmols). The final product was obtained as white solid, 0.40 g in 85% yield.

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 8.02 (ddd, *J* = 7.6 Hz, *J* = 3.7 Hz, *J* = 1.5 Hz, 1H, Ph), 7.32-7.16 (m, 15H, Ph), 6.94-6.88 (m, 3H, Ph), 4.96 (d, *J* = 8.1 Hz, 1H, C*H*N), 4.40 (ddd, *J* = 8.1 Hz, *J* = 5.2 Hz, *J* = 5.2 Hz, 1H, C*H*O), 3.65-3.50 (m, 6H, CH_2), 3.35 (s, 3H, CH_3);

^{31}P-NMR (161.97 MHz, $CDCl_3$)δ: -2.8 (s, PPh_2);

***3.3.S7. C6** Synthesis of the (4R,5S)-5-((4-(1-benzyl-1H-1,2,3-triazol-4-yl)butoxy)methyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole,* **61**

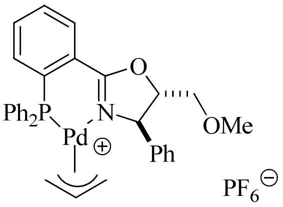


Following the general procedure **P5**, have been used fluorooxazoline (0.053 g, 0.11 mmol) dissolved in dry THF (2.0 mL) and $KP(Ph)_2$ 0.5 M in THF (0.30 mL, 0.16 mmols). The final product was obtained as yellow viscous oil, 0.070 g in 92% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.93-7.90 (m, 1H, Ph), 7.30-7.08 (m, 22H, 21H, Ph,1H, triazole), 6.85-6.82 (m, 2H, Ph), 5.38 (s, 2H, $CH_2C_6H_5$), 4.87 (d, J = 8.0 Hz, 1H, CHN), 4.26 (ddd, J = 8.0 Hz, J = 5.0 Hz, J = 5.0 Hz, 1H, CHO), 3.47-3.33(m, 4H, CH_2O, O CH_2), 2. 63 (t, 2H, J = 8.0Hz, CH_2-triazole), 1.68-1.60 (m, 2H, CH_2), 1.57-1.50 (m, 2H, CH_2);
^{31}P-NMR (161.97 MHz, $CDCl_3$) δ: -3.0 (s, PPh_2);

3.3.S8.D. Phosphinooxazoline allyl – palladium complexes

3.3.S8. D.1. *Synthesis of the (η^3–allyl)[(4R,5S)-2-(2-(diphenylphosphino)phenyl)-5-(methoxymethyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49a*



Following the general method **P7** was employed **55a** (0.45 g, 1.0 mmol), $[Pd(C_3H_5)Cl]_2$ (0.19 g, 0.53 mmols) and NH_4PF_6 (0.16 g, 1.02 mmols) in absolute ethanol (5.0 mL). The complex was obtained as a white-yellow precipitated, 0.56 g in 76% yield.

$[\alpha]_D^{23}$ = -70.43 (c = 1.0 $CHCl_3$);
IR(film) ν: 3066, 2924, 1625, 1474, 1435, 1195, 1048, 841,784, 694 cm^{-1}.
^{1}H-RMN (500 MHz, $CDCl_3$) δ: 8.31 (ddd, J = 8.0 Hz, J = 4.4 Hz, J = 1.2 Hz, 2H, Ph), 7.71-7.06 (m, 32H, Ph), 4.63 (b.s., 2H, CHO), 3.83-3.67 (m, 5H, CH_2, H_{aPexo}); *endo*: 6.96 (d, J = 7.3 Hz, 2H, H_o Ph-CHN), 5.73 (tt, J = 13.0 Hz, J = 7.0 Hz, 1H, H_c), 5.34 (d, J = 7.5 Hz, 1H, CHN), 4.60 (b.s., 1H, H_{sP}), 3.39 (s, 3H, CH_3O), 3.22 (d, J = 6.3 Hz, 1H, H_{sN}), 2.74 (d, J = 11 Hz, 1H, H_{aP}), 2.61 (d, J = 12.5 Hz, 1H, H_{aN});

exo: 6.92 (d, *J* = 7.5 Hz, 2H, H_o Ph-CHN), 5.38 (d, *J* = 7.5 Hz, 1H C*H*N), 5.15 (tt, *J* = 13.3 Hz, *J* = 6.7 Hz, 1H, H_c), 4.22 (b.s.,1H, H_{sp}), 3.38 (s, 3H, CH_3O), 3.31 (d, *J* = 6.3 Hz, 1H, H_{sN}), 2.78 (t, *J* = 12 Hz, 1H, H_{aN});

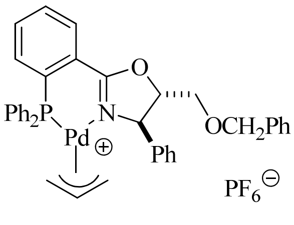
^{13}C-RMN (100.6 MHz, $CDCl_3$) δ: 134.4 (*C*H, Ph), 134.2 (*C*H, Ph), 133.7 (*C*H, Ph), 133.5 (*C*H, Ph), 133.5 (*C*H, Ph), 133.4 (*C*H, Ph), 133.0 (*C*H, Ph), 132.2 (*C*H, Ph), 132.0 (*C*H, Ph), 132.0 (*C*H, Ph), 129.9 (*C*H, Ph), 129.8 (*C*H, Ph), 129.7 (*C*H, Ph), 129.6 (*C*H, Ph), 129.3 (*C*H, Ph), 129.0 (*C*H, Ph), 128.9 (*C*H, Ph), 128.9 (*C*H, Ph), 126.9 (*C*H, Ph), 87.5 (*C*HO), 76.0 (*C*H-N), 72.2 (CH_2), 59.5 (CH_3); *endo*: 165.2 (*C*N), 139.3 (*C*, Ph), 121.2 (*C*H, alyll), 79.2 (d, *J* = 29 Hz CH_2 alyll *trans* P), 57.2 (CH_2 alyll *trans* N); *exo*: 165.2 (*C*N), 139.1 (*C*, Ph), 121.3 (*C*H, alyll), 80.9 (d, *J* = 30.3 Hz CH_2 alyll *trans* P), 56.2 (CH_2 alyll *trans* N);

^{31}P-RMN (161.9 MHz, $CDCl_3$) δ: *exo*: 25.0 (s, PPh_2), *endo*: 24.5 (s, PPh_2);

MS (FAB) *m/z*= 598 ($M^+ - PF_6$, 100 %).

Elemental analysis Calcd. for: $C_{32}H_{31}NO_2PPdPF_6$: C, 51.66; H, 4.20; N, 1.88, Obtained: C, 51.17; H, 4.30; N, 1.96.

***3.3.S8. D.2**. Synthesis of the (η^3–allyl)-[(4R,5S)-5-(benzyloxymethyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49b*



Following the general method **P7** was employed **55b** (0.53 g, 1.0 mmol), $[Pd(C_3H_5)Cl]_2$ (0.19 g, 0.53 mmols) and NH_4PF_6 (0.16 g, 1.02 mmols) in absolute ethanol (5.0 mL). The complex was obtained as a yellow solid, 0.54 g in 65% yield. $[\alpha]_D^{23}$ = -49.49 (*c* = 0.95 $CHCl_3$);

IR(film) ν: 3062, 2921, 1622, 1433, 964, 832, 731, 692 cm^{-1}

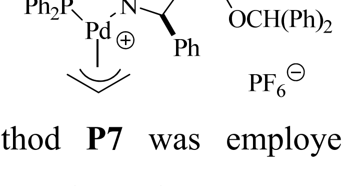
^{1}H-RMN (400 MHz, $CDCl_3$) δ: 8.31 (m, 2H, Ph), 7.67-6.98 (m, 42H, Ph), 4.59 (m, 3H, C*H*O, H_{sPendo}), 3.76 (m, 5H, CH_2, H_{aPexo}); *endo*: 6.78 (d, *J* = 7.0 Hz, 2H, H_o PhCHN), 5.66 (tt, *J* = 13.2 Hz, *J* = 7.2 Hz, 1H, H_c), 5.27 (d, *J* = 7.4 Hz, 1H, C*H*N), 4.51 (s, 2H, CH_2), 3.16 (d, *J* = 6.5 Hz, 1H, H_{sN}), 2.60 (d, *J* = 12.0 Hz, 1H, H_{aP}), 2.57 (d, *J* = 12.6 Hz, 1H, H_{aN}); *exo*: 6.82 (d, *J* = 7.8 Hz, 2H, H_O PhCHN), 5.38 (d, *J* = 7.5 Hz, 1H C*H*N), 5.29 (d, *J* = 7.4 Hz, 1H, C*H*N), 5.08 (tt, *J* = 13.5 Hz, *J* = 7.1 Hz, 1H, H_c), 4.50 (s, 2H, CH_2), 4.19 (t, *J* = 7 Hz, 1H, H_{sP}), 3.26 (d, *J* = 6.7 Hz, 1H, H_{sN}), 2.70 (d, *J* = 10.1 Hz, 1H, H_{aN});

^{13}C-RMN (100.6 MHz, $CDCl_3$)δ: 137.5 (*C*), 134.5 (*C*H), 133.7 (*C*H), 133.6 (*C*H), 133.5 (*C*H), 133.4 (*C*H), 133.2 (*C*H), 133.0 (*C*H), 132.2 (*C*H), 132.1 (*C*H), 129.8 (*C*H), 129.7 (*C*H), 129.6 (*C*H), 129.4 (*C*H), 129.1 (*C*H), 128.5 (*C*H), 128.1 (*C*H), 127.9 (*C*H), 126.9 (*C*H), 121.4 (*C*H, allyl), 87.5 (*C*H-O), 76.5 (*C*H-N), 73.6 (*C*H_2-Ph), 69.4 (*C*H_2-O), *endo*: 165.1 (*C*=N), 79.1 (d, *J* = 29.1 Hz, CH_2, C_P), 57.5 (*C*H_2, C_N); *exo*: 165.2 (*C*=N), 81.4 (d, *J* = 29.2 Hz, *C*H_2, C_P), 56.1 (*C*H_2,C_N);

^{31}P-RMN (161.9 MHz, $CDCl_3$)δ: *exo*: 25.1 (s, PPh_2), *endo*: 24.5 (s, P Ph_2) ppm.

HRMS(ESI+ve): Calcd. for: $C_{38}H_{35}NO_2PPd$ (M^+-PF_6^-): 674.1440, Obtained: 674.1467.

3.3.S8. D.3. *Synthesis of the (η^3–allyl)-[(4R,5S)-5-(benzhydryloxymethyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49c*



Following the general method **P7** was employed **55c** (0.6 g, 1.0 mmol), $[Pd(C_3H_5)Cl]_2$ (0.19 g, 0.53 mmols) and NH_4PF_6 (0.16 g, 1.02 mmols) in absolute ethanol (5.0 mL). The final product, was obtained as a yellow solid, 0.57 g in 64% yield.

$[\alpha]_D^{23}$ = -60.76 (c=1.2 $CHCl_3$);

IR(film) ν: 3028, 1623, 1476, 1433, 1114, 1064, 831, 783, 695 cm^{-1}.

^{1}H-RMN (500 MHz, $CDCl_3$) δ: 8.17 (b.s., 2H, Ph), 7.68-6.97 (m, 52H, Ph), 5.44 (s, 2H, C*H*Ph_2), 4.65-4.61 (m, 2H, C*H*-O), 3.86 (dd, *J* = 11.1 Hz, *J* = 3.6 Hz, 2H, C*H*H), 3.78 (dd, *J* = 11.5 Hz, *J* = 5.6 Hz, 2H, CH*H*); *endo*: 6.76 (d, *J* = 7.5 Hz, 2H, H_o PhCHN), 5.62 (t, *J* = 13.6 Hz, *J* = 8.0 Hz, 1H, H_c), 5.24 (d, *J* = 7.5 Hz, 1H C*H*N), 4.48 (b.s., 1H, H_{sP}), 3.15 (d, *J* = 6.3 Hz, 1H, H_{sN}), 2.67 (d, *J* = 11 Hz, 1H, H_{aP}), 2.61 (t, *J* = 11 Hz, 1H, H_{aN}); *exo*: 6.70 (d, *J* = 7.5 Hz, 2H, H_o PhCHN), 5.27 (d, *J* = 7.2 Hz, 1H C*H*N), 5.09 (tt, *J* = 13.5 Hz, *J* = 7.6 Hz, 1H, H_c), 4.29 (b.s, 1H, H_{sP}), 3.62 (dd, *J* = 11 Hz, 1H, H_{aP}), 3.29 (d, *J* = 6.3 Hz, 1H, H_{sN}), 2.71 (d, *J* = 11 Hz, 1H, H_{aN});

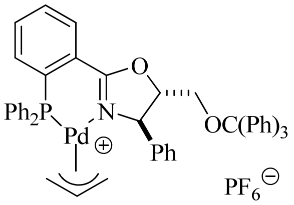
^{13}C-RMN (100.6 MHz, $CDCl_3$) δ: 134.5 (*C*H, Ph), 133.8 (*C*H, Ph), 133.7 (*C*H, Ph), 133.6 (*C*H, Ph), 133.2 (*C*H, Ph), 133.0 (*C*H, Ph), 132.1 (*C*H, Ph), 132.0 (*C*H, Ph), 129.9 (*C*H, Ph), 129.7 (*C*H, Ph), 129.5 (*C*H, Ph), 129.3 (*C*H, Ph), 129.0 (*C*H, Ph), 128.4 (*C*H, Ph), 128.1 (*C*H, Ph), 127.7 (*C*H, Ph), 127.0 (*C*H, Ph), 126.8 (*C*H, Ph), 121.4 (*C*H, allyl), 87.3 (*C*H-O), 84.4 (*C*HPh_2), 76.9 (*C*H-N), 68.9 (*C*H_2), *endo:* 165.1 (*C*=N), 141.4 (*C*, Ph), 78.8 (d, *J* = 30.0 Hz, *C*H_2 alyll *trans* P), 57.7 (*C*H_2 alyll *trans* N), *exo:* 165.0 (*C*=N), 141.5 (*C*, Ph), 81.0 (d, *J* = 30.0 Hz, *C*H_2 alyll *trans* P), 56.0 (*C*H_2 alyll *trans* N);

^{31}P-RMN (161.9 MHz, $CDCl_3$) δ: *exo*: 25.1 (s, PPh_2), *endo*: 24.4 (s, PPh_2);

EM (FAB) *m/e*: 750 (M^+ - PF_6).

Elemental analysis Calcd. for: $C_{44}H_{39}NO_2PPdPF_6$: C, 58.97; H, 4.39; N, 1.56, Obtained: C, 58.44; H, 4.49; N, 1.61.

3.3.S8. D.4. *Synthesis of the (η^3–allyl)-[(4R,5S)-5-trytiloxymethyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49d*



Following the general method **P7** was employed **55d** (0.68 g, 1.0 mmol), $[Pd(C_3H_5)Cl]_2$ (0.19 g, 0.53 mmols) and NH_4PF_6 (0.16 g, 1.02 mmols) in absolute ethanol (5.0 mL). The final product, was obtained as a yellow-green solid, 0.61 g in 63% yield.

$[\alpha]_D^{23}$ = -58.41 (c = 0.24 $CHCl_3$).

IR(film) ν: 3055, 1620, 1483, 1438, 1149, 1098, 832, 745, 695 cm^{-1}.

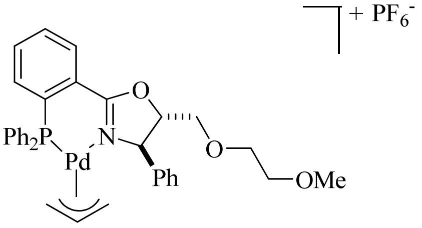
^{1}H-RMN (500 MHz, $CDCl_3$)δ: 8.26 (m, 2H), 7.18-6.65 (m, 64H), 5.07 (d, *J* = 7.5 Hz, 2H, C*H*N), 4.48 (b.s., 2H, C*H*O), 3.49 (m, 4H), 2.65 (m, 3H, H_{aNexo}, H_{aPendo}, H_{aNendo}), endo: 5.38 (b.s.,1H, H_c), 4.33 (b.s., 1H, H_{sP}), 2.95 (b.s., 1H, H_{sN}); exo: 5.65 (b.s., 1H, H_c), 4.03 (b.s., 1H, H_{sP}), 3.65 (m, 1H, H_{aP}), 3.26 (b.s., 1H, H_{sN});

^{13}C-RMN (100.6 MHz, $CDCl_3$)δ: 165.1 (*C*N), 143.1 (*C*, Ph), 138.1 (*C*,Ph), 134.7 (*C*H, Ph), 133.9 (*C*H, Ph), 133.8 (*C*H, Ph), 133.7 (*C*H, Ph), 133.7 (*C*H, Ph), 133.2 (*C*H, Ph), 133.1 (*C*H, Ph), 133.0 (*C*H, Ph), 132.9 (*C*H, Ph), 132.2 (*C*H, Ph), 132.1 (*C*H, Ph), 129.9 (*C*H, Ph), 129.8 (*C*H, Ph), 129.7 (*C*H, Ph), 129.6 (*C*H, Ph), 129.4 (*C*H, Ph), 129.2 (*C*H, Ph), 129.0 (*C*H, Ph), 128.7 (*C*H, Ph), 128.5 (*C*H, Ph), 128.5 (*C*H, Ph), 128.1 (*C*H, Ph), 127.7 (*C*H, Ph), 127.5 (*C*H, Ph), 127.4 (*C*H, Ph), 126.8 (*C*H, Ph), 87.5 (*C*H-O), 87.4 (*C*-$(Ph)_3$), 77.0 (*C*H-N), 64.0 (*C*H_2), 62.9 (*C*H_2, allyl *trans* N) 58.5 (*C*H_2, allyl *trans* N);

^{31}P-RMN (161.9 MHz, $CDCl_3$) δ: *exo*: 25.1 (s, PPh_2), *endo*: 24.6 (s, PPh_2);

HRMS(ESI+ve): Calcd. for: $C_{50}H_{43}NO_2PPd$ (M^+-PF_6^-): 826.2066, Obtained: 826.2097.

***3.3.S8. D5.** Synthesis of the (η^3–allyl) [(4R,5S)-2-(2-(diphenylphosphino)phenyl)-5-((2-methoxyethoxy)methyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49e*



Following the general method **P7** was employed **55e** (0.1 g, 0.202 mmol), $[Pd(C_3H_5)Cl]_2$ (39.0 mg, 0.106 mmol) and NH_4PF_6 (33.0 mg, 0.205 mmol) in 15 mL of absolute ethanol. The final product was obtained as a white solid, 0.10 g in 63% yield.

$[\alpha]_D^{23}$ = -60.94 (*c* = 0.71 en $CHCl_3$);

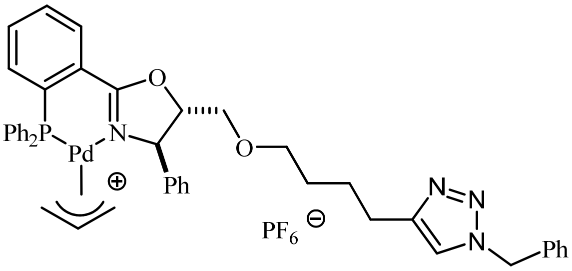
IR (film) ν: 3062, 2919, 1627, 1437, 1119, 1100, 839, 733, 698 cm-1.

^{1}H-RMN (500 MHz, $CDCl_3$) δ: 8.32 (ddd, *J* = 8.1 Hz, *J* = 4.2 Hz, *J* = 1.2 Hz, 2H, Ph), 7.73-7.18 (m, 32H, Ph), 6.90 (bs, 4H, H_o Ph-CHN), 5.36 (bs, 2H, C*H*-N), 4.70-4.66 (m, 2H, C*H*O), 3.89 (dd, *J* = 11.5 Hz, *J* = 3.5 Hz, 2H, C*H*HCHO), 3.86 (dd, *J* = 11.5 Hz, *J* = 5.5 Hz, 2H, CH*H*CHO), 3.74-3.67 (m, 4H, CH_2), 3.56-3.54 (m, 4H, CH_2), 3.35 (s, 6H, CH_3O); *endo*: 5.71 (bs, 1H, H_c), 4.60 (bs, 1H, H_{sP}), 3.24 (bs, 1H, H_{sN}), 2.74 (bs, 1H, H_{aP}), 2.65 (bs, 1H, H_{aN}); *exo*: 5.15 (bs, 1H, H_c), 4.19 (bs, 1H, H_{SP}), 2.74 (bs, 1H, H_{aP}) (H_{sN} and H_{aN} signals overlap with other signals);

^{13}C-RMN (75 MHz, $CDCl_3$) δ: 165.1 (*C*=N), 139.2 (*C*, Ph), 134.3 (*C*H, Ph), 133.7 (*C*H, Ph), 133.5 (*C*H, Ph), 133.4 (*C*H, Ph), 133.2 (*C*H, Ph), 132.1 (*C*H, Ph), 132.0 (*C*H, Ph), 129.8 (*C*H, Ph), 129.7 (*C*H, Ph), 129.5 (*C*H, Ph), 129.3 (*C*H, Ph), 128.9

(*C*H, Ph), 126.9 (*C*H, Ph), 121.3 (*C*H, allyl), 87.5 (*C*HO), 76.2 (*C*HN), 71.6 (*C*H_2), 70.9 (*C*H_2), 70.7 (*C*H_2), 58.9 (*C*H_3), 58.5 (*C*H_2, allyl);
^{31}P-RMN (121 MHz, $CDCl_3$) δ: *exo*: 25.0 (s, PPh_2), *endo*: 24.5 (s, PPh_2).
MS (FAB) *m/e*: 642 ($M^+ - PF_6$, 100 %).

3.3.S8. D6. *Synthesis of the (η^3-allyl)-[(4R,5S)-5-((4-(1-benzyl-1H-1,2,3-triazol-4-yl)butoxy)methyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49f*



Following the general method **P7** was employed **61** (0.07 g, 0.1mmol), 0.02 g (0.55 mmols) of $[Pd(C_3H_5)Cl]_2$ and NH_4PF_6 (0.018 g, 0.11 mmols) in absolute ethanol (9.0 mL). The final product was obtained as orange solid, 0.074 g in 79% yield.
$[\alpha]^{23}_D$= -30.26 (c = 1.10 $CHCl_3$);
IR (film) ν: 2926,1637, 1480, 1361, 1119, 836 cm^{-1};
^{1}H-NMR (400 MHz, $CDCl_3$)δ: 8.28-8.25 (m, 2H, Ph), 7.74-7.08 (m, 42H, Ph,2H, triazole), 6.87 (d, *J* = 7.5 Hz, 4H, Ho, PhCHN), 5.70 (bs, 1H, $H_{c_{endo}}$), 5.45 (s, 4H, C*H_2*C_6H_5), 5.30 (d, *J* = 7.0 Hz, 2H, C*H*N), 4.68-4.71 (m, 2H, C*H*O), 3.82 (dd, *J* = 11.5, *J* = 3.5, 2H, C*H*HO), 3.70 (dd, *J* = 11.5, *J* = 3.5, 2H, CH*H*O), 3.53 (bt, 4H, O C*H_2*), 2.62 (bt, 4H, CH_2-triazole), 1.67-1.60 (m, 4H, CH_2), 1.57-1.50 (m, 4H, CH_2) ppm; the allylic protons could not be assigned due to *endo*-*exo* equilibrium

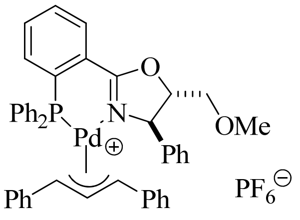
exchange. Were proceeded low temperature experiments but without any improvement;

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 139.5 (*C*, Ph), 134.8 (*C*H, Ph), 133.9 (*C*H, Ph), 133.8 (*C*H, Ph), 133.5 (*C*H, Ph), 133.3 (*C*H, Ph), 132.7 (*C*H, Ph), 132.6 (*C*H, Ph), 132.2 (*C*H, Ph), 131.9 (*C*H, Ph), 129.8 (*C*H, Ph), 129.7 (*C*H, Ph), 129.5 (*C*H, Ph), 129.4 (*C*H, Ph), 129.2 (*C*H, Ph), 128.9 (*C*H, Ph), 128.7 (*C*H, Ph), 128.6 (*C*H, Ph), 128.0 (*C*H, Ph), 127.0 (*C*H, Ph), 87.2 (*C*HO), 76.5 (*C*HN), 71.0 (CH_2O), 69.9 (OCH_2), 54.0 ($CH_2C_6H_5$), 28.7 (CH_2), 25.7 (CH_2), 25.2 (CH_2) ppm; the allylic carbons could not be assigned due to endo-exo equilibrium. Were proceeded low temperature experiments but without any improvement;

^{31}P-NMR (161.97 MHz, $CDCl_3$) δ: *exo* 25.0 (s, PPh_2), *endo* 24.5 (s, PPh_2);

HRMS (TOF MS ES+) calcd for $C_{44}H_{44}N_4O_2PPd$ (M^+-PF_6^-): 797.2237, found 797.2233.

*3.3.S8. **D** 7. Synthesis of the(η^3-1,3-diphenylallyl)- [(4R,5S)-2-(2-(diphenylphosphino)phenyl)-5-(methoxymethyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 62*



Following the general method **P7** was employed **55a** (0.06 g, 0.13 mmol), $[Pd(C_3H_3)(C_6H_5)_2Cl]_2$ (0.047 g, 0.07 mmols) and NH_4PF_6 (0.033 g, 0.2 mmols) in absolute ethanol (9.0 mL). The final product was obtained as yellow solid, 0.06 g in 50% yield.

$[\alpha]_{23}^{D}$ = -325.3 (c = 0.34 en $CHCl_3$).

IR (KBr) ν: 3062, 2929, 1628, 1491, 1437, 1119, 1100, 837, 735, 695 cm^{-1}.

^{1}H-RMN (500 MHz, $CDCl_3$)δ: 7.70-6.60 (m, 56H, Ph), 4.34-4.31 (m, 2H, CH-O); *endo*: 8.22 (ddd, *J* = 8.0 Hz, *J* = 4.2 Hz, *J* = 1.0 Hz, 1H, Ph), 6.53-6.48 (m, 1H, H_c), 4.78 (t, *J* = 11.2 Hz, 1H, H_{aP}), 4.68 (d, *J* = 12 Hz, 1H, H_{aN}), 4.46 (d, *J* = 5.5 Hz, 1H, C*H*-N), 3.29-3.20 (m, 2H, CH_2), 3.22 (s, 3H, CH_3O); *exo*: 8.26 (ddd, *J* = 8.0 Hz, *J* = 4.0 Hz, *J* = 1.2 Hz, 1H, Ph), 6.29 (dd, *J* = 14 Hz, *J* = 10.5 Hz, 1H, H_c), 6.20 (d, *J* = 8.5 Hz, 1H, H_{aP}), 4.26 (d, *J* = 11 Hz, 1H, H_{aN}), 4.23 (d, *J* = 5 Hz, 1H, C*H*N), 3.53 (dd, *J* = 11 Hz, *J* = 5.2 Hz, 1H, C*H*H), 3.50 (dd, *J* = 11 Hz, *J* = 4.5 Hz, 1H, CH*H*), 3.47 (s, 3H, CH_3O);

^{13}C-RMN (75 MHz, $CDCl_3$)δ: 165.1 (*C*=N), 139.2 (*C*, Ph), 138.9 (*C*, Ph), 137.9 (*C*, Ph), 135.8 (*C*, Ph), 135.3 (*C*H, Ph), 133.4 (*C*H, Ph), 133.2 (*C*H, Ph), 133.0 (*C*H, Ph), 132.1 (*C*H, Ph), 131.6 (*C*H, Ph), 131.2 (*C*H, Ph), 129.6 (*C*H, Ph), 129.3 (*C*H, Ph), 129.2 (*C*H, Ph), 128.6 (*C*H, Ph), 128.4 (*C*H, Ph), 128.3 (*C*H, Ph), 127.8 (*C*H, Ph), 127.1 (*C*H, Ph), 126.8 (*C*H, Ph), 126.7 (*C*H, Ph), 125.9 (*C*H, Ph), 125.7 (*C*H, Ph), 86.1 (*C*HO), 72.3 (CH_2), 59.6 (CH_3); *endo*: 111.2 (*C*H central allyl), 95.7 (*C*H allyl *trans* P), 74.8 (*C*H allyl *trans* N), 71.2 (*C*H-N); *exo*: 110.7 (d, $J_{C\text{-}P}$= 5.2 Hz, *C*H central allyl), 103.1 (d, $J_{C\text{-}P}$ = 22.1 Hz, *C*H allyl *trans* P), 70.2 (*C*HN), 69.1 (d, $J_{C\text{-}P}$ = 7 Hz, *C*H allyl *trans* N);

^{31}P-RMN (121 MHz, $CDCl_3$) δ: *endo*: 22.5 (s, PPh_2); *exo*: 17.7 (s, PPh_2).

MS (FAB) *m/e*: 750 ($M^+ - PF_6$ 100 %).

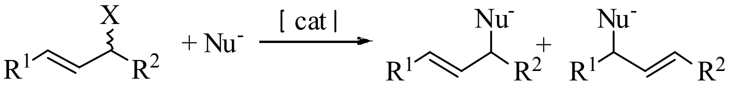
CHAPTER II

ALLYLIC ALKYLATION REACTION

ALLYLIC ALKYLATION REACTION

I. INTRODUCTION AND AIMS

The stereoselective formation of C-C bonds represents an important challenge in asymmetric synthesis. The palladium catalyzed allylic alkylation reaction has proved to be a useful process in the synthesis of natural products and in the creation of carbon frameworks of diverse organic molecules.[1] (see Scheme II.1.)



Scheme II.1. Allylic alkylation reaction

The allylic alkylation reaction is of importance in organic synthesis as racemic substrates can be converted into optically active products in the presence of a chiral catalyst. The enantiomerically enriched alkylation product is formed due to the electronic and steric control of the chiral complex over the allylic substrate. Since the initial report of the catalyzed allylic alkylation, many efforts have been devoted to the optimization of the catalytic process.

The first η^3-palladium allyl complexes, involved in the allylic alkylation reaction, were isolated and identified thirty years ago from the reaction of dienes and palladium(II) salts.[1,2] The first catalytic version of the allylic alkylation was

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[1] Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-93.
[2] Frost, C. G.; Howart, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089-122.

reported in 1973 using the chiral (+)-DIOP ligand using dimethyl malonate as the nucleophile with moderate stereoselectivity (24% ee).[1]

In the allylic alkylation reaction, the most common substrates described in the literature are allylic acetates and carbonates.[1] Phosphate substrates[3] represent good alternatives when more reactive leaving groups are required. Substrates containing these leaving groups (AcO, ROCOO and occasionally $(RO)_2POO$) are the most studied in the field of allylic alkylation as they shown low reactivity towards nucleophiles unless a catalyst is employed.[4] Leaving groups with higher reactivity, such as halides or trifluoroacetates have not been considered in asymmetric allylic alkylation reactions, as the uncatalyzed process could compete with the catalyzed reaction.[5]

A broad range of carbon and heteroatom nucleophiles have been reported in the allylic substitution reaction.[1] The C-nucleophiles mostly used are the malonates and acetyl acetonates,[6] which have became the standard nucleophiles for testing new catalysts. Thus, many other nucleophiles have been studied: α–amino esters,[7] α-amino phosphonates,[8] cyclopentadienide,[9] and enantiopure nitrogen-containing nucleophiles.[10] Efficient catalytic systems have also been developed for the intramolecular version.[11] The nucleophiles have been classified as ¨hard¨ and ¨soft¨ depending on the stereochemical outcome of the reaction (overall retention or

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[3] Lloydjones, G. C.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1995**, *34*, 462-464.

[4] Pfaltz, A.; Lautens, M. *Comprehensive Asymmetric Catalysis* **1999**, Chapter 24.

[5] Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett* **1994**, *35*, 8595-8598.

[6] von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1993**, *32*, 566-8.

[7] Baldwin, I. C.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1995**, *6*, 1515-18.

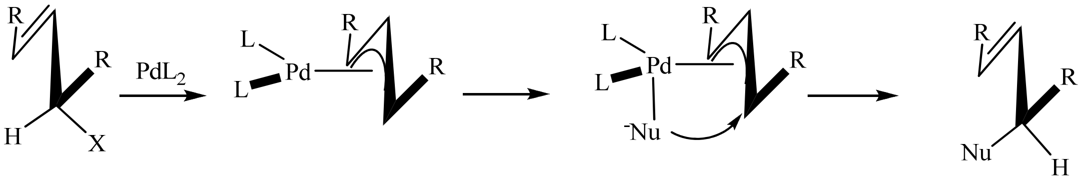
[8] Baldwin, I. C.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1995**, *6*, 679-82.

[9] Suzuka, T.; Kawatsura, M.; Okada, A.; Hayashi, T. *Tetrahedron: Asymmetry* **2003**, *14*, 511-515.

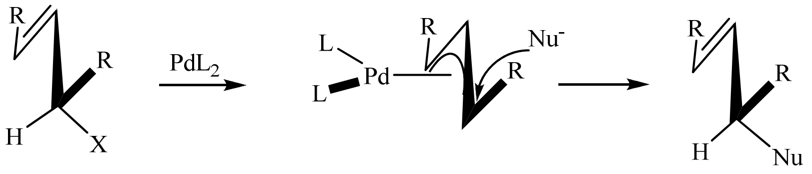
[10] Humphries, M. E.; Clark, B. P.; Regini, S.; Acemoglu, L.; Williams, J. M. J. *Chirality* **2003**, *15*, 190-195.

[11] Koch, G.; Pfaltz, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2213-2216.

inversion of the configuration at the allyl system).[12] The ¨hard¨ nucleophiles are derived from the conjugated acids with a pK_a higher than 25. In this case, hard nucleophiles bind to the metal center. Subsequent attack of the bound nucleophile to the allyl unit results in the product of opposite configuration, with respect to the starting material (see Scheme II.2.). ¨Soft¨ nucleophiles, defined as those derived from conjugated acids whose pK_a is lower than 25, lead in turn to the product with overall retention of the configuration at the allyl carbon. Bond breaking and making events take place in this case outside the coordination sphere of the metal, concretely from the face of the allyl unit opposite to the metal (see Scheme II.3.).



Scheme II.2. Allylic alkylation with hard nucleophiles



Scheme II.3. Allylic alkylation with soft nucleophiles

A wide variety of structurally different substrates have been used in asymmetric alkylation reactions.[4] Symmetrically substituted allyl systems have been commonly used in this transformation (see Scheme II.4.). This kind of substrates might be racemic in allylic alkylations involving soft nucleophiles: both enantiomers of the

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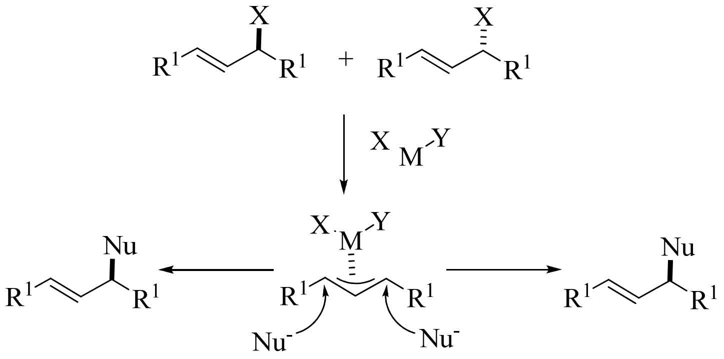
[12] Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.

substrate lead to the same allyl complex. The enantioselectivity of the reaction depends in this case on the ability of the ligand in inducing a different reactivity in the two terminal allyl carbons.



Scheme II.4. Allylic alkylation reaction of symmetrical allyl substrates

Desymmetrization of the allyl system depends on the electronic and/or steric effects of the ligands. In the case of *P,N* -ligands, asymmetrisation takes place due to the *trans* effect of the P and N donor groups. As shown in the Scheme II.5.a, the Pd - C bond *trans* to the P - atom is significantly longer [13] thus favoring the attack of the nucleophile at that position. In other kind of ligands such as chiral bisoxazolines,[14] desymmetrisation arises from a sterical interaction between the ligand and substrate substituents (Scheme II.5. b).

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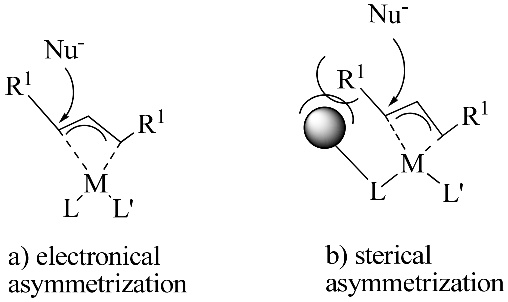
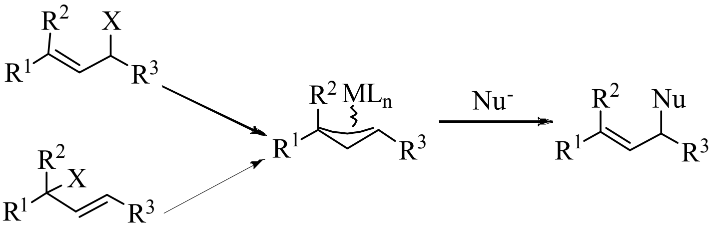
[13] Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214.
[14] Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339-345.

UNIVERSITAT ROVIRA I VIRGILI
MODULAR PHOSPHINOOXAZOLINES: SYNTHESIS AND EVALUATION IN ALLYLIC SUBSTITUTIONS
Dana Madeleine Popa
ISBN:978-84-691-8862-0/DL:T-1275-2008



Scheme II.5. Asymmetrization of the allyl system

Allylic alkylation has also been studied with unsymmetrically substituted substrates (see Scheme II.5.). In this case, the two isomeric allyl substrates indicated in Scheme II.6, lead to the same allyl complex. The higher the ability a ligand has to differentiate the two allyl termini towards the incoming nucleophile, the higher the induced selectivity will be. Electronic and steric desymmetrization effects operate for these substrates too, as in symmetrical substrates.



Scheme II.6. Allylic alkylation reaction of unsymmetrical allyl substrates

Many different catalysts have been studied for this transformation and chiral complexes of Pd, W, Ir, Mo, Rh, Ru, Re, Pt have been shown to give high levels of enantioselectivity. However, chiral palladium complexes are the most widely used and studied in this field. There have been several breakthroughs and insightful mechanistic studies in the field, and now a myriad of chiral Pd-coordination compounds capable of differentiating the reactivity of the two allyl termini are known. Of particular interest are the seminal work by Trost, which lead in 1992 to efficient design of C2 ligands[15] and of Williams,[16] Pfaltz,[6] and Helmchen,[17] which lead in 1993 to the novel phosphinooxazolines (PHOX) ligands with C1 symmetry. These seminal results led to highly efficient ligands for allylic alkylation that, as we mentioned before, present a high potential as a synthetic methodology.

Chiral complexes of metals such as W, Mo, Rh, Ru, Ir, Pt, Re, have been less studied in asymmetric alkylation. However, compared to Pd, these metals are interesting as they show different reactivities and selectivities. Chiral complexes of W,[18] Mo,[19] Rh,[20] Ru,[21] Ir[22] with PHOX mediated the allylic alkylation with a reversal of regioselectivity compared to the palladium ones. As far as the chiral metallic complexes of PHOX ligands are concerned, Ir-PHOX[23,24,25] and Rh-PHOX[26,27] complexes were used for the allylic alkylation of mono substituted allylic compounds giving predominantly the branched alkylation product, the opposite tendency than for the Pd-PHOX complexes. Re-PHOX,[28] Pt-PHOX[29,30]and W-

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[15] Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Amer. Chem. Soc.* **1992**, *114*, 9327-43.
[16] Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149-3150.
[17] Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769-1772.
[18] Trost, B. M.; Hung, M. H. *J. Amer. Chem. Soc.* **1983**, *105*, 7757-7759.
[19] Trost, B. M.; Lautens, M. *J. Amer. Chem. Soc.* **1982**, *104*, 5543-5545.
[20] Evans, P. A.; Nelson, J. D. *J. Amer. Chem. Soc.* **1998**, *120*, 5581-5582.
[21] Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945-1953.
[22] Takeuchi, R.; Kashio, M. *J. Amer. Chem. Soc.* **1998**, *120*, 8647-8655.
[23] Carmona, D.; Ferrer, J.; Lorenzo, M.; Santander, M.; Ponz, S.; Lahoz, F. J.; Lopez, J. A.; Oro, L. A. *Chem. Commun.* **2002**, 870-871.
[24] Garcia-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459-5470.
[25] Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741-742.
[26] Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713-1715.
[27] Carmona, D.; Ferrer, J.; Lalaguna, E.; Lorenzo, M.; Lahoz, F. J.; Elipe, S.; Oro, L. A. *Eur. J. Inorg. Chem.* **2002**, 259-263.
[28] Kniess, T.; Correia, J. D. G.; Domingos, A.; Palma, E.; Santos, I. *Inorg. Chem.* **2003**, *42*, 6130-6135.
[29] Blacker, A. J.; Clark, M. L.; Loft, M. S.; Williams, J. M. J. *Chem. Commun.* **1999**, 913-914.
[30] Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Williams, J. M. J. *Organometallics* **1999**, *18*, 2867-2873.

PHOX[31] complexes are also known and have been efficiently used in allylic alkylation reaction.

A summary of several chiral PHOX type ligands used in allylic alkylations are shown in Table II.1. The evaluation of the catalytic activity for newly designed ligands in the Pd-mediated allylic alkylation reaction is generally performed with 1,3-diphenyl-1 propene, **63,** using dimethyl malonate as the nucleophile. Enantiomeric exceses indicated in Table II.1. correspond to this combination of substrate and nucleophile. The ligand framework has been varied at several positions, for example at the phosphorous atom, as in examples **77** to **81** (58 % ee to 95 % ee). Another source of diversity has been the spacer between the two coordinative hetero atoms as in examples **82** to **95** (49 % ee to 99 % ee). Phosphinooxazoline ligands bearing ferrocenyl units close to the nitrogen and also at the phosphorous, have been also used with good results, **96** to **98** (99 % ee and 98 % ee).

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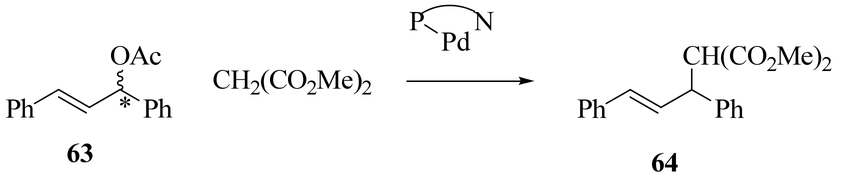
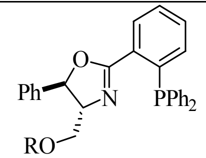
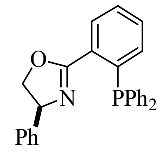
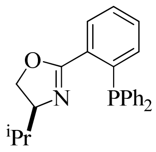
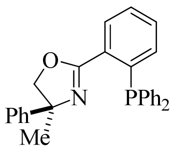
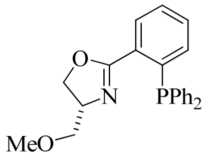
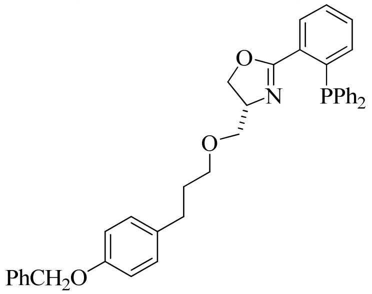
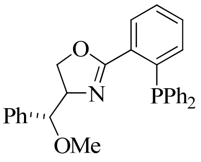
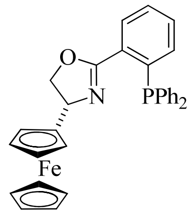
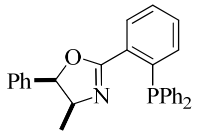
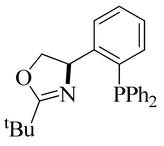
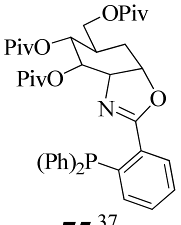
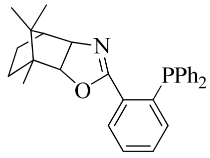
[31] Sava, X.; Marinetti, A.; Ricard, L.; Mathey, F. *Eur. J. Inorg. Chem.* **2002**, 1657-1665.



Scheme II.7. Enantioselective allylic alkylation of the 1,3-diphenyl allylic substrate

Table II.1. PHOX ligands in the alkylation reaction

 **65**[6] (PHOX) (85% ee, *Pfaltz*)	 **66**[16] (92% ee, *Williams*)	 **67**[17] (99% ee, *Helmchen*)	 **68**[32] (97% ee, *Plattner*)
 **69**[33] (90% ee, *Fang*)	 **70** [33] (65% ee, *Fang*)	 **71**[34] (99% ee, *Moberg*)	 **72** [35] (99% ee, *Moyano*)
 **73** [38] (88% ee, *Muzart*)	 **74** [36] (98% ee, *Zhang*)	 **75** [37] (98% ee, *Kunz*)	 **76** [38] (93% ee, *Muzart*)

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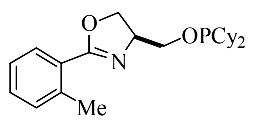
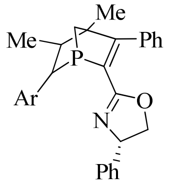
[32] Zehnder, M.; Schaffner, S.; Neuburger, M.; Plattner, D. A. *Inorg. Chim. Acta* **2002**, *337*, 287-298.
[33] Chen, R. J.; Fang, J. M. *J. Chin. Chem. Soc.* **2005**, *52*, 819-826.
[34] Froelander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *J. Org. Chem.* **2005**, *70*, 9882-9891.
[35] Moreno, R. M.; Bueno, A.; Moyano, A. *J. Organomet. Chem.* **2002**, *660*, 62-70.
[36] Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460-6471.
[37] Glaeser, B.; Kunz, H. *Synlett* **1998**, 53-54.
[38] Ganchegui, B.; Chevrin, C.; Bouquillon, S.; Le Bras, J.; Henin, F.; Muzart, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 2635-2639.

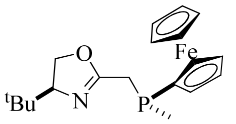
Table II.1. PHOX ligands in the alkylation reaction



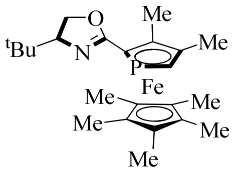
77[46]
(58% ee, *Gómez*)



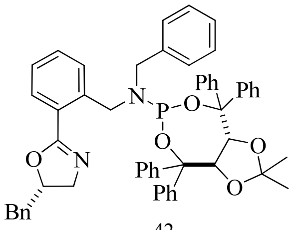
78[39]
(94% ee, *Gilbertson*)



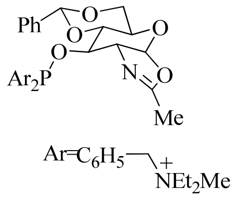
79[40]
(95% ee, *Imamoto*)



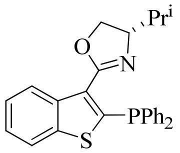
80[41]
(82% ee, *Fu*)



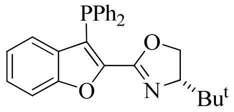
81[42]
(88% ee, *Guiry*)



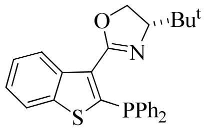
82[43]
(92% ee, *Uemura*)



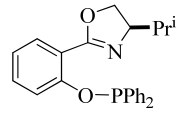
83[44]
(97% ee, *Tietze*)



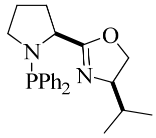
84[44]
(86% ee, *Tietze*)



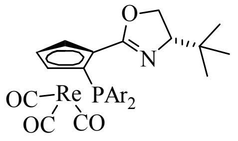
85[45]
(99% ee, *Cozzi*)



86[46]
(82% ee,*Gómez*)

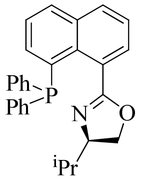


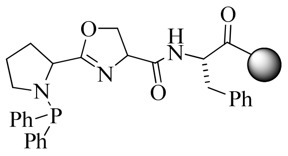
87[47]
(94% ee, *Gilbertson*)

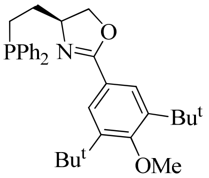


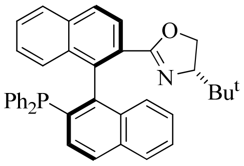
88[48]

(73% ee, *Bolm*)









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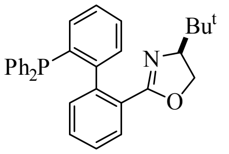
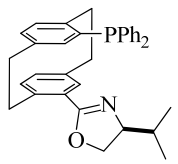
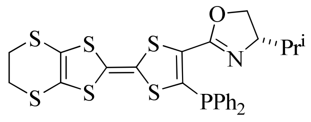
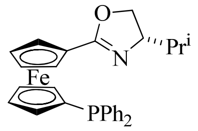
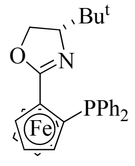
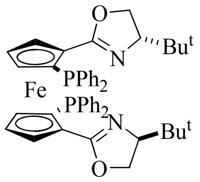
[39] Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885-2888.
[40] Danjo, H.; Higuchi, M.; Yada, M.; Imamoto, T. *Tetrahedron Lett.* **2004**, *45*, 603-606.
[41] Shintani, R.; Lo, M. M. C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695-3697.
[42] Bronger, R. P. J.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, *18*, 1094-1102.
[43] Hashizume, T.; Yonehara, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2000**, *65*, 5197-5201.
[44] Tietze, L. F.; Lohmann, J. K. *Synlett* **2002**, 2083-2085.
[45] End, N.; Stoessel, C.; Berens, U.; di Pietro, P.; Cozzi, P. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2235-2239.
[46] Franco, D.; Gomez, M.; Jimenez, F.; Muller, G.; Rocamora, M.; Maestro, M. A.; Mahia, J. *Organometallics* **2004**, *23*, 3197-3209.
[47] Xu, G. P.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *43*, 2811-2814.
[48] Bolm, C.; Xiao, L.; Kesselgruber, M. *Org. Biomol. Chem.* **2003**, *1*, 145-152.

Table II.1. PHOX ligands in the alkylation reaction

89[49] (49% ee, *Guiry*)	**90**[50] (69% ee, *Meldal*)	**91**[51] (82% ee, *Burges*)	**92**[52] (96% ee, *Ikeda*)
			
93[53] (88% ee, *Ikeda*)	**94**[54] (82% ee, *Bolm*)	**95**[55] (85% ee, *Avarvari*)	**96**[56] (99% ee, *Ikeda*)
			
	97[57] (99% ee, *Ahn*)	**98**[58] (98% ee, *Zhang*)	

In the allylic alkylation reaction, many different substrates have been employed. Examples of different substrates and the enantioselectivities obtained in the palladium-PHOX mediated alkylation with dimethyl malonate as nucleophile, are presented in Table II.2.

In the case of cyclic allylic substrates, ligands **101** and **102** showed better activity (entry 1 Table II.2.). The larger biphenyl substituent selectively favored either the *exo* or *endo* forms and thus the enantioselectivity was increased. The PHOX ligand

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[49] McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151-4202.

[50] Benito, J. M.; Christensen, C. A.; Meldal, M. *Org. Lett.* **2005**, *7*, 581-584.

[51] Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206-215.

[52] Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343-4346.

[53] Zhang, W.; Xie, F.; Yoshinaga, H.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2006**, 1185-1188.

[54] Whelligan, D. K.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 4609-4618.

[55] Rethore, C.; Suisse, I.; Agbossou-Niedercorn, F.; Guillamon, E.; Llusar, R.; Fourmigue, M.; Avarvari, N. *Tetrahedron* **2006**, *62*, 11942-11947.

[56] Zhang, W.; Yoneda, Y.-I.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1998**, *9*, 3371-3380.

[57] Ahn, K. H.; Cho, C. W.; Park, J. W.; Lee, S. W. *Tetrahedron: Asymmetry* **1997**, *8*, 1179-1185.

[58] Liu, D.; Xie, F.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 585-588.

102 can be considered as the improved version of ligand **101**. The manganese tricarbonyl group present in the latter ligand did not allow the formation of other unfavorable species.[59]

For small alkylic substrates (entry 2 Table II.2.), ligands with bulky substituents at the oxazoline moiety have been designed. The *exo* form is favored with this strategy. The bulky substituent pushes the allylic substrates nearer to the equatorial phenyl group, the steric interactions are stronger for the *endo* isomer, and the *exo-endo* ratio is thus increased.

The alkylation of monosubstituted substrates results in the predominant formation of the branched or the lineal product depending on the metal used. Mo, W, Fe, Rh and Ir complexes favour the formation of the branched products while Pd catalyst predominantly give lineal products (entry 3 Table II.3.).[12]

PHOX ligand **107**, gave high ee's in the allylic alkylation of some geminally hindered disubstituted substrates (entry 4 Table II.2.). Ligand **108** (entry 5 Table II.2.) has been used in the allylic alkylation of vinylogous sulfonates of *β*-phenylcinnamyl alcohol derivatives.

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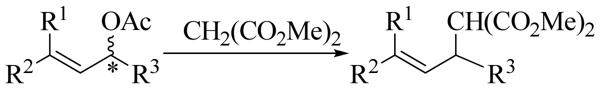
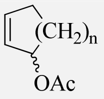
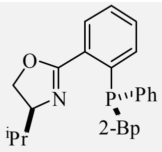
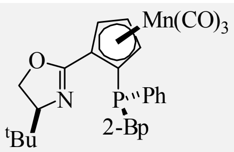
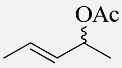
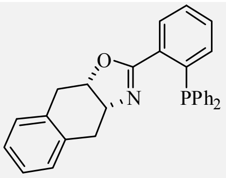
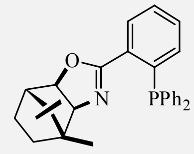
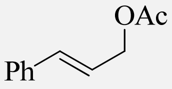
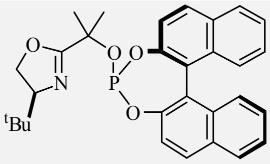
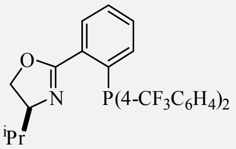
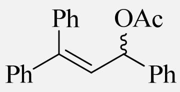
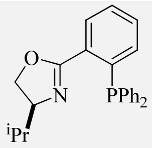
[59] Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336-345.



99a-d **100a-d**

Scheme II.8. Allylic alkylation of substrates **99a-d** with dimethyl malonate

Table II.2. *P,N* ligands in the allylic alkylation of substrates **99a-d**

Entry	Substrate	PHOX ligand	
1			
	99a	**101**[60] (83% ee, n=3, *Sennhenn)*	**102**[61] (99% ee, n=3, *Helmchen*)
2			
	99b	**103**[62] (90% ee, *Helmchen*)	**104**[62] (58% ee, *Helmchen*)
3			
	99c	1 mol % $[(C_3H_5)PdCl]_2$, 2.4 mol % **105**[63] (86% ee, B:L [a] 69:31, *Pretor*)	2 mol % Ir(COD)Cl, 4 mol % **106**[25] (91% ee, B:L [a] 95:5, *Bartels*)
4			
	99d	**107**[64]	

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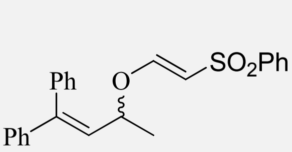
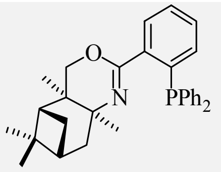
[60] Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595-8.
[61] Kudis, S.; Helmchen, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 3047-3050.
[62] Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727-5730.
[63] Pretot, R.; Lloyd-Jones, G. C.; Pfaltz, A. *Pure Appl. Chem.* **1998**, *70*, 1035-1040.
[64] Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535-46.

Entry	Substrate	PHOX ligand
		(99% ee, *Williams*)
5		
	99e	**108**[65] (90% ee, *Evans*)

a) branched : lineal substitution products

Other *P,N*-ligands have been tested in the asymmetric allylic alkylation. We present in the following table the most representative examples together with the observed enantioselectivities. Ligands containing ferrocenyl units (ligands **109 -116** in Table II.3.) and binaphtyl rings (ligands **124-127**), have been studied. The nitrogen donor group is contained in an iminophosphite (ligands **117-119**), iminophosphine, (ligands **120**, **121**), pyridine, (ligand **122**), quinolinophane (ligand **123**), sulfinyl imine (ligand **128**), phosphinosulfoxime (ligands **129-131**), and tertrahydroisoquinoline units (ligand **132**).

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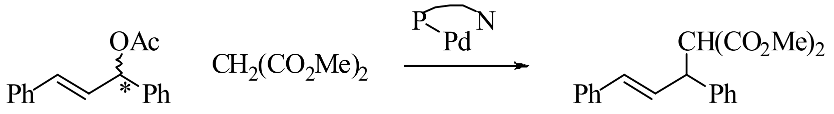
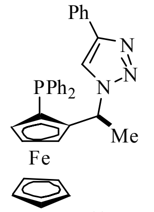
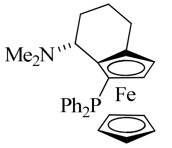
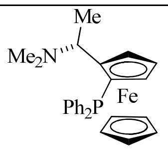
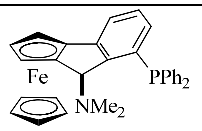
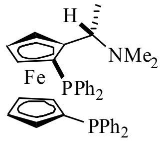
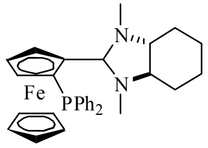
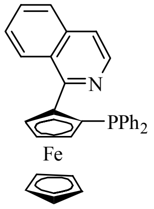
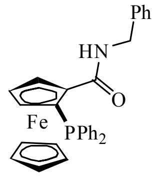
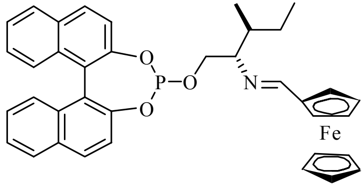
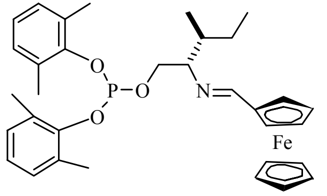
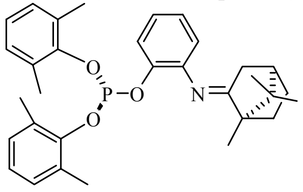
[65] Evans, P. A.; Brandt, T. A. *Org. Lett.* **1999**, *1*, 1563-1565.



63 **64**

Scheme II.9. Allylic alkylation of the 1,3-diphenyl allylic substrate

Table II.3. *P, N* ligands in the allylic alkylation with dimethyl malonate nucleophile

 **109**[66] (79% ee, *Fukuzawa*)	 **110**[67] (71% ee, *Fukuzawa*)	 **111**[67] (54% ee, *Fukuzawa*)	 **112**[67] (96% ee, *Fukuzawa*)
 **113**[68] (54% ee, *Fuji*)	 **114**[69] (99% ee, *Jin*)	 **115**[70] (86% ee, *Knochel*)	 **116**[71] (90% ee, *Stepnicka*)
 **117**[72] (60% ee, *Gavrilov*)	 **118**[73] (97% ee, *Gavrilov*)	 **119**[74] (94% ee, *Gavrilov*)	

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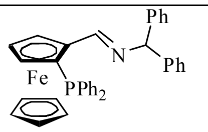
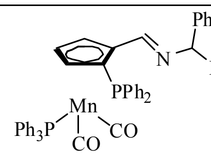
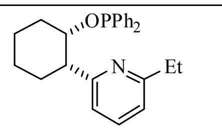
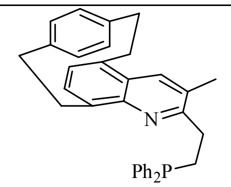
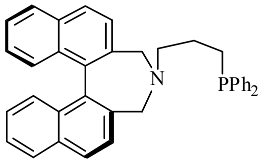
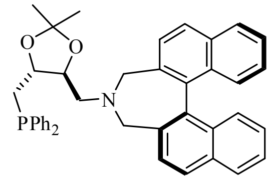
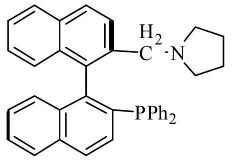
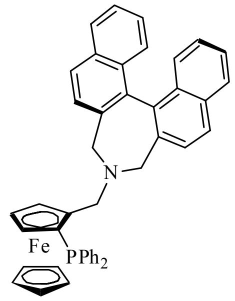
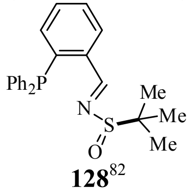
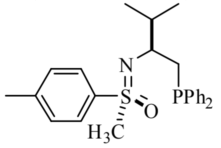
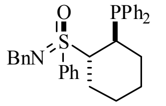
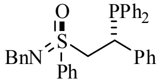
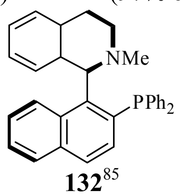
[66] Fukuzawa, S.-i.; Oki, H.; Hosaka, M.; Sugasawa, J.; Kikuchi, S. *Org. Lett.* **2007**, *9*, 5557-5560.
[67] Fukuzawa, S.-I.; Yamamoto, M.; Hosaka, M.; Kikuchi, S. *Eur. J. Org. Chem.* **2007**, 5540-5545.
[68] Kinoshita, N.; Kawabata, T.; Tsubaki, K.; Bando, M.; Fuji, K. *Tetrahedron* **2006**, *62*, 1756-1763.
[69] Jin, M.-J.; Takale, V. B.; Sarkar, M. S.; Kim, Y.-M. *Chem. Commun.* **2006**, 663-664.
[70] Kloetzing, R. J.; Knochel, P. *Tetrahedron: Asymmetry* **2006**, *17*, 116-123.
[71] Lamac, M.; Tauchman, J.; Cisarova, I.; Stepnicka, P. *Organometallics* **2007**, *26*, 5042-5049.
[72] Gavrilov, K. N.; Maksimova, M. G.; Zheglov, S. V.; Bondarev, O. G.; Benetsky, E. B.; Lyubimov, S. E.; Petrovskii, P. V.; Kabro, A. A.; Hey-Hawkins, E.; Moiseev, S. K.; Kalinin, V. N.; Davankov, V. A. *Eur. J. Org. Chem.* **2007**, 4940-4947.
[73] Gavrilov, K. N.; Tsarev, V. N.; Maksimova, M. G.; Bondarev, O. G.; Rastorguev, E. A.; Lyubimov, S. E.; Petrovskii, P. V.; Davankov, V. A. *J. Mol. Catal. A: Chem.* **2006**, *259*, 267-274.

Table II.3. *P, N* ligands in the allylic alkylation with dimethyl malonate nucleophile

 **120**[75] (90% ee, *Chung*)	 **121**[75] (98% ee, *Chung*)	 **122**[76] (94% ee, *Zhou*)	 **123**[77] (58% ee, *Ruzziconi*)
 **124**[78] (96% ee, *Kubota*)	 **125**[79] (87% ee, *Sinou*)	 **126**[80] (94% ee, *Ha*)	 **127**[81] (97% ee, *Widhalm*)
 **128**[82] (93% ee, *Ellman*)	 **129**[83] (93% ee,*Reggelin*)	 **130**[84] (97% ee, *Gais*)	 **131**[84] (82% ee, *Gais*)
		 **132**[85] (78% ee, *Li*)	

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[74] Gavrilov, K.; Tsarev, V.; Zheglov, S.; Korlyukov, A.; Antipin, M.; Davankov, V. *Synthesis* **2007**, 1717-1723.

[75] Lee, J. H.; Son, S. U.; Chung, Y. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2109-2113.

[76] Liu, Q.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 2101-2104.

[77] Ruzziconi, R.; Santi, C.; Spizzichino, S. *Tetrahedron: Asymmetry* **2007**, *18*, 1742-1749.

[78] Kubota, H.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 6689-92.

[79] Mikhael, I.; Goux-Henry, C.; Sinou, D. *Tetrahedron: Asymmetry* **2006**, *17*, 1853-1858.

[80] Kim, K. H.; Jeong, C.-K.; Kim, D.-H.; Ha, D.-C. *Tetrahedron: Asymmetry* **2006**, *17*, 1688-1692.

[81] Widhalm, M.; Mereiter, K.; Bourghida, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2983-2986.

[82] Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 545-548.

[83] Spohr, V.; Kaiser, J. P.; Reggelin, M. *Tetrahedron: Asymmetry* **2006**, *17*, 500-503.

[84] Lemasson, F.; Gais, H.-J.; Raabe, G. *Tetrahedron Lett.* **2007**, *48*, 8752-8756.

[85] Feng, J.; Bohle, D. S.; Li, C.-J. *Tetrahedron: Asymmetry* **2007**, *18*, 1043-1047.

In conclusion, the asymmetric alkylation reaction has witnessed great advances over the last few years. Several research groups have designed a large number of very efficient ligands and have studied the different factors affecting this transformation allowing a greater understanding of the process.

II. MECHANISTIC CONSIDERATIONS

Asymmetric allylic alkylation reaction is an important organic transformation. Hence the understanding of the mechanistic and catalyst structure-activities are essential for the optimization of the process.

In the palladium catalyzed allylic alkylation reaction, the so-called ¨soft¨ nucleophiles (such as stabilized carbanions or amines) have been investigated in more detail than the ¨hard¨ ones. The standard solvent used in the reaction is tetrahydrofuran (THF), but dimethylformamide (DMF) or less polar solvents such as dichloromethane have also been used. Carbanions are normally used as nucleophiles, since their C-H counterparts are inactive in the neutral form.[12] Sodium salts were firstly used in allylic alkylations, however, these kinds of nucleophiles suffer from low solubility in standard organic solvents. This problem was overcome by generating the carbanion, from the neutral form, in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate (Scheme**.**II.10).[86] Under these conditions, one silyl group is transferred from BSA to the acetate and the anion of *N*-(trimethylsilyl)acetamide is thus generated. This compound, in turn, deprotonates dimethyl malonate, whose carbanion attacks the allyl substrate and generates an increasing concentration of this specie as the reaction progresses. For this reason, only catalytic amounts of acetate are required for the reaction to fully proceed.

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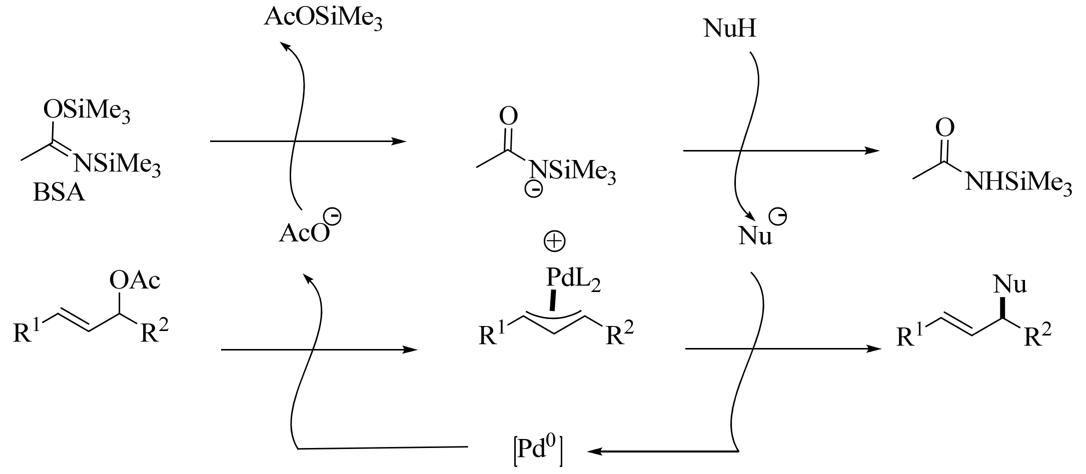
[86] El Gihani, M. T.; Heaney, H. *Synthesis-Stuttgart* **1998**, 357-375.



Scheme II.10. Generation of the carbanion

The mechanism of the palladium catalyzed allylic alkylation reaction has been deeply investigated.[12,87,59] The general catalytic cycle is presented in Scheme II.11 and starts from Pd(0) allyl complex. If a Pd(II) PHOX complex is used, this compound must first be transformed into a Pd(0) species in order to be catalytically active. It has been reported that the attack of the nucleophile to the cationic Pd(II) specie results in the generation of the Pd(0) active complex (see Scheme II.11). [88] The catalytic cycle starts with the formation of a palladium allyl complex followed by elimination of the leaving group X (normally acetate) in the oxidative addition step.[89] Both enantiomers of the allylic substrate lead to the same allyl complex **133**; thus, any stereochemistry in the starting substrate is lost during this step. For this reason, racemic substrates are suitable substrates in this transformation. The cationic η^3-palladium allyl complexes formed after the oxidative addition step are stable in the absence of a nucleophile and can be isolated and studied if desired. These palladium complexes containing 1,3-disubstituted allyl moieties can give rise to

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[87] Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257-276.
[88] Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Amer. Chem. Soc.* **1985**, *107*, 2033-46.
[89] Jacobsen, E. N.; Pfaltz.A.; Yamamoto, H. E. *Comprehensive Asymmetric Catalysis I-III*, **1999**.

several isomers, depending on the stereochemical relationship between the substituents of the allyl group and the central allyl hydrogen: *syn-syn*, *syn-anti*, *anti-syn* and *anti-anti* isomers. Furthermore, each of those isomers can have an *exo* and an *endo* arrangement of the allyl moiety. These isomeric species are able to interconvert due to several fluxional processes. Details concerning the intermediates and isomerization processes will be presented in another section of this chapter and only isomers **134** *exo-syn-syn* and *endo-syn-syn* are depicted in Scheme II.11. for the sake of clarity. Enatioselectivity is determined by the regioselective attack of the nucleophile onto one of the allylic terminus of the palladium complex.[90] The Pd(II) center activates the allylic termini and attack occurs preferentially at C1 or C3. Although attack at C2 is in principle possible, it is not common.[91] The Pd-olefin complex resulting after the addition of the nucleophile readily dissociates, the substitution products are released, and the active palladium complex is thus regenerated and can re-enter in the cycle.

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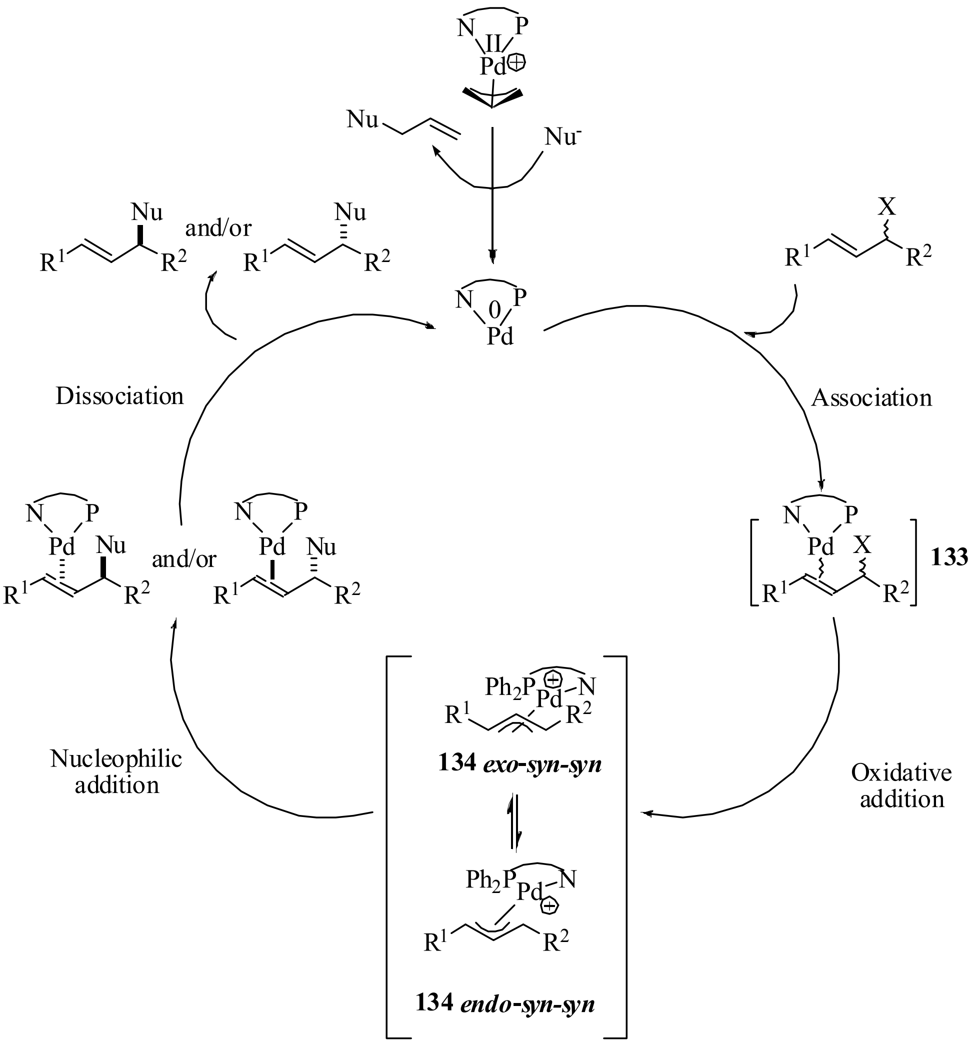
[90] Faller, J. W.; Chao, K. H.; Murray, H. H. *Organometallics* **1984**, *3*, 1231-1240.

[91] Castano, A. M.; Aranyos, A.; Szabo, K. J.; Baeckvall, J.-E. *Angew. Chem. Int. Ed.* **1995**, *34*, 2551-3.



Scheme II.11. The catalytic cycle of the asymmetric alkylation reaction

Kinetic resolution considerations

If an allylic asymmetric alkylation does not proceed to full conversion, a kinetic resolution process can be observed.[88] Kinetic resolution may occur during the complexation of the substrate with a chiral palladium complex.[92] It has been observed, in most of the cases, that the unreacted substrate has the opposite absolute configuration when compared to the substitution product. This indicates that one of the enantiomers of the allylic substrate forms the η^3- palladium allyl complex **135** (association followed by oxidative addition in Scheme II.12) faster than the other. This discrimination between the two enantiomers of the substrate has been shown to be temperature dependent.[92] The acetate anion could be involved in another mechanism by which kinetic resolution might arise in the allylic alkylation reactions.

Amatore et al[93] have suggested that the acetate ion is not a simple leaving group but may play a more active role in the catalytic process. They reported that the acetate ion may compete with the nucleophile in the attack of the cationic π-palladium allyl complexes **135** *endo syn-syn* and **135** *exo syn-syn* (Scheme II.12). It is not clearly established if the acetate ion acts as a soft or hard nucleophile. The first class of nucleophile should lead to the initial substrate with retention of the configuration whereas the latter should render the enantiomer of the substrate with opposite configuration. The competition between the acetate and the desired

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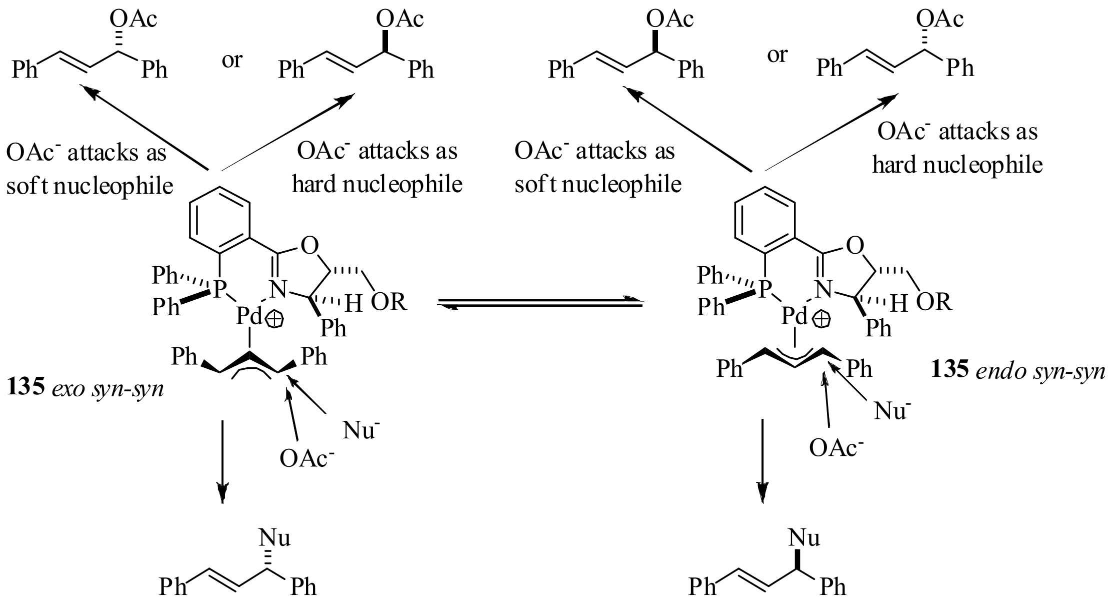
[92] Ramdeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 3118-3121.

[93] Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L. *Chem. Eur. J.* **1999**, *5*, 466-473.

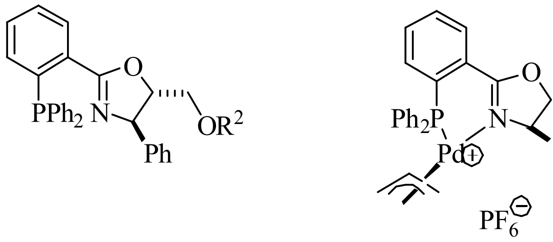
nucleohile should become more intense as the concentration of the acetate ion increases.[93]



Scheme II.12. Role of the acetate ion in the overall equilibrium of the reaction

III. ALLYLIC ALKYLATION CATALYZED BY Pd-PHOX COMPLEXES

The synthesis of a diverse family of PHOX **55a-f** has been described in chapter I. This library of ligands offers the possibility of systematically varying steric congestion around the Pd-centre by changing the CH_2OR^2 group. To test the effect of structural variations on the catalytic activity, the palladium allyl complexes **49a-e** containing an unsubstituted allyl moiety were used as catalytic precursors in model asymmetric allylic reactions.



55 **49**

Figure II.1. Modular PHOX ligands and palladium complexes

The allylic alkylation of *rac*-(*E)*-3-acetoxy-1,3-diphenyl-1-propene **63**,[94] was chosen as the model reaction to study. In this way, **63** was alkylated in dichloromethane at room temperature in the presence of 2.5 mol% of allyl-Pd complex, the nucleophile being generated from dimethyl malonate with *N,O*-bis-(trimethylsilyl) acetamide (BSA) and a catalytic amount of potassium acetate. The results of the enantioselective allylic alkylation are shown in Table II.4. In some cases (entries 3 and 4), full conversions were not achieved, even after prolonged reaction times. In such cases, a dynamic kinetic resolution of the substrate was

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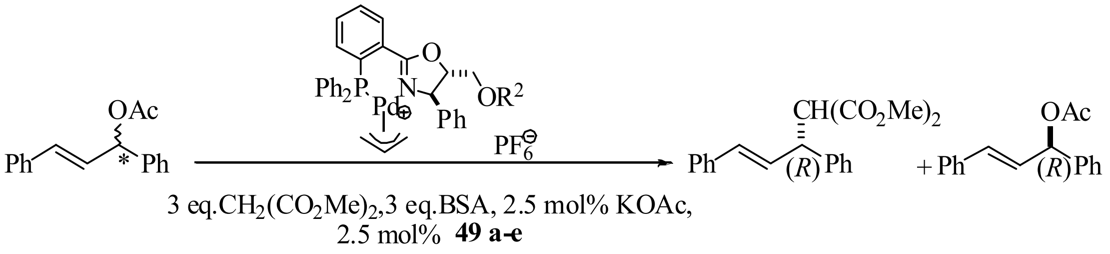
[94] The required substrate, *rac*-*E*-3-acetoxy-1,3-diphenyl-1-propene **63**, was obtained from commercially available alcohol using described methods (Auburn, P. R.; Mackenzie, P. B.; Bosnich, B., *J. Am. Chem. Soc.* **1985,** *107*, 2033).

observed and the optical purity of the recovered allyl substrate is also reported in Table II.4.



63 **64** **63**

Scheme II.13 Asymmetric allylic alkylation of *rac-(E)*-3-acetoxy-1, 3-diphenyl-1-propene

Table II.4. Ligand fine-tuning in the alkylation of *rac-(E)*-3-acetoxy-1, 3-diphenyl-1-propene

Entry	**Catalyst**	**Time(h)**	**Conv.(%)**[a,b]	**64,ee(%)**[c]**(*R*)**[d,e]	**63,ee(%)(*R*)**[95]
1	**49a** (R^2=Me)	4	>99	96	-
2	**49b** (R^2=CH_2Ph)	4.3	>99	85	-
3	**49c** (R^2=$CHPh_2$)	27	87	87	43
4	**49d** (R^2=CPh_3)	27	60	83	8
5	**49e** (R^2=$CH_2CH_2OCH_3$)	4.5	>99	86	-
6	**49f** (R^2=bezyltriazole)	0.8	>99[f]	84	-

a) general reaction conditions: 2.5 mol % **49**, 2.5 mol % KOAc 3eq. $CH_2(COOCH_3)_2$, 3eq. BSA, CH_2Cl_2 room temperature; b) conversion determined by ^{1}H-NMR;[32] c) absolute configuration *R*; d)$[\alpha]_D$ = +4.10 (c = 0.65 EtOH);[35] e) ee- determined by HPLC using a chiral column (ODH); f) neat reaction conditions : 2.5 % mol **49**, 2.5 % mol KOAc 3eq. $CH_2(COOCH_3)_2$, 3eq. BSA, room temperature.

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[95] Reetz, M. T.; Sostmann, S. *J. Organomet. Chem.* **2000**, *603*, 105-109.

Total conversion of the **63** was achieved at room temperature with catalysts **49a,b** and **e** in relatively short reaction times of one to four hours (entries 1, 2 and 5 in Table II.4). The activity of the catalysts decreased with the size of the protecting group,[96] and full conversions were not obtained for ligands **49c,d** (entries 3 and 4, Table II.4). The best enantioselectivity of 96% ee, (entry 1 in Table II.4) was observed with catalyst **49a** bearing the least bulky substituent at C5 in the oxazoline ring. The enantioselectivities obtained with the ligands from the rest of the family ranged from 83 % ee to 87% ee. For the complexes **49c** and **49d** the unreacted acetate had an enantiomeric excess of 43% ee and 8% ee respectively (entry 3 and 4). Under the studied conditions, ligand **49a** gave the best results from the whole library.

For ligands **49a-d**, looking for the optimal reaction conditions a wide range of temperatures from -10ºC to 55ºC was examined. Thermal activation or microwave irradiation[97] were used to carry out the alkylation reaction at the desired temperature.

The initial study on the temperature effects was carried out with ligand **49a**.Very good enantioselectivities were observed across the whole temperature range (94-97% ee). The best enantioselectivity was achieved at 35 ºC, 97% ee, entry 4, Table II.5.). Under microwave irradiation conditions, the reaction time could be shortened to 15 min achieving complete conversion in this period of time, with no loss of enantioselectivity (entry 6 in Table II.5.).

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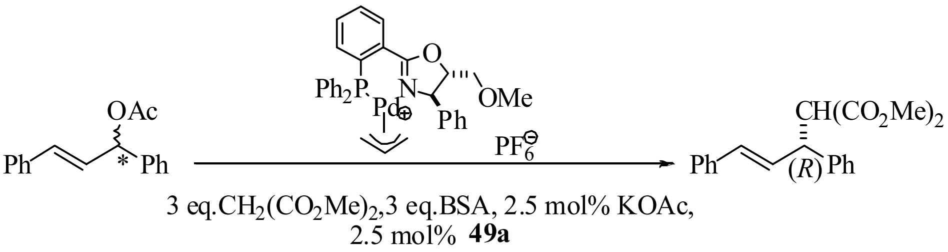
[96] These observations refer only to solvent reaction conditions.

[97] For previous work on microwave-promoted allylic alkylation with phosphinooxazoline ligands, see: Kaiser, N. F. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *J. Organomet. Chem.* **2000**, *603*, 2-5;Bremberg, U.; Lutsenko, S.; Kaiser, N.-F.; Larhed, M.; Hallberg, A.; Moberg, C. *Synthesis* **2000**, 1004-1008;Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717-727.

Together, these results represent a remarkable example of good performance of a ligand in asymmetric allylic alkylations under microwave irradiation. The exceptional good temperature/selectivity profile renders catalyst **49a** optimal for future applications in large scale because almost no temperature control would be required in order to achieve high enantioselectivities.



63 **64**

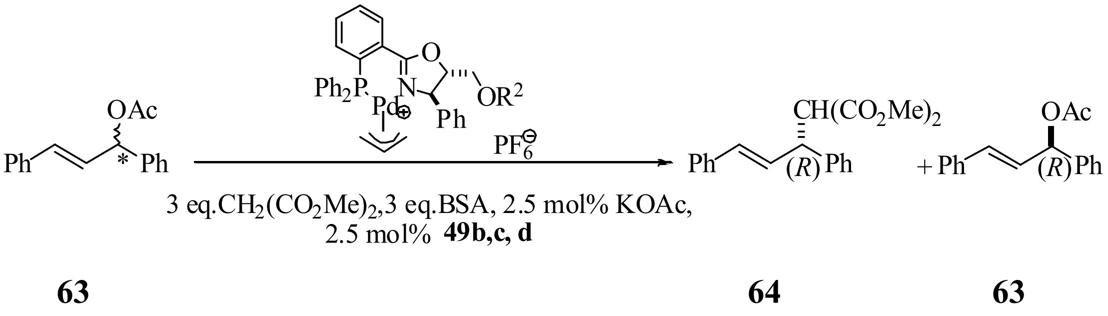
Scheme II.14 Allylic alkylation of **63** with catalyst **49a**

Table II.5. Optimization procedure for catalyst **49a** in the alkylation of **63**

Entry	T(ºC)	Time(h)	Conv.(%)$^{a, b}$	ee (%)^{c}(*R*)$^{d, e}$
1	-10	24	>99	94
2	0	7	>99	95
3	24	4	>99	96
4	35	2.5	>99	97
5	35^{f}	1	96	95
6	55^{g}	0.25	99	95
7	45	2	>99	95

a) general reaction conditions: 2.5 mol % **49a**, 2.5 mol % KOAc 3eq. $CH_2(COOCH_3)_2$, 3eq. BSA, CH_2Cl_2 room temperature; b) conversion determined by ^{1}H-NMR;[32] c) absolute configuration R; d)$[\alpha]_D = +4.10$ (c = 0.65 EtOH);[35] e) ee- determined by HPLC using a chiral column (ODH); f) MW irradiation; g) MW irradiation, the reaction was carried out in acetonitrile.

A similar study on the effects of the temperature on the enantioselectivity mediated by **49b,c** and **d** in the allylic alkylation of substrate **63** was carried out. The conversions and enantioselectivities obtained under different reaction conditions have been summarized in Table II.6. Optical purity of the recovered starting substrate has been included in the cases where full conversion was not observed.



Scheme II.14 Allylic alkylation of **63** with catalyst **49b,c** and **d**

Table II.6. Optimization of the akylation conditions for catalyst **49b**,**c**,**d**.

Entry	**R^2**	**T(ºC)**	**Time(h)**	**Conv.(%)**[a,b]	**64,ee(%)**[c]**(*R*)**[d,e]	**63,ee(%)(*R*)**[95]
1	CH_2Ph	-10	28	58	90	24
2		0	28	58	91	25
3		24	4.3	>99	85	-
4		35	3	>99	87	-
5	$CHPh_2$	-10	27	65	89	43
6		0	27	74	89	40
7		24	27	87	87	43
8		35	3	>99	85	-
9	CPh_3	-10	42	14	86	-
10		0	27	9	86	-
11		24	27	60	83	8
12		35	4	>99	78	-

a) general reaction conditions: 2.5 mol % **49**, 2.5 mol % KOAc 3eq. $CH_2(COOCH_3)_2$, 3eq. BSA, CH_2Cl_2 room temperature; b) conversion determined by ^{1}H-NMR;[32] c) absolute configuration R; d)$[\alpha]_D = +4.10$ (c = 0.65 EtOH);[35] e) ee- determined by HPLC using a chiral column (ODH).

The activity of **49b** was tested across a temperature range of -10ºC to 35ºC (entries 1-4 in Table II.6). Good enantioselectivities were observed ranging from 85% ee to 91 % ee, lower temperatures provided slightly higher enantioselectivities at the expense of conversion (compare entry 1 and 4). When full conversion was not achieved, the remaining substrate had a noticeable ee (24 % ee, 25 % ee entry 1 and 2).

Interestingly, the reaction mediated by ligand **55c** proceeded without significant variation in the enantioselection in the range of studied temperatures (89-85% ee from -10ºC to 35ºC, entries 5-8 in Table II.6). Again, though, lower temperatures facilitated the alkylation in somewhat higher selectivity whereas conversion dramatically dropped (from total conversion to 65%, cf. entries 5 and 8).

The PHOX-Pd complex bearing the bulkiest substituent in the CH_2OR^2 group, **49d**, turned out to be the least efficient catalyst both in terms of conversion and enantioselection (78 -86 % ee, entries 9-12). Total conversion could only be accomplished at 35ºC but with lower enantioselectivity (78% ee, entry 12).

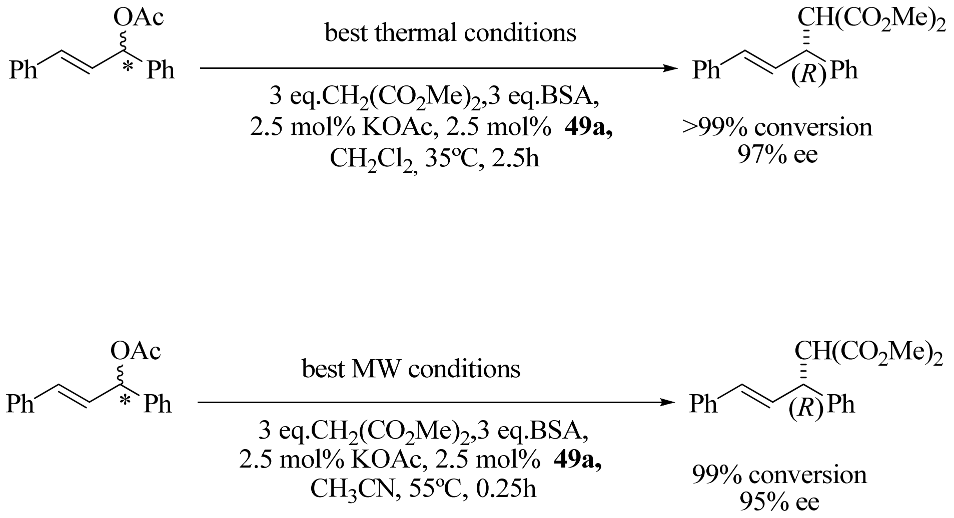
It is clear from the results already presented that **49a**, containing a methoxymethyl substituent, is the optimal ligand amongst those in the studied series. Steric congestion around the palladium center appears to be detrimental for the catalytic efficiency of the PHOX-Pd complexes in allylic alkylation. Enantioselectivity also decreased with increasing the bulk of the substituent in the CH_2OR^2 chain for a given temperature. Furthermore, conversion dramatically drops following the same tendency (see Table II.7).

Table II.7. Influence of the R^2 substituent in the alkylation reaction

Entry	R^2	Conversions			Enantioselectivities		
		0ºC	**24ºC**	**35ºC**	**0ºC**	**24ºC**	**35ºC**
1	Me	>99	>99	>99	95	96	97
2	CH_2Ph	58	>99	>99	91	85	87
3	$CHPh_2$	74	87	>99	89	87	85
4	CPh_3	9	60	>99	86	83	78

Temperature effects on the enatioselectivity with the same Pd-PHOX complex are more difficult to fully rationalize, as the ligands showed slightly different behaviour respect to temperature. With the optimal ligand **55a**, the best performance in terms of enantioselectivity was achieved at 35ºC (97% ee, entry 1 Table II.7). The rest of catalysts showed the highest enatioselectivity at 0ºC, according to a behaviour often observed in asymmetric catalysis: the lower the temperature, the higher the enantioselectivity, usually, at the expense of activity.[89]

As far as the use of the optimal catalyst, **49a**, under microwave irradiation conditions is concerned, the reaction time could be dramatically shortened (15 minutes for complete conversion) without almost any loss in enantioselectivity (see entry 6 in Table II.5 and scheme below).



Scheme II.15. Best results for **49a** under thermal and MW conditions

With the optimized conditions for the allylic alkylation of model substrate **63** in hand, the scope of the reaction with alkyl substituted **99b**, **136a** cyclic **136b**, aryl di- and monosubstituted **99c**, **136c** and trisubstituted allyl acetates **99d**, **136d** was studied (Figure II.2).

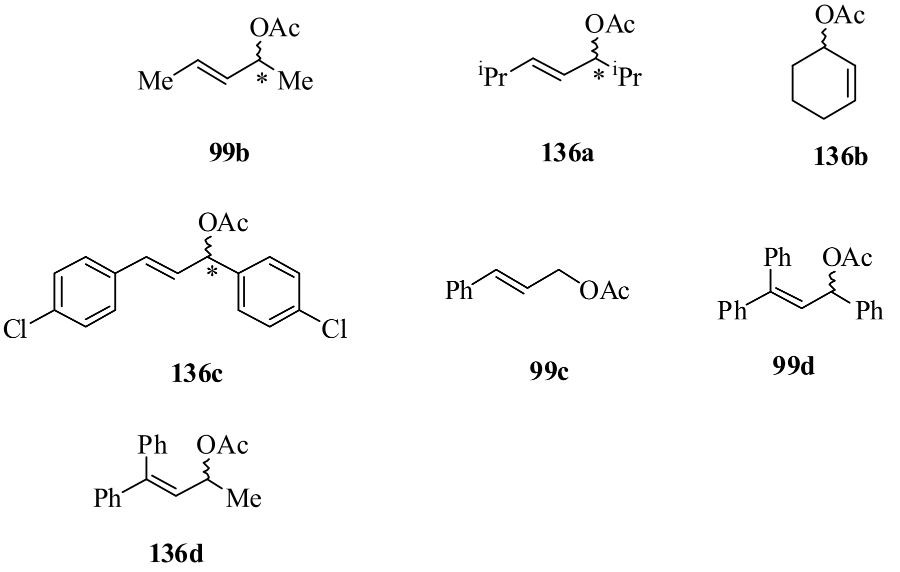


Figure II.2. Studied scope substrates

Allylic acetates **99b,d** and **136a-d** were not commercially available and were synthesized in racemic form by acetylation of the corresponding allylic alcohols,[98, 99] which in turn were prepared, if not commercially available, by reduction of the corresponding α,β-unsaturated carbonyl[68] or 1,3 dicarbonyl compounds[100] or by addition of PhLi or MeMgBr to the 3,3-diphenylacrylaldehide.[101]

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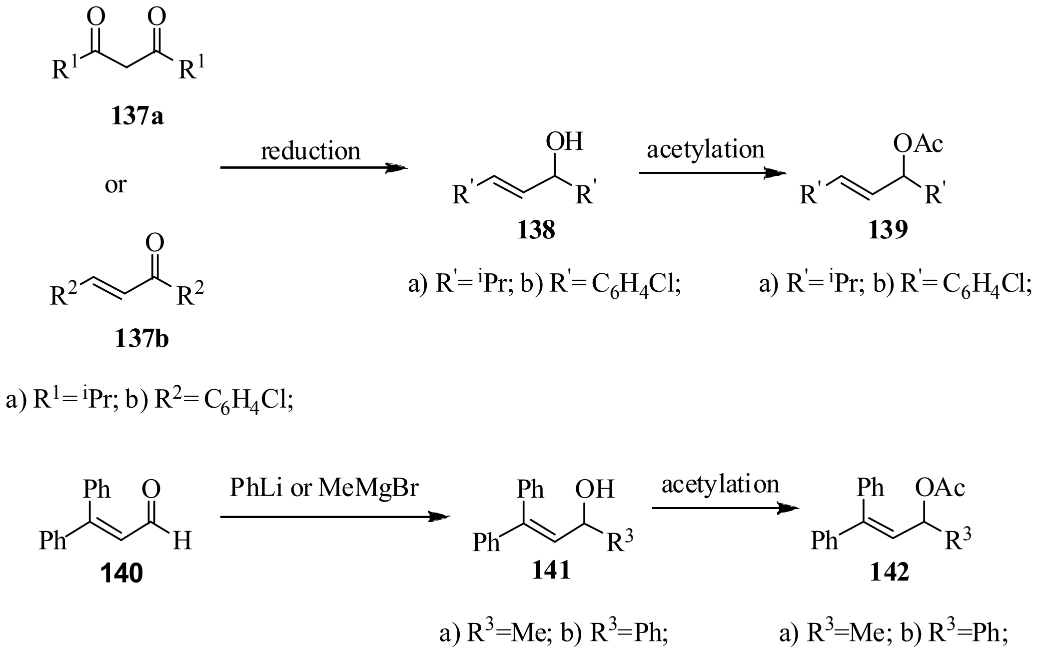
[98] Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Payne, S. C.; Semones, M. A.; Liebeskind, L. S. *Organometallics* **1995**, *14*, 4132-56.

[99] Jia, C.; Mueller, P.; Mimoun, H. *J. Mol. Catal. A: Chem.* **1995**, *101*, 127-36.

[100] Jacoby, C.; Braekman, J. C.; Daloze, D. *Tetrahedron: Asymmetry* **1995**, *6*, 753-756.

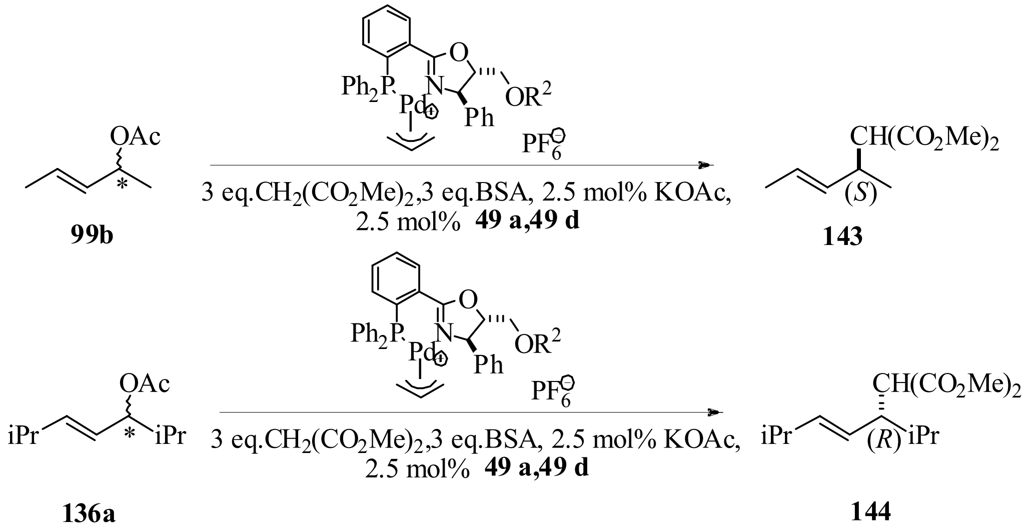
[101] Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723-3730.



Scheme II.16. Preparation of the non-commercial alcohols and their acetylation

As far as the allylic alkylation of substrates **99** and **136** are concerned, they were carried out under standard conditions using BSA and catalytic amounts of KOAc to generate the carbon nucleophile (malonic ester's carbanion).

The allylic disubstituted substrates **99b** and **136a** were subject to the alkylation conditions already discussed using Pd-PHOX-allyl complexes **49a** and **49d**. Results have been summarized in Table II.8.



Scheme II.17. Allylic alkylation of **99b** and **136a**

Table II.8. Enantioselective allylic alkylation of **99b** and **136a**

Entry	**Catalyst**	**Substrate**	**T(ºC)**	**Time(h)**	**Conv.(%)^{a,b}**	**ee (%)**
1	**49a**	**99b**	15	24	38	$44\,^{c}(S)^{d,\,e}$
2	**49a**	**99b**	25	24	87	$49\,^{c}(S)^{d,\,e}$
3	**49a**	**99b**	35	4.5	91	$48\,^{c}(S)^{d,\,e}$
4	**49a**^{f}	**99b**	60	3.5	>99	$35\,^{c}(S)^{d,\,e}$
5	**49d**	**99b**	25	24	92	$41\,^{c}(S)^{d,\,e}$
6	**49a**	**136a**	45	24	0	-
7	**49d**	**136a**	45	24	0	-
8	**49a**	**136a**	MeCN/80ºC, MW	8	54^{g}	$92(R)^{h,\,i}$

a) general reaction conditions: 2.5 mol % **49**, 2.5 mol % KOAc 3eq. $CH_2(COOCH_3)_2$, 3eq. BSA, CH_2Cl_2; b) conversion determined by ^{1}H-NMR;[32] c) absolute configuration *S*; d)$[\alpha]_D = -1.50$ (c = 1.6 in $CHCl_3$);[35] e) ee-determined by GC using a chiral stationary phase; f) MW conditions, 50W, 60ºC , CH_3CN; g) it refers to isolated yields; h)ee determined using ^{1}H-NMR techniques, 6 eq Eu(hcf)$_3$ to 1 eq of substrate; i) absolute configuration *R*.[102]

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[102] Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Amer. Chem. Soc.* 2000, *122*, 7905-7920.

Both Pd-PHOX catalytic species mediated the alkylation of *rac*-4-acetoxy-2-pentene (**99b**) with moderate enantioselectivities (35-49% ee, see entry 1-5 in Table II.8) under all reaction conditions tested. The reactions were carried out across a wide temperature interval (15-60ºC). Higher temperatures allowed full conversion of the substrate (entry 4). The obtained product had an opposite stereochemistry outcome compared with the model substrate. The reversal in the absolute configuration is particularly noteworthy, since a parallel behaviour is, to the best of our knowledge, unprecedented in this transformation. This aspect will be discussed in the forthcoming section of this chapter.

The allylic alkylation of the 1,3-diisopropylallyl acetate[103] did not proceed under thermal conditions (entry 6 and 7 in Table II.8). Under microwave irradiation, the product was obtained in moderate conversion and high ee (54% conversion, 92% ee, entry 8 in Table II.8). It is interesting to point out that no reversal in the stereoselectivity is observed in the alkylation of the diisopropyl substituted substrate, where the allyl system bears bulkier alkyl substituents. This reversal of stereoselectivity appears to be related to the small size of the methyl substituents, and the possible change that this can provoke in the stereochemistry/reactivity of the intermediate.

The asymmetric allylic alkyation of cyclic substrates such as *rac*-3-acetoxy-1-cyclohexene[104] was studied under the standard reaction conditions and in a temperature interval ranging from 15ºC to 60ºC. Catalysts **49a** and **49d** (see Scheme II.18 and Table II.9) were used to study the stereochemical bias on the allylic

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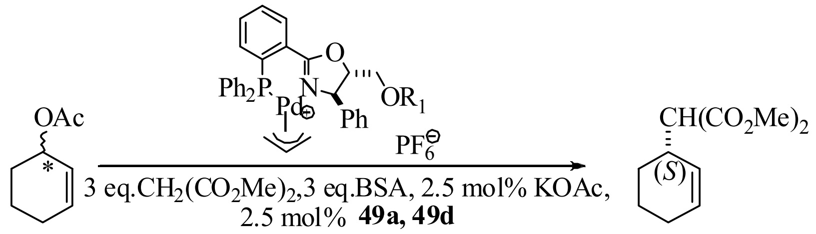
[103] The 1, 3-diisopropyl-2-propenylacetate was synthesized starting with the reduction of the 2, 6-dimethylheptane-3, 5-dione with $LiAlH_4$ leading to (*E*)-2, 6-dimethylhept-4-en-3ol[100] and followed by the acetylation through described method.[98,99]

[104] The 3-acetoxy-1-cyclohexene was not commercially available and was synthesized starting from the corresponding alcohol by acetylation, employing described methods.[98,99]

alkylation as a function of the bulkiness of the alkoxy substituent. Similar to previous results, catalyst **49a** mediated the alkylation with a higher selectivity than **49d** (56% ee, compared to 29% ee, entry 2 and 5 from Table II.9).



136b **145**

Scheme II.18. Allylic alkylation of *rac*-3-acetoxy-1-cyclohexene

Table II.9. Results obtained in the alkylation of the *rac*-3-acetoxy-1-cyclohexene

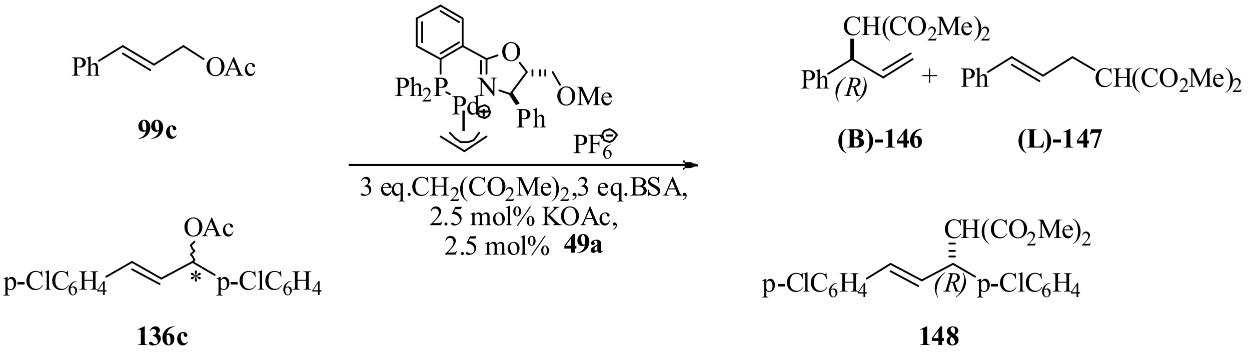
Entry	**Catalyst**	**T(ºC)**	**Time(h)**	**Conv.(%)[a, b]**	**ee (%)[c](*S*)[d, e]**
1	**49a**	15	24	37	56
2	**49a**	25	24	40	56
3	**49a**	35	24	32	52
4	**49a**[f]	60	3.5	>99	34
5	**49d**	25	24	35	29

a) general reaction conditions: 2.5 mol % **49**, 2.5 mol % KOAc 3eq. $CH_2(COOCH_3)_2$, 3eq. BSA, CH_2Cl_2; b) conversion determined by ^1H-NMR; c) absolute configuration *S*; d)$[\alpha]_D$ = -3.8 (c = 0.65 in $CHCl_3$);[35] e) ee-determined by GC using a chiral stationary phase; f) MW conditions, 50W, 60ºC , CH_3CN;

Conversions were low under all the conditions tested, except when microwave irradiation was used (99% conversion), though lower ee's were observed(34% ee, entry 4 Table II.9).

Aryl disubstituted and monosubstituted allyl acetates were also studied in the asymmetric alkylation mediated by Pd-PHOX-allyl complex **49a**.

Allylic alkylation of cinnamyl acetate[105] led to the substitution product in a lineal to branched ratio of 93/7 and with an enantiomeric excess of 82% ee (see entry 1 in Table II.10). This is in agreement with literature, which reports that allylic substitution of monosubstituted substrates mostly proceeds with formation of the linear product in Pd-mediated allylic transformations.[24,25]



Scheme II.19. Allylic alkylation of substrates **99c** and **136c**

Very good enantioselectivities have also been achieved in the allylic alkylation of substrate **136c**[106] which has not previously been reported with PHOX-based catalysis.

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[105] This compound is commercially available.

[106] The reduction of the 1, 3-bis (*para*-chlorophenyl)-propenone to the corresponding alcohol followed by the acetylation led to the 3-acetoxy-1,3-bis (*para*-chlorophenyl) -1-propene substrate.[68]

Table II.10. Asymmetric allylic alkylation of substrates **99c** and **136c** with catalyst **49a**

Entry	Substrate	Solvent/Temperature	Time(h)	Conv.(%)[a, b]	ee (%)(*R*)
1	**99c**	CH_2Cl_2/rt	4	>99[c]	82 [d,e]
3	**136c**	THF/-10 ºC	17	95	98
4	**136c**	THF/rt	1.5	> 99	91
5	**136c**	THF/85ºC, MW	2.5	> 99[e]	93[f,g]

a) general reaction conditions: 2.5 mol % **49a**, 2.5 mol % KOAc 3eq. $CH_2(COOCH_3)_2$, 3eq. BSA; b) conversion determined by ^{1}H-NMR; c) linear to branched product ratio was 93/7; d) absolute configuration *R*;[107] e) ee- determine by HPLC, OJ column;[102] e) ^{1}H-NMR characterization[108]; f) ee- detrmined by HPLC, ADH column; g) absolute configuration *R*.[109]

Allylic alkylation of **136c** with dimethyl malonate was studied across a range of temperature -10ºC to 85ºC using Pd complex **49a.** Optimal conditions for achieving high enantioselectivities involve the use of low temperatures (-10ºC, entry 3, Table II.10). However, long reaction times are required. Alkylation at higher thermal levels under microwave irradiation shortened the reaction time (85ºC, 2.5h, conversion >99%) at the expense of a somehow lower enantioselectivity (93% ee).

Lastly, the asymmetric alkylation of trisubstituted allylic acetates **99d** and **136d**[110] was studied.

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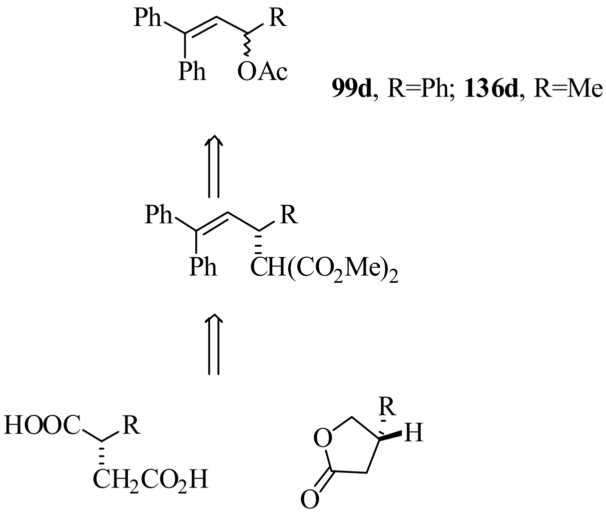
[107] You, S. L.; Zhu, X. Z.; Luo, Y. M.; Hou, X. L.; Dai, L. X. *J. Amer. Chem. Soc.* 2001, *123*, 7471-7472.

[108] Albano, V. G.; Bandini, M.; Monari, M.; Marcucci, E.; Piccinelli, F.; Umani-Ronchi, A. *J. Org. Chem.* 2006, *71*, 6451-6458.

[109] Albano, V. G.; Bandini, M.; Melucci, M.; Monari, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2005**, *347*, 1507-1512.

[110] The starting acetates were obtained in two steps from the commercial 3, 3-diphenylacrylaldehyde by addition of PhLi or methyl magnesium bromide[101] followed by acetylation using acetic anhydride, DMAP and triethylamine.[64]



99d, R=Ph; **136d**, R=Me

Scheme II.20. Chiral products obtained from **99d** and **136d**

Asymmetric alkylation of *rac*-3-acetoxy-1,1,3-triphenyl-1-propene, **99d** and *rac*-3-acetoxy-1,1-diphenyl-1-butene, **136d** constitutes an efficient entry to key enantiopure synthons for the synthesis of chiral γ-lactones and succinic acids (Scheme II.20.).[64,111]

The allylic alkylation of the substrate **99d** (see Scheme II.21) was first studied under the optimized conditions developed for the model substrate **63** (2.5 mol% **49a**, rt). Although the selectivities were high under these conditions (95% ee, entry 1, Table II.11.), conversions remained low even after 96h (complete conversion could not be achieved (90%) in THF at reflux, entry 2, Table II.11.). Microwave assisted allylic alkylation conditions turned out to be more effective for this kind of substrates, with complete conversion being achieved in acetonitrile at 130ºC with a minimal decrease of the enantioselectivity (93% ee, entry 4). More surprisingly, the enantiomeric excesses which were achieved with the two catalysts tested **49a** and **49d** under microwave irradiation (cf. entry 4 and entry 5 to entry 1) were only slightly lower than those observed at room temperature.

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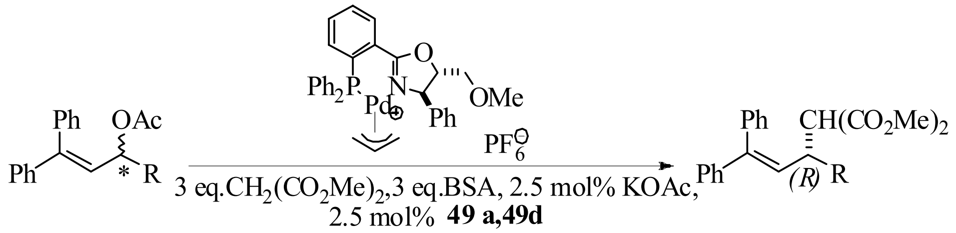
[111] Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 461-2.

Finally, the reaction was carried out with substrate **136d** and the alkylation product was obtained with complete conversion and lower selectivity, 70% ee under microwave irradiation at 130ºC (entry 7). To conclude, microwave activation was the technique of choice for the allylic alkylation reaction onto hindered allyl substrates.



99d (R=Ph) **149**

136d (R=Me) **150**

Scheme II.21. Allylic alkylation of **99d** and **136d** with dimethylmalonate

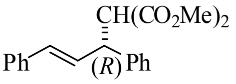
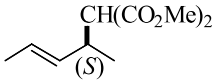
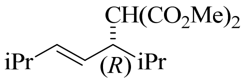
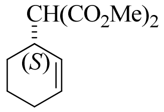
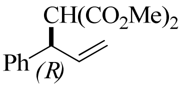
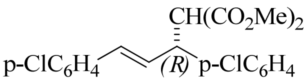
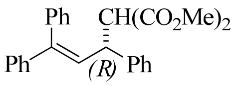
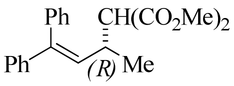
Table II.11. Enantioselective allylic alkylation for substrates **99d** and **136d**

Entry	Substr	Cat.	Solvent/Temp.	Time (h)	Conv.(%)[a,b]	ee(%)(R)[c,d]
1	**99d**	**49a**	DMF /30ºC	96	42	94[e]
2	**99d**	**49a**[g]	THF /70ºC	38	90	94[e]
3	**99d**	**49a**	THF /65ºC, MW	5	10	96[e]
4	**99d**	**49a**	CH$_3$CN /130ºC, MW	2	99	94[e]
5	**99d**	**49d**	CH$_3$CN / 130ºC, MW	2	96	91[e]
6	**136d**	**49a**	CH$_3$CN/100ºC, MW	2	64	72[f]
7	**136d**	**49a**	CH$_3$CN /130ºC, MW	2	100	70[f]

a) general reaction conditions: 2.5 mol % **49**, 2.5 mol % KOAc 3eq. CH$_2$(COOCH$_3$)$_2$, 3eq. BSA; b)Conversion determined by ^{1}H-NMR; c) absolute configuration *R*; d) ee dermined by HPLC separation method e)**149** $[\alpha]_D$ = +114.3 (c = 0.3 in CHCl$_3$);[64] f) **150** $[\alpha]_D$ = +10.16 (c = 0.36 in EtOH);[64] g) 10 mol % **49a**.

The best alkylation conditions for each substrate are summarized in Table II.12.

Table II.12. Best results obtained in the alkylation reaction

Entry	Product	Rc.cond.[a]	Conv. (%)	ee (%)
1	 **64**	MeCN/55ºC, MW, 0.25h	99	95
2	 **143**	CH_2Cl_2/25ºC, 24h	87	49
3	 **144**	MeCN/80ºC, MW, 8h	54	92
4	 **145**	25ºC, 24h	40	56
5	 **146**	25ºC, 4h	>99[b]	82
6	 **148**	THF/85ºC, MW 2.5 h	> 99	93
7	 **149**	CH_3CN /130ºC, MW, 2h	99	94
8	 **150**	CH_3CN /130ºC, MW, 2h	> 99	70

a) general reaction conditions: 3 eq.$CH_2(CO_2Me)_2$, 3 eq.BSA, 2.5 mol% KOAc, 2.5 mol% **49 a**; b) linear to branched product ratio was 93/7;

In conclusion, the palladium allyl complexes of the PHOX ligands, described in this work have turned out to be very efficient catalysts in the asymmetric alkylation of several allylic substrates with malonate-derived nucleophiles. The degree of stereoinduction achieved with the catalytic system developed in this work is comparable with the best ones known in the literature for allylic alkylations.

Furthermore, though mediocre, the results obtained for cyclic substrates with the palladium allyl PHOX complexes described in this work should be highlighted. Classical PHOX ligands lead to no enantioselection in the allylic alkylation of these substrates.[59]

Excellent results have been obtained in terms of ee in the alkylation of allyl systems bearing bulky substituents at the carbon atom undergoing alkylation such as **99c** and **136a**. For all these systems, enantioselectivities recorded with **49a** are among the highest for PHOX type ligands.

The allylic alkylation under microwave assisted conditions turned out to be extremely efficient in terms of conversion and selectivity for hindered substrates and should be considered as the method of choice. In particular, the results obtained with catalyst **49a** for substrates **63,** at 55ºC (total conversion in 15 min. with 95% ee, entry1, Table II.12.)**,** **136a** (92% ee, entry3, Table II.12.), **136c**(93% ee, entry6, Table II.12.), at 80-85 ºC, and for **99d** (94% ee, entry7, Table II.12.) and **136d** (70% ee, entry 8, Table II.12.), at 130 ºC, confirm the remarkably wide selectivity-temperature profile of this catalyst.

Isomers rationalisation

The Pd-catalyzed enantioselective C-C bond-forming reactions studied in this work start from racemic substrates and proceeds via symmetric palladium allyl complexes **151**. It should be recalled that complexes **151** containing the 1,3-disubstituted allyl moiety can give rise to several isomers, depending on the stereochemical relationship between the substituents of the allyl group and the central allyl hydrogen: *syn-syn*; *syn-anti*, *anti-syn* and *anti-anti* isomers.[112] Furthermore, each of those isomers can have an *exo* or *endo* arrangement of the allyl moiety. These isomeric species can interconvert due to several fluxional processes (Scheme II.22.). The *anti-anti* isomers (not depicted in Scheme II.22.) have a very limited abundance given their lower stability and are normally not detected.[112e] It has been reported in the literature that the most abundant isomer in the case of 1,3-diphenyl substituted allyl systems corresponds to the *exo-syn-syn* isomer, followed by the *endo-syn-syn*, the ratio ranging from 4:1 to 12:1.[112a,f,h,i,113] The same trend has been found for the 1,3-dimethylallyl precursor,[112e,g] although *syn-anti* diastereomers are stable enough as to be also observed as minor components of the equilibrium mixture in this case. Furthermore, the relative abundance of the different diastereomers of the 1,3-dimethylallyl system depends on the substitution pattern of

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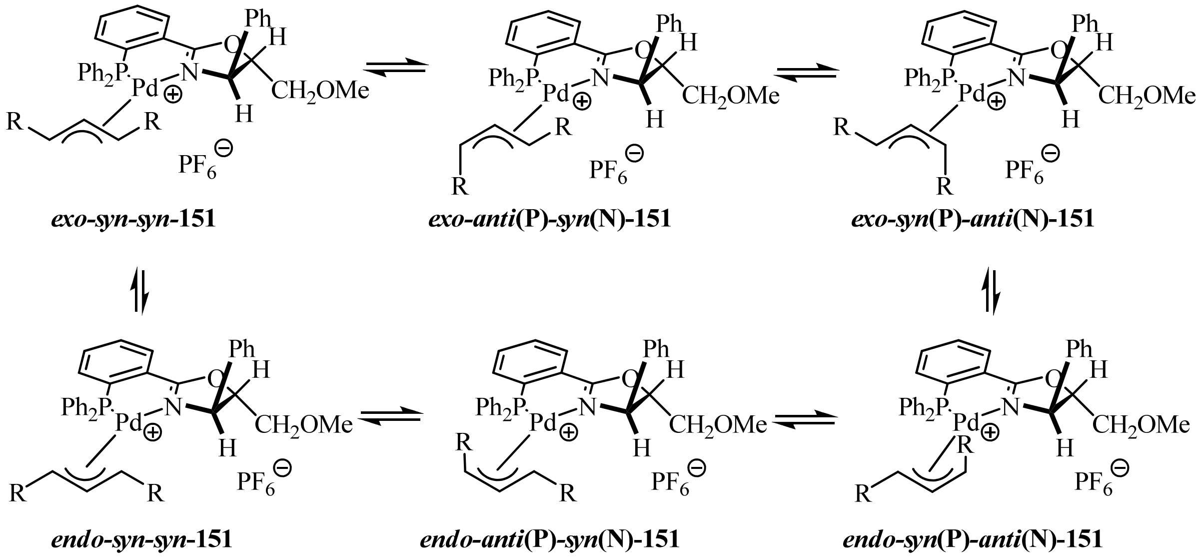
[112] a)Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523-6; b)Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *155*, 35-68; c)Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Amer. Chem. Soc.* **1996**, *118*, 1031-7; d) Liu, S. Y.; Muller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **2000**, *83*, 1256-1267; e)Kollmar, M.; Goldfuss, B.; Reggelin, M.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2001**, *7*, 4913-4927; f)Dotta, P.; Kumar, P. G. A.; Pregosin, P. S. *Magn. Reson. Chem.* **2002**, *40*, 653-658; g) Liu, S.; Muller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283-293; h) Schaffner, S.; Mueller, J. F. K.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1998**, *81*, 1223-1232; i) Zehnder, M.; Schaffner, S.; Neuburger, M.; Plattner, D. A. *Inorg. Chim. Acta* **2002**, *337*, 287-298.

[113] Baltzer, N.; Macko, L.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **1996**, *79*, 803-812.

the sp^3 carbon next to nitrogen in the oxazoline ring: if this is a quaternary carbon, the *syn-anti* isomers predominate.[112i]



Scheme II.22. Isomer's fluxional process

In asymmetric allylic alkylation, the enantioselectivity of the process is determined by the regioselectivity of the attack of the nucleophile onto the palladium allylic intermediate. The higher ability a ligand has to differentiate the two allyl termini towards the incoming nucleophile, the higher selectivity will be induced. In this complex scenario of reaction pathways arising from the different precursors and attack positions, it is normally accepted that the major process arise from the ***exo-syn-syn*-151** precursor, with attack of the nucleophile onto the allyl carbon *trans* to the phosphorus atom (Scheme II.23.).[59,112a] The *(R)* configuration of the final product **64** for the 1,3-diphenyl substituted starting material **63** would be in agreement with this assumption. In an analogous way, the attack of the nucleophile onto the allyl carbon *trans* to the phosphorus substituent of the precursor ***endo-syn*(*P*)-*anti*(*N*)-151** would lead to the major enantiomer of the substitution product

64 as well. However, this reaction pathway is probably less important as the previous one, since the ***endo-syn*(P)-*anti*(N)-151** precursor is predicted to be much less abundant than the ***exo-syn-syn***.[114] In principle, the substitution product with the *R* configuration could also arise from attack of the nucleophile onto the allyl carbon *trans* to nitrogen in precursors ***endo-syn-syn*-151** and ***exo-anti*(P)-*syn*(N)-151**. However, it is normally accepted that these two reaction pathways are irrelevant, as the allyl carbon *trans* to phosphorus is much more reactive towards nucleophiles (the chemical shift of the carbon atom *trans* to phosphorus was observed at 103.1 ppm in ^{13}C-NMR for ***exo-syn-syn*-151** (R=Ph), whereas the chemical shift of the carbon atom *trans* to the nitrogen was observed at 69.1 ppm).

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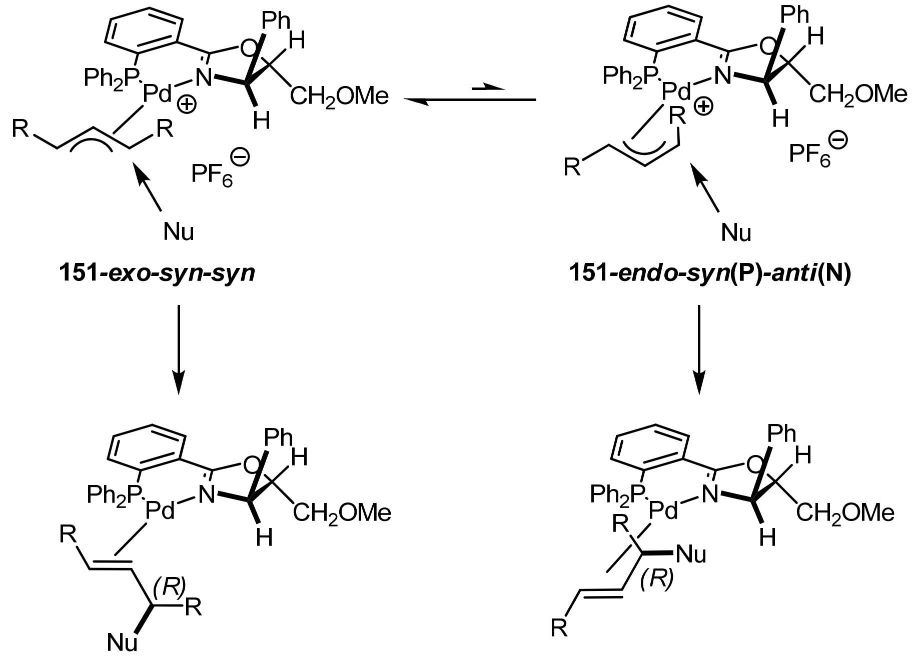
[114] The ionic palladium complex **62** with R=Ph was prepared from standard diphenylallyl palladium dimer and phosphinooxazoline **55a** in the presence of NH_4PF_6. The ^{31}P-NMR spectra of the complex showed six signals at 81.7, 40.5, 34.9, 27.8, 24.7, and 23.1 ppm with relative intensities 0.09:0.06:0.05:0.26:0.1:1.00. The most abundant isomer was assigned as ***exo-syn-syn*-62** by comparison of selected ^{1}H-, ^{13}C- and ^{31}P-NMR data with reported values in the literature. The second more abundant was assigned as the ***endo-syn-syn*-151** by the same arguments as before. No further assignments were possible due to heavily signal overlapping and low intensity of the signals of the rest of the isomers.



Scheme II.23. Possible reaction pathways leading to *R* alkyaltion product

To better understand the reversal of the absolute configuration when moving from the 1,3-diphenylallyl to the 1,3-dimethylallyl substrate, we have performed and report here the results of a theoretical study on the relevant *syn:anti* isomers of the π-allyl palladium complexes of phosphinooxazoline **55a** (**152,Me** and **62,Ph**). A two-layer ONIOM approach has been used for these studies,[115] with the partitioning shown in Figure 2. The high-level layer was treated at the highest, B3LYP/LanL2DZ level. The rest of the molecule was included into the low-level layer and treated at the semi-empirical AM1 level. Therefore, the two-layer ONIOM approach used in the present studies is denoted as ONIOM (B3LYP/LanL2DZ: AM1). The considered geometries were optimized with respect to all geometrical parameters, and the ONIOM total energy was computed. All calculations were performed without symmetry constraints using the Gaussian 03 program.[116]

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[115] Dapprich, S.; Komaromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J. *J. Mol. Struct.* **1999**, *462*, 1-21.

[116] M. J. Frisch; et al. *Gaussian 03,* R. C.-G., Inc.: Pittsburgh PA, **2003**.

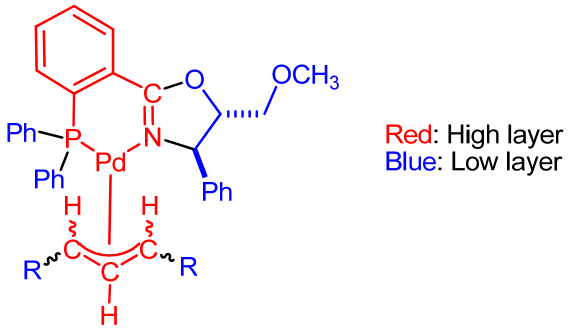

Figure II.4. Molecular partition for ONIOM calculations

The *syn-syn* and the two possible *syn-anti* diastereomers were calculated for both *exo* and *endo* arrangements of **152,Me** and **62,Ph**.[117] Results of the calculated ONIOM total energy and relative energy have been summarized in Table II.13. The molecular structures of the minimal energy isomers of **62,Ph** and **152,Me** are shown in Figure II.4. with key atomic distances. From the methodological point of view, it is important to note that the optimized distances show a good overall agreement with those found in the crystal structure of **49a** (see Table II.13), only the Pd-P distance in the π-allyl complexes being slightly overestimated by the calculations.

---

[117] The *anti-anti* diastereomers are predicted to be of very high energy content and have not been considered (See reference[112e]).

Table II.13.ONIOM total energy (in atomic units) and relative energy (in kcal.mol^{-1}) of the relevant stereoisomers of **62,Ph** and **152,Me**

	62,Ph (1,3-Diphenylallyl)		**152,Me** (1,3-Dimethylallyl)	
	ONIOM Total Energy [a.u.]	**Rel. Energy [kcal.mol^{-1}]**	**ONIOM Total Energy [a.u.]**	**Rel. Energy [kcal.mol^{-1}]**
endo-anti(**P*****)-syn(*****N*****)***[a]	-576.5771334	3.04	-576.6357478	3.13
endo-syn(**P*****)-anti(*****N*****)***	-576.5670563	9.36	-576.6285414	7.65
endo-syn-syn	-576.5793477	1.65	-576.6310965	6.05
exo-anti(**P*****)-syn(*****N*****)***	-576.5706163	7.13	-576.6312656	5.94
exo-syn(**P*****)-anti(*****N*****)***	-576.5738638	5.09	-576.6407325	0.00
exo-syn-syn	-576.5819787	0.00	-576.6336009	4.48

[a] This denotes that the substituent in the allyl terminus proximal to P is in *anti* arrangement and the substituent in the allyl terminus proximal to N is *syn*.

With respect to the stereochemical outcome of the reactions, and assuming a reactant-like character of the transition states for the malonate attack to the cationic complexes **62**, the energetic ordering of the different stereoisomers and the well-based[118,112a] assumption that the nucleophilic attack will take place at the allyl terminus *trans* to phosphorus dictate the stereochemistry of the reaction product.

Very interestingly, the calculations predict that the alkylation of 1,3-diphenylallyl acetate will take place through intermediate ***exo-syn-syn*****-62,Ph** and will lead to a *R* product, as experimentally observed. In the same manner, the calculations predict that the alkylation of 1,3-dimethylallyl acetate will take place through intermediate ***exo-syn(*****P*****)-anti(*****N*****)*****-152,Me** and will lead to a *S* product, as experimentally observed. Thus, the ONIOM calculations provide an explanation for

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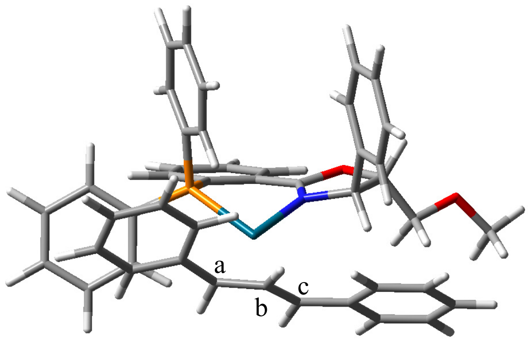
[118] Pfaltz, A.; Drury, W. J., III *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5723-5726.

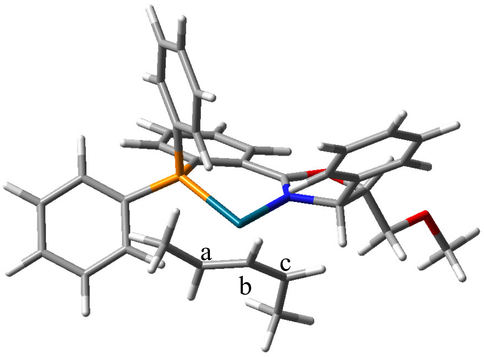
the reversal of enantioselectivity in the alkylations of 1,3-diphenylallyl and 1,3-dimethylallyl acetate with the same catalytic system based on the nature of the most stable π-allyl palladium intermediates containing these systems. The stability of the different stereoisomers contributing to the description of these intermediates appears to be importantly controlled by the size of the 1,3-substituents in the allyl system.[119]

Noteworthy, the ONIOM calculations provide clues for the understanding of the different reactivity recorded with the 1,3-diphenylallyl and 1,3-dimethylallyl substrates. Taking the 1,3-diphenylallyl system (**62,Ph**) as a reference (see Figure 3), a comparison of the distance between palladium and the carbon atom *trans* to phosphorus (Pd-C$_c$) in the *exo-syn-syn* stereoisomer with that found in the minimal energy stereoisomer of **152,Me** (2.321 Å *vs.* 2.269 Å) tends to indicate that substrate **63** should exhibit a higher reactivity than **99b**.



***exo-syn-syn*-62,Ph**

Pd-N: 2.118 Å
Pd-C$_a$: 2.193 Å
Pd-C$_b$: 2.278 Å
Pd-C$_c$: 2.321 Å
Pd-P: 2.442 Å



_exo-syn(_P_)-anti(_N)-152,Me

Pd-N: 2.105 Å
Pd-C$_a$: 2.213 Å
Pd-C$_b$: 2.265 Å
Pd-C$_c$: 2.269 Å
Pd-P: 2.431 Å

---

[119] DFT calculations have also been used to rationalize changes in enantioselectivity in Pd-catalyzed allylic alkylation with hydroxyl-containing ligands. Hydrogen bonds with Pd(0) as the proton acceptor in the intermediate complexes appear to play an important role in this case. See ref 34).

Figure II.5. ONIOM optimized molecular structures of the minimal energy stereoisomers of **62,Ph** and **152,Me**

IV. EXPERIMENTAL PROCEDURES

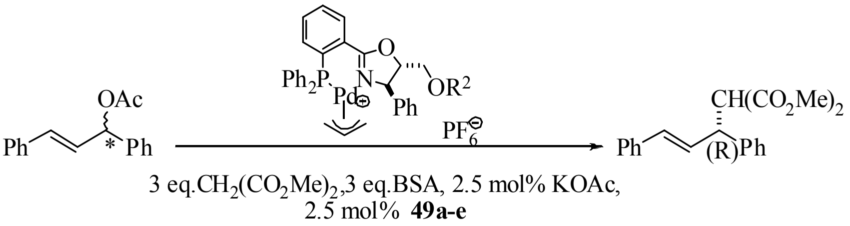
IV.1. General synthesis methods

Employed procedures

The generally employed procedures together with the used material and apparatus were presented in the experimental section of chapter II.

IV.1.1. General procedure for palladium-catalyzed allylic alkylation. Thermal conditions.

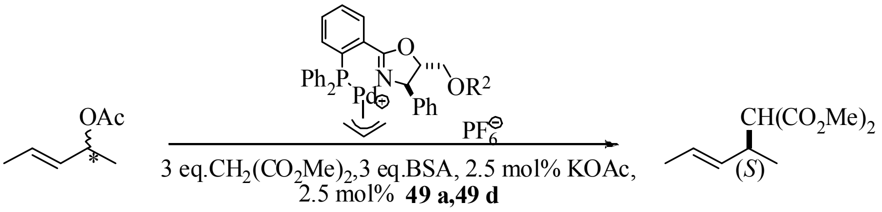
P1. Allylic alkylation of rac-*E*-3-acetoxy-1,3-diphenyl-1-propene, 63



63 **64**

A solution of substrate **63** (0.250 g, 1.0 mmol) in CH_2Cl_2 (2.0 mL) was added at room temperature to a solution **49a-e** (0.025 mmol) in CH_2Cl_2 (2.0 mL) under argon. Dimethyl malonate (0.396 g, 0.350 mL, 3.0 mmol) and BSA (0.610 g, 0.740 mL, 3.0 mmol) were syringed into the previous solution and a catalytic amount of KOAc (0.004 g, 0.04 mmol) was lastly added under argon. The mixture was stirred at room temperature for 48h (unless stated otherwise stated). The reaction mixture was then diluted with diethyl ether, filtered over Celite, and washed with water (4 x 10.0 mL). The organic phase was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure. The crude mixture was filtered through a short SiO_2 pad eluting with ethyl acetate. The conversion of the reaction was measured after removing the solvent by ^1H-NMR[32] of the crude mixture (unless stated otherwise). Dimethyl malonate was mostly removed *in vacuum* (130ºC, 0.4 mBar) and the enantiomeric excesses were determined from the residue by HPLC on an OD-H column (0.5 mL/min *n*-hexane/*iso*-propanol 99:1): (*R*)-**64** Rt = 23min, (*S*)-**64** Rt = 25min.

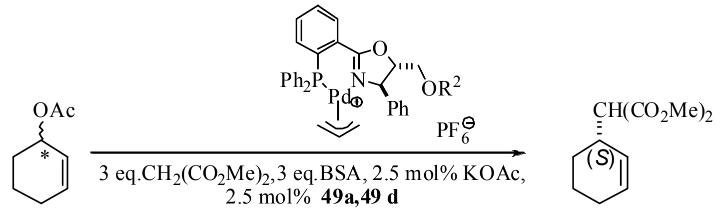
P2. Allylic alkylation of rac-4-acetoxy-2-pentene, 99b



99b **143**

The procedure was analogous to the one described for **63 (**diphenyl allyl substrate**)** but using **49a** and **49d** as catalysts and **99b (**dime-allyl substrate**)** as starting material, and CH_2Cl_2 in a temperature interval of 15ºC to 60ºC. The final alkylation product was identified by ^1H-NMR.[32] The enantiomeric excesses were determined by GC on a FS-cyclodex-β-Dex column (80 ºC): (*R*)**-143** Rt = 68.0 min, (*S*)**-143** Rt = 69.2 min.

P3. Allylic alkylation of rac-3-acetoxy-1-cyclohexene, 136b



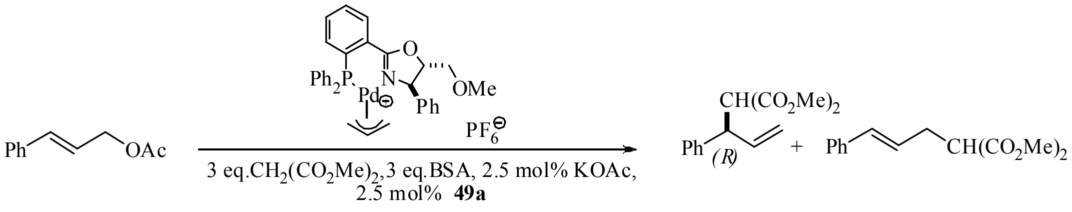
136b **145**

The procedure was analogous to the one described for **63** but using **49a** and **49d** as catalyst and **136b** as starting material, and CH_2Cl_2 in an interval of temperatures of 15ºC to 60ºC. The final alkylation product was identified by ^{1}H-NMR.[120] The enantiomeric excesses were determined by GC on a FS-cyclodex-β-Dex column (10 min at 90 ºC, 1 ºC/min up to 130 ºC, 15 min at 130 ºC, 5 ºC/min up to 150 ºC, 15 min at 50 ºC): (*S*)-**145** Rt = 57.0 min, (*R*)-**145** Rt = 57.4 min.

---

[120] Franzen, J.; Baeckvall, J.-E. *J. Amer. Chem. Soc.* **2003**, *125*, 6056-6057.

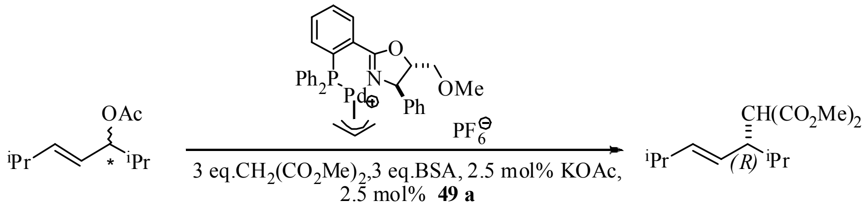
P4. Allylic alkylation of cynnamyl acetate, 99c



99c **146** **147**

The procedure was analogous to the one described for **63** but using **49a** as catalyst, **99c** as starting material, and CH_2Cl_2 at rt. The enantiomeric excesses were determined by HPLC on an OJ-H[102] column (0.7 mL/min *n*-hexane/*iso*-propanol 97:3): (*S*)-**146** Rt = 26.7 min, (*R*)-**146** Rt = 28.4 min.

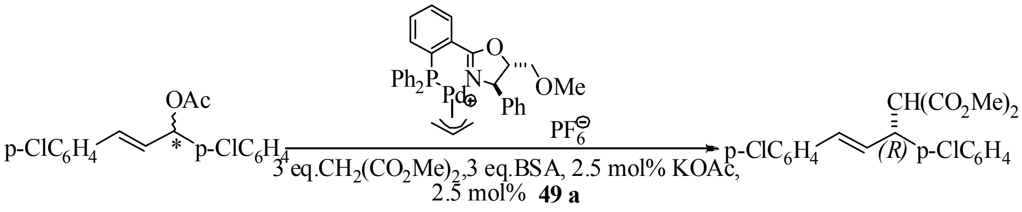
P5. Allylic alkylation of *rac*-1, 3-diisopropyl-2-propenylacetate, 136a



136a **144**

The procedure was analogous to the one described for **63** but using **49a** as the catalyst, **136a** as starting material, and CH_3CN at 80ºC. The enantiomeric excesses were determined by ^{1}H-NMR techniques, 6 eq Eu(hcf)$_3$ to 1 eq of substrate. The absolute configuration was determined as R by comparison of the rotation angle to data literature.[102]

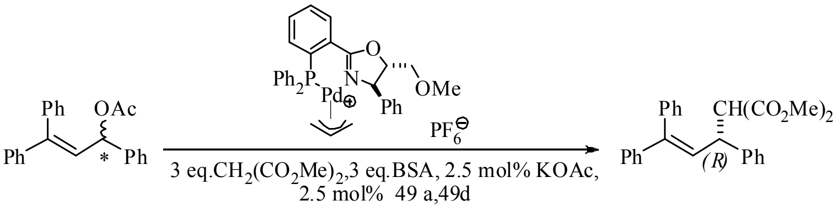
P6. Allylic alkylation of *rac*-*E*-3-acetoxy-1, 3- (*para*-chlorophenyl) -1-propene, 136c



136c **148**

The procedure was analogous to the one described for **63** but using **49a** as the catalyst, **136c** as starting material, and THF as solvent at the indicated temperatures. The final alkylation product was identified by ^{1}H-NMR.[108] The enantiomeric excesses were determined by HPLC[109] on an AD-H column (0.8 mL/min *n*-hexane/*iso*-propanol 85:15): (*R*)-**148** Rt = 19.3 min, (*S*)-**148** Rt = 29.5 min.

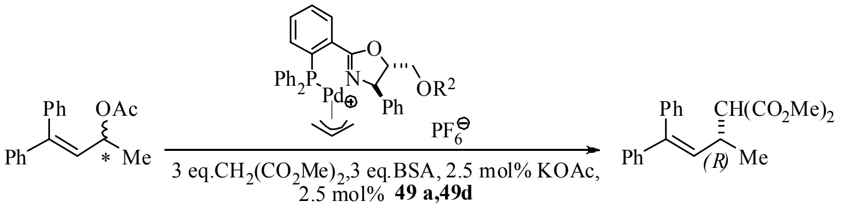
P7. Allylic alkylation of *rac*-*E* -3-acetoxy-1,1,3-triphenyl-1-propene, 99d



99d **149**

The procedure was analogous to the one described for **63** but using **49a** and **49d** as the catalyst, **99d** as starting material, and DMF or THF as solvents at the temperatures indicated. The final alkylation product was identified by ^{1}H-NMR.[64] The enantiomeric excesses were determined by HPLC on AD-H column (0.3 mL/min *n*-hexane/*iso*-propanol 97:3): (*R*)-**149** Rt = 49.4 min, (*S*)-**149** Rt = 51.6 min.

P8. Allylic alkylation of rac-E- 3-acetoxy-1,1-diphenyl-1-butene, 136d



136d **150**

The procedure was analogous to the one described for **63** but using **49a** and **49d** as the catalyst, **136d** as starting material, CH_3CN as solvents at the temperatures indicated. The final alkylation product was identified by ^{1}H-NMR.[64] The enantiomeric excesses were determined by ^{1}H-NMR using the Eu(hcf)$_3$ reagent. The spectrum was done in $CDCl_3$ using 6.0 mmols of allylic alkylation product respect to 1.0 mmol of Eu(hcf)$_3$.

General procedure for palladium-catalyzed allylic alkylation. Microwave-assisted conditions.

The reaction mixture for racemic allylic acetates **63**, **99b**, **136a**, **136b**, **136c,** **99c**, **99d** and **136d** using **49a** as the catalyst was prepared in the appropriated solvent (see the corresponding Tables) in an analogous way as described before for the thermal conditions. The reaction mixture was heated in a microwave reactor for the reaction time and at the temperature indicated in the corresponding experimental section. Enantiomeric excesses for **64**, **143**, **144**, **145** and **146** were measured as described before. The enantiomeric excesses for **150** and **144** were determined by ^{1}H-NMR using the Eu(hcf)$_3$ chiral chemical shift reagent. The spectra was done in $CDCl_3$ using 6.0 equivalents of alkylated final product with respect to one equivalent of the Eu(hcf)$_3$. The enantiomeric excess was measured by integrating suitable signals from the two diastereomeric complexes.

The configuration of the final products was established by comparison either with reported chromatographic elution orders or optical rotations: (+)-(*R*)-**64**[35]; (+)-(*R*)-**149**;[54] (+)-(*R*)-**150**;[54] (-)-(*S*)-**143**[35]**;** (-)-(*S*)-**145**[35]**; 146** (Chiralcel OJ);[107] (*S*)- **146** Rt 24.9 min., (*R*)- **146** Rt 27.7 min. and (-)-(*S*)-**144**.[102]

CHAPTER III

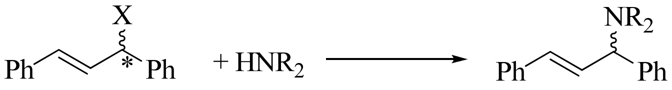
ALLYLIC AMINATION REACTION

ALLYLIC AMINATION REACTION

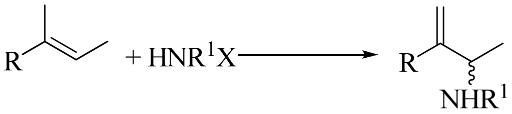
I. INTRODUCTION AND AIMS

Allylamines are important synthons in organic chemistry as the allylamine moiety is found in many natural products.[1] Many important optically active compounds, such as α- and β- aminoacids,[2] alkaloids[3] and aza-carbohydrates[4] can be prepared from allylamines by functionalization, reduction or oxidation of the double bond present in this family of compounds.

The synthesis of allylamines is generally achieved via one of the following synthetic strategies: allylic substitution with nitrogen nucleophiles (Scheme III.1) or the direct amination of alkenes (Scheme III.2).



Scheme III.1. Nucleophilic allylic substitution



Scheme III.2. Direct amination of alkenes

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[1] Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2943.

[2] a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Amer. Chem. Soc.* **1989**, *111*, 6301-6311; b) Burgess, K.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758-4763; c) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411-1420.

[3] a)Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087-11110; b) Ichikawa, Y.; Ito, T.; Nishiyama, T.; Isobe, M. *Synlett* **2003**, 1034-1036; c) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Amer. Chem. Soc.* **2001**, *123*, 1004-1005.

[4] a)Trost, B. M.; Vanvranken, D. L. *J. Amer. Chem. Soc.* **1993**, *115*, 444-458; b) Martin, R.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.*, **2000**, *2*, 93-5.

Intense research has been carried out in the field of allylic amination. Many different transition metal complexes, involving nickel,[5] iridium,[6] iron,[7] rhodium,[8] ruthenium,[9] molybdenum,[10] cobalt,[11] and palladium[12] have been reported as catalysts for the reaction. Among all the transition metal complexes described in the literature for this reaction, palladium complexes are the most widely investigated,[1] though to a lower extent than for the allylic alkylation with carbon nucleophiles (chapter II).

A wide variety nitrogen containing derivatives of both primary (benzylamine,[13] *N*-(*tert*-butoxycarbonyl)phosphoramidite anions,[14] sulfamic acid (H_2NSO_3H)[15]) and secondary (di-tert-butyl iminocarbonate ($(Boc)_2NNa$),[16] phtalimide,[17] dialkylamines,[18] sodium diformylamide ($NaN(CHO)_2$),[19] aziridines,[20] morfoline[21]) types, have been studied and used as nucleophiles in the asymmetric allylic amination (Scheme III.1). Generally, nitrogen nucleophiles have proved to be less reactive than the malonates in the metal mediated allylic substitution.[12]

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[5] Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429-1434.

[6] Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Amer. Chem. Soc.* **2005**, *127*, 15506-15514.

[7] Singh, S.; Nicholas, K. M. *Synth. Commun.* **2001**, *31*, 3087-3097.

[8] Evans, P. A.; Lai, K. W.; Zhang, H. R.; Huffman, J. C. *Chem. Commun.* **2006**, 844-846.

[9] Fernandez, I.; Hermatschweiler, R.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2006**, *25*, 323-330.

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[13] Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Amer. Chem. Soc.* **1992**, *114*, 9327-43.

[14] Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689-1708.

[15] Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3139-3143.

[16] Connell, R. D.; Rein, T.; Aakermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845-9.

[17] Xu, G. P.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *43*, 2811-2814.

[18] Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Amer. Chem. Soc.* **2001**, *123*, 9525-9534.

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[20] Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Amer. Chem. Soc.* **2004**, *126*, 5086-5087.

[21] Faller, J. W.; Wilt, J. C. *Org. Lett.* **2005**, *7*, 633-636.

UNIVERSITAT ROVIRA I VIRGILI
MODULAR PHOSPHINOOXAZOLINES: SYNTHESIS AND EVALUATION IN ALLYLIC SUBSTITUTIONS
Dana Madeleine Popa
ISBN:978-84-691-8862-0/DL:T-1275-2008

In a similar way to the allylic alkylation reaction, allylic acetates, carbonates and phosphates are the most common substrates in allylic amination. Substrates containing more reactive leaving groups, such as halides or sulfonates, have not been considered in amination reactions since they would react with the substrates in the absence of catalysts. Furthermore, the substrate's leaving group may influence the enantioselectivity of the reaction,[22] as the leaving group can form an ion pair with the cationic *π*-allyl-palladium intermediate and act as counterion (discussed in the mechanistic section of this chapter).

A wide variety of structurally different *P,N*-ligands have been developed for this transformation. As discussed for allylic alkylation, desymmetrization takes place upon the formation of a π-allyl-metal complex, due to the different *trans* effect of the *P*- and *N*- donor groups. The two allylic termini of the substrate are electronically discriminated as indicated in Figure III.1 below: Pd-C bonds *trans* to the P-atom are significantly lengthened and this results in an increased carbocationic character in the carbon atoms *trans* to phosphorous and in increased reactivity towards nucleophiles.[23]

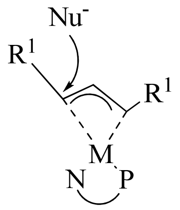

Figure III.1. Electronic desymmetrization of the π-allyl system

An overview of some of the most efficient *P,N*-ligands for the asymmetric allylic amination is presented in Table III.1. Enantiomeric excesses indicated there correspond to the asymmetric amination of *E*-1,3-diphenyl-1-propene acetate or carbonate with benzylamine as the nitrogen nucleophile.

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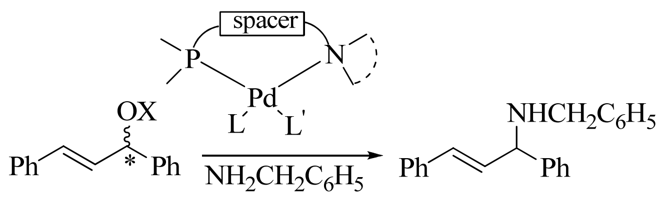
[22] a)Trost, B. M.; Organ, M. G.; Odoherty, G. A. *J. Amer. Chem. Soc.* **1995**, *117*, 9662-9670; b) Trost, B. M.; Bunt, R. C. *J. Amer. Chem. Soc.* **1996**, *118*, 235-236.
[23] Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214.



63, X=Ac
153, X=OCOOMe

154

Scheme III.3. Enantioselective amination with benzylamine

Ligand structural diversity has included variation of the substituents on the phosphorous atom, the nature of the spacer between the *P*- and *N*-donor groups, and the nature of the *N*-donor group (see Table III.1).

Phosphinooxazolidine ligand **155** (60% ee),[24] iminophosphine **162** (64% ee),[25] biferrocene ligands **170** (41% ee)[26] and Moberg's ligand **172** (39% ee)[27] performed with moderate enatioselectivities. Other ligand structures such as: the glucosamine derived phosphinite **156** (93% ee),[28] ferrocene ligand **168** (97% ee),[2a] phosphinoimidazoline ligand **158** (95% ee),[29] phosphanorbornadiene-imines **160** (90% ee),[30] camphor-derived *P,N* ligands **161** (87% ee)[31] and chiral hydrazone ligand **167** (93% ee)[32] mediated the asymmetric amination of **63** or **153** with high enantioselectivities. The best results in this transformation have

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[24] Jin, M.-J.; Jung, J.-A.; Kim, S.-H. *Tetrahedron Lett.* **1999**, *40*, 5197-5198.

[25] Zablocka, M.; Koprowski, M.; Donnadieu, B.; Majoral, J.-P.; Achard, M.; Buono, G. *Tetrahedron Lett.* **2003**, *44*, 2413-2415.

[26] Xiao, L.; Weissensteiner, W.; Mereiter, K.; Widhalm, M. *J. Org. Chem.* **2002**, *67*, 2206-2214.

[27] Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258-3270.

[28] Tollabi, M.; Framery, E.; Goux-Henry, C.; Sinou, D. *Tetrahedron: Asymmetry* **2003**, *14*, 3329-3333.

[29] Jin, M.-J.; Kim, S.-H.; Lee, S.-J.; Kim, Y.-M. *Tetrahedron Lett.* **2002**, *43*, 7409-7411.

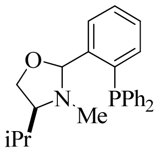
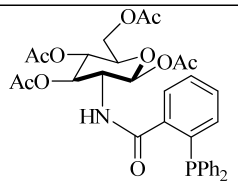
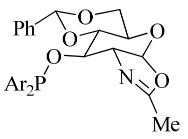
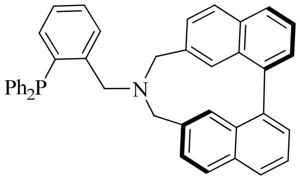
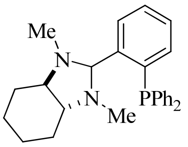
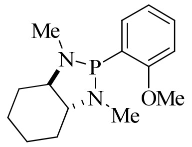
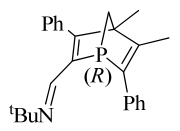
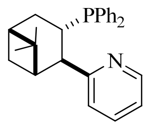
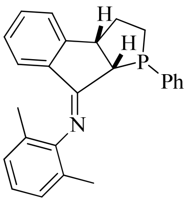
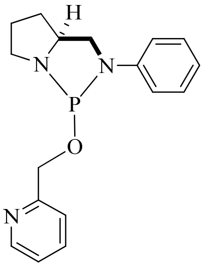
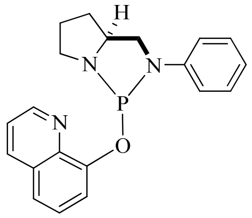
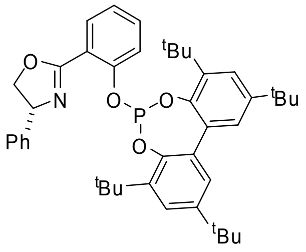
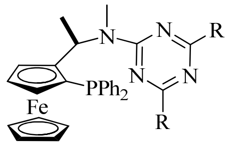
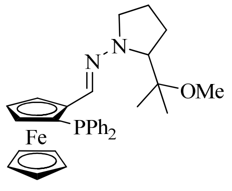
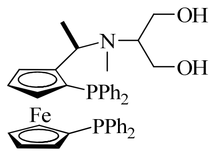
[30] Mercier, F.; Brebion, F.; Dupont, R.; Mathey, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3137-3140.

[31] Bunlaksananusorn, T.; Luna, A. P.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240-2242.

[32] Mino, T.; Ogawa, T.; Yamashita, M. *J. Organomet. Chem.* **2003**, *665*, 122-126.

been reported by Togni with ferrocenyl pyrazole ligand, **171**[33] and by Claver, with phosphite-oxazoline ligand, **165**[34].

Table III.1. Donor bidentate *P,N*-ligands in the asymmetric amination with benzylamine

 **155**[24] (60% ee, *Jin*)	 **156**[28] (93% ee, *Sinou*)	 **82**[35] (92% ee, *Uemura*)	 **157**[36] (84% ee, *Koga*)
 **158**[29] (95% ee, *Jin*)	 **159**[37] (78% ee, *Wills*)	 **160**[30] (90% ee, *Mercier*)	 **161**[31] (87% ee, *Knochel*)
 **162**[25] (64% ee, *Buono*)	 **163**[38] (93% ee, *Buono*)	 **164**[38] (93% ee, *Buono*)	 **165**[34] (99% ee, *Claver*)
 R = phenoxy **166**[39] (94% ee, *Zheng*)	 **167**[32] (93% ee, *Mino*)	 **168**[2a] (97% ee, *Hayashi*)	

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[33] Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Amer. Chem. Soc.* **1996**, *118*, 1031-1037.

[34] Pamies, O.; Dieguez, M.; Claver, C. *J. Amer. Chem. Soc.* **2005**, *127*, 3646-3647.

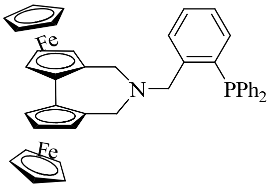
[35] Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374-9380.

[36] Kubota, H.; Koga, K. *Heterocycles* **1996**, *42*, 543-7.

[37] Tye, H.; Smyth, D.; Eldred, C.; Wills, M. *Chem. Commun.* **1997**, 1053-1054.

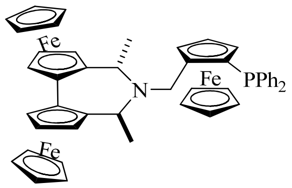
[38] Constantieux, T.; Brunel, J. M.; Labande, A.; Buono, G. *Synlett* **1998**, 49-50.

Table III.1. Donor bidentate *P,N*-ligands in the asymmetric amination with benzylamine



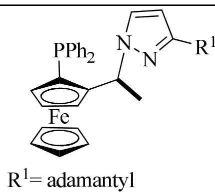
169[26]

(86% ee, *Widlham*)



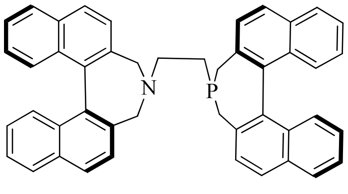
170[26]

(41% ee, *Widlham*)



171[33]

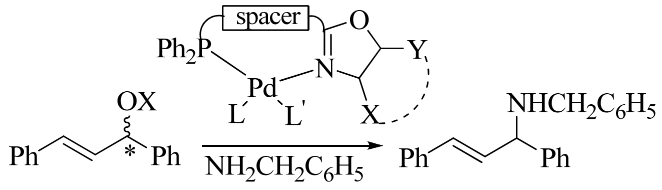
(99% ee, *Togni*)



172[27]

(39% ee, *Moberg*)

Palladium-phosphinooxazoline complexes, have been particularly well studied in the asymmetric allylic amination reaction. The results obtained for the amination of the usual allyl substrate with benzylamine as nucleophile (see Scheme III.4) are summarized in Table III.2.



63, X=Ac
153, X=COOMe

154

Scheme III.4. Allylic amination with benzylamine

In all the reported phosphinooxazoline ligands (PHOX), the substituents at phosphorous have been restricted to the phenyl group. Although the most common spacer has been a 1,2-disubstituted phenyl ring, a binaphthyl group, a

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[39] Hu, X.-P.; Chen, H.-L.; Zheng, Z. *Adv. Synth. Catal.* **2005**, *347*, 541-548.

cyclopentadienyl and several ferrocene units have also been reported. It should be recalled at this point, that no examples of PHOX which incorporate modularity at C-5 of the oxazoline ligand have been reported for this transformation.

In general, the use of Pd-PHOX complexes in the asymmetric allylic amination has been highly successful. Pfaltz's PHOX, **66**,[40] provided high enantioselectivity in the model amination reaction (94% ee). Pfaltz showed that the substituents on the oxazoline moiety play an important role in the enantioselectivity: by changing the phenyl substituent to an ^{i}Pr group, the enantioselectivity decreased from 94% ee to 87% ee. On the other hand, if sterically demanding substituents are introduced on the oxazoline moiety, such as in **173**[41] the enantioselectivity increased to 97%ee.

Ferrocenyl-containing PHOX ligands **174**,[42]**175**[43] and **176**,[44] have proven to be efficient ligands for the amination of the diphenylallyl substrate. Depending on the position of the diphenylphosphino group, enantioselectivities range from 72% ee (compound **174**) to 97% ee (compounds **175** and **176**).

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[40] Vonmatt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573-584.

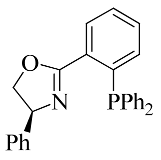
[41] Sudo, A.; Saigo, K. *J. Org. Chem.* **1997**, *62*, 5508-5513.

[42] Malone, Y. M.; Guiry, P. J. *J. Organomet. Chem.* **2000**, *603*, 110-115.

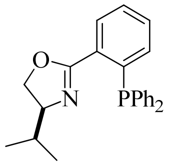
[43] You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *J. Org. Chem.* **2002**, *67*, 4684-4695.

[44] Deng, W.-P.; You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W.; Sun, J. *J. Amer. Chem. Soc.* **2001**, *123*, 6508-6519.

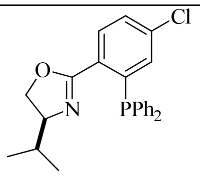
Table III.2. PHOX ligands in the asymmetric amination with benzylamine



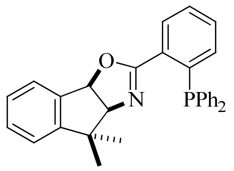
66[40]
(94% ee, *Pfaltz*)



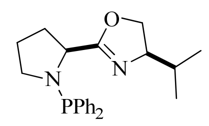
67[40]
(87% ee, *Pfaltz*)



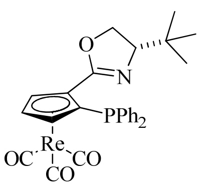
172[45]
(67% ee, *Bunt*)



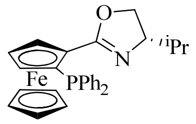
173[41]
(97% ee, *Saigo*)



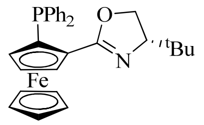
87[17]
(93% ee,*Gilbertson*)



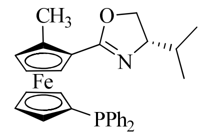
88[46]
(97% ee, *Bolm*)



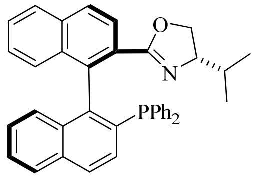
174[42]
(72% ee, *Guiry*)



175[43]
(97% ee, *Xia*)



176[44]
(97% ee, *Xia*)



177[47]
(92% ee, *Pregosin*)

The asymmetric allylic amination has received less attention than the asymmetric allylic alkylation, hence, ligand optimization for a wide variety of substrates has not been carried out. Furthermore, catalytic systems that have been developed and optimized for one kind of substrate have, in many cases, poor substrate scope.

The best results obtained with Pd- or Ir-PHOX and other *P,N*-ligands in the amination of different substrates with benzylamine are summarized in Table III.3.

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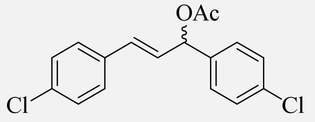
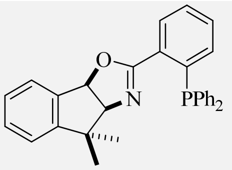
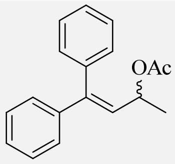
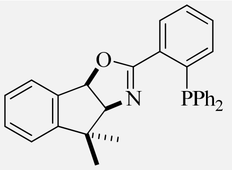
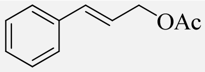
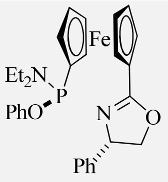
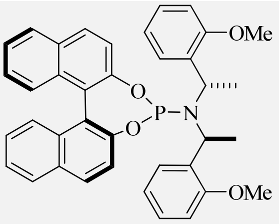
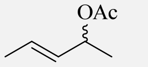
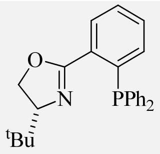
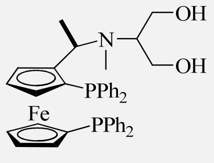
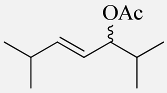
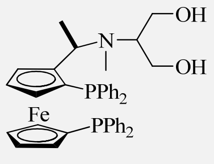
[45] Constantine, R. N.; Kim, N.; Bunt, R. C. *Org. Lett.* **2003**, *5*, 2279-2282.
[46] Bolm, C.; Xiao, L.; Kesselgruber, M. *Org. Biomol. Chem.* **2003**, *1*, 145-152.
[47] Selvakumar, K.; Valentini, M.; Woerle, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 1207-1215.

Saigo's sterically demanding ligand **173**[41] has been successfully employed in the amination of the chloro disubstituted allylic substrate **136c** and for the geminally substituted substrate **136d**, obtaining excellent enantioselectivies (95% ee and 98% ee respectively, entries 1 and 2 in Table III.3).

The regioselectivity in the allylic substitution of cinnamyl acetate **99c**, is dependent on the metal used in the catalytic system. Ir complexes preferentially lead to the formation of branched products, whereas Pd complexes normally favor the formation of achiral linear products.[12] Xia's PHOX-ferrocenyl ligand, **178,** contrary to the general observations on the regioselectivity dictated by the metal, lead to the major formation of the branched product (branched to lineal 94:6, 94% conversion, 98% ee, see entry 3 in Table III.3). Phosphoramidite ligand **179**, is among the best *P,N* ligands for iridium catalyzed amination of cinnamyl acetate (branched to linear 98:2, 98 % conversion, 97 % ee, entry 3 in Table III.3). The allylic amination of the unhindered alkyl substrate **99b** proceeds with only moderate selectivities with PHOX-type ligands (57% ee, entry 4 in Table III.3). On the other hand *P,N* ferrocenyl ligand **168** has provided the best results for this kind of allylic substrates (entry 4 and 5 in Table III.3).

Table III.3. Best *P,N* -ligands for the amination of substrates **99c,b** and **136a,c,d** with benzylamine

Entry	**Substrate**	**PHOX ligand**	***P,N*-ligand**
1			
	136c R^1=H; R^2=R^3=C_6H_5Cl	**173**[41] (95% ee, *Saigo*)	
2			
	136d R^2=R^3= C_6H_5; R^1= CH_3	**173**[41] (98% ee, *Saigo*)	
3			
	99c R^1=H; R^2= C_6H_5; R^3=H	**178**[48] (98% ee, *Xia*)	**179**[49] (97% ee[b], *Alexakis*)
4			
	99b R^1=H; R^2=R^3=CH_3	**180**[40] (57% ee[a], *Pfaltz*)	**168**[2] (73% ee, *Hayashi*)
5			
	136a R^1=H; R^2=R^3=^iPr		**168**[2] (97% ee, *Hayashi*)

a) branched to lineal ratio 94:6; as catalyst Pd-PHOX; b) branched to lineal 98:2; as catalyst Ir-PHOX.

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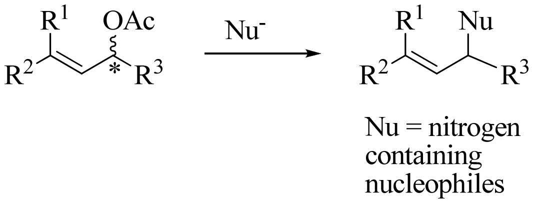
[48] You, S. L.; Zhu, X. Z.; Luo, Y. M.; Hou, X. L.; Dai, L. X. *J. Amer. Chem. Soc.* **2001**, *123*, 7471-7472.

[49] Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. Eur. J.* **2006**, *12*, 3596-3609.

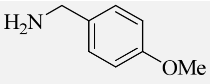
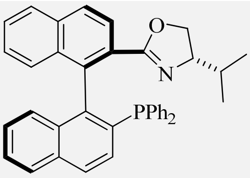
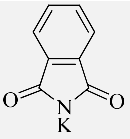
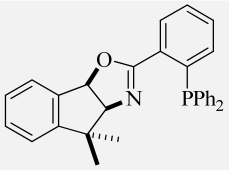
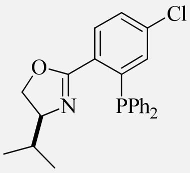
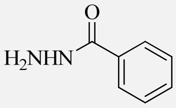
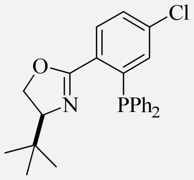
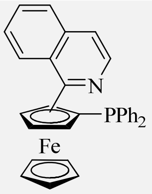
Other nitrogen nucleophiles have also been reported in this transformation (Scheme III.5).



Scheme III.5. Allylic amination reaction

Of the representative results presented in the amination reaction with PHOX and other *P*,*N*-ligands, Xia's phosphinooxazoline, **176**, Claver's phosphite-oxazoline, **165** and Togni's ferrocenyl-pyrazole ligand should be recalled as the most efficient ligands for the amination of the model amination reaction (R^1=R^3=Ph, R^2=H and Nu=$PhCH_2NH_2$).

Table III.4. *P,N* ligands in the amination of diphenyl acetate with nitrogen – nucleophiles

Entry	Nucleophile	PHOX ligand	*P,N*-ligand
1			
	181	**177**[47] (97% ee, *Pregosin*)	
2			
	182	**173**[41] (99% ee, *Saigo*)	**172**[50] (96% ee, *Williams*)
3			
	183	**184**[40] (97% ee, *Pfaltz*)	**185**[51] (83% ee, *Knochel*)

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[50] Jumnah, R.; Williams, A. C.; Williams, J. M. J. *Synlett* **1995**, 821-822.
[51] Kloetzing, R. J.; Knochel, P. *Tetrahedron: Asymmetry* **2006**, *17*, 116-123.

II. MECHANISTIC ISSUES

Asymmetric allylic amination is a versatile reaction of significant importance in organic synthesis and its further optimization depends on the understanding of the mechanistic aspects. It was demonstrated that the palladium catalyzed asymmetric amination follows basically the same mechanistic path as the one for the alkylation reaction with carbon-nucleophiles.[1]

We present here a summary of the main steps of the asymmetric allylic amination (for details see mechanistic section of Chapter II). The catalytic cycle of the allylic substitution[1] involves olefin coordination to the metal center (association followed by oxidative addition which renders a mixture of cationic palladium complexes). These palladium allyl complexes containing 1,3-disubstituted allyl moieties can give rise to several isomers, depending on the stereochemical relationship between the substituents of the allyl group and the central allyl hydrogen: *syn-syn*, *syn-anti*, *anti-syn* and *anti-anti* isomers. Furthermore, each of those isomers can have an *endo* or *exo* arrangement of the allyl moiety. All these isomeric species are interconverting due to several fluxional processes. Only the more abundant ones,[33] *exo-syn-syn* and *endo-syn-syn* are depicted in Scheme III.6. The attack of the nucleophile on the cationic π-allyl palladium isomers generates a Pd(0) complex which might be stabilized by coordination to the olefin.[52] The nitrogen containing nucleophile attacks the allylic terminus *trans* to phosphorous.[53] It has been reported that equilibrium between cationic palladium complexes is faster than the nucleophilic attack itself.[52]

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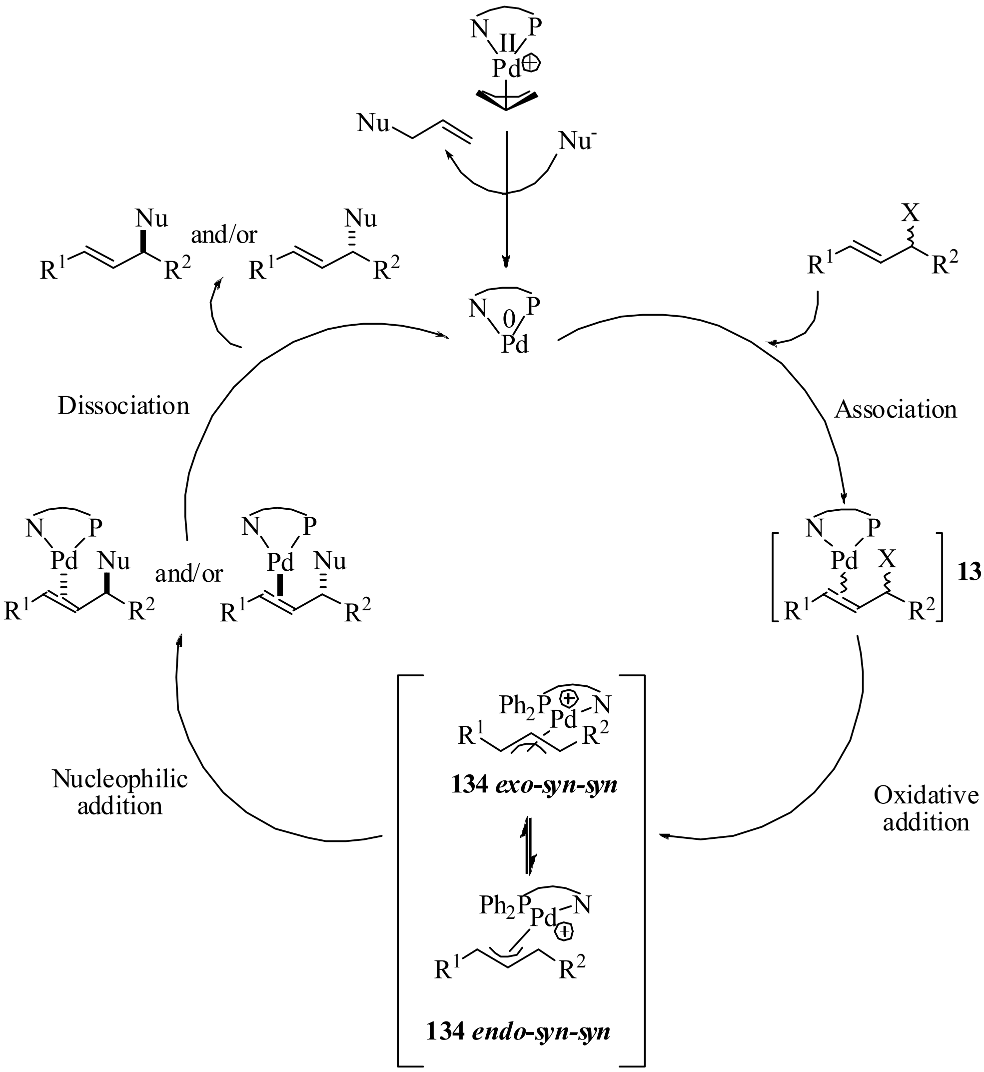
[52] Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Amer. Chem. Soc.* **1985**, *107*, 2033-46.
[53] Blochl, P. E.; Togni, A. *Organometallics* **1996**, *15*, 4125-4132.



Scheme III.6. Catalytic cycle of the asymmetric amination reaction

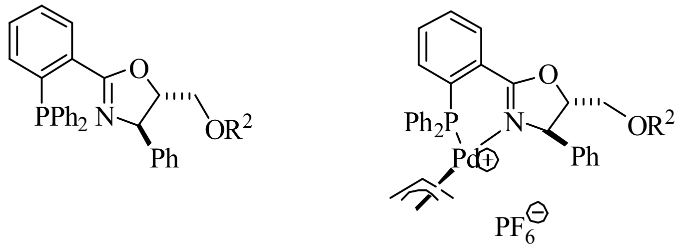
Asymmetric allylic aminations not proceeding to full conversion may result in a kinetic resolution of the starting substrate.[54] This phenomenon can be rationalized in an analogous way to the one summarized for carbon nucleophiles (see Chapter II).

---

[54] a)Gais, H.-J.; Eichelmann, H.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Tetrahedron: Asymmetry* **1998**, *9*, 235-248; b) Dominguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 4289-4291; c) Hayashi, T.; Yamamoto, A.; Ito, Y. *Journal of the Chemical Society, Chemical Communications* **1986**, 1090-2; d) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237-2240; e) Reetz, M. T.; Sostmann, S. *J. Organomet. Chem.* **2000**, *603*, 105-109.

III. ALLYLIC AMINATION CATALYZED BY Pd-PHOX COMPLEXES

The synthesis and characterization of a new family of C-5 substituted PHOX ligands (Figure III.2) together with their palladium allyl complexes has been described in chapter II. This library of ligands offers the possibility of systematically varying the sterical congestion around the Pd-center by changing the CH_2OR^2 group. In the present work, palladium complexes **49** containing an unsubstituted allyl moiety have been used as catalytic precursors in the asymmetric amination reactions. Their catalytic activity has been tested for a number of substrates and nitrogen-nucleophiles.



55 **49**

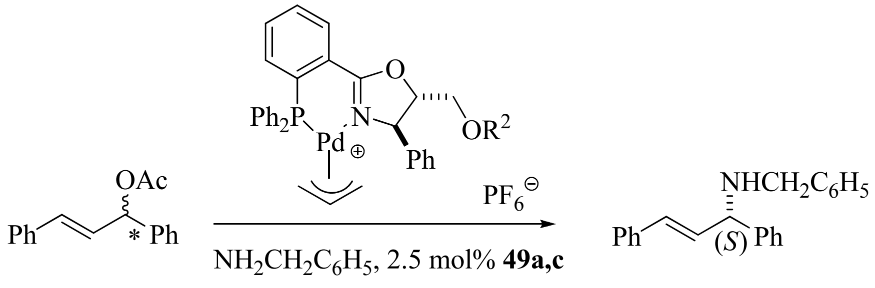
Figure III.2. Modular PHOX ligands and palladium complexes

Reaction conditions were optimized using the allylic amination of *rac*-(*E)*-3-acetoxy-1,3-diphenyl-1-propene **63** with benzylamine. Evaluation of the catalytic activity of our Pd-PHOX complexes with other nitrogen nucleophiles follows this study on the optimization of the reaction conditions.

III.1. Allylic amination of *rac*-(*E)*-3-acetoxy-1,3-diphenyl-1-propene, 63, with benzylamine as a model system for the optimization of the reaction conditions with Pd-PHOX complexes 49a-d and f

Both nitrogen and carbon-nucleophiles derived from C-H acidic compounds, should be considered as soft nucleophiles. In this way, allylic amination mediated by Pd-PHOX complexes follows the same mechanistic pathway as the allylic alkylation with carbon nucleophiles. However, an important difference with respect to the allylic alkylation should be pointed out: amine deprotonation is not required for the allylic substitution reaction to proceed. Primary and secondary amines are nucleophilic enough to attack one of the termini of the allylic substrate,[40] though amines react slower than carbanions in this transformation. Thus, amination reactions are normally performed with primary and secondary amines without any previous activation in solution (e.g. THF).[40]

Taking into account these considerations, initial studies on the model amination reaction (Scheme III.7) were carried out using [Pd(η^3-C_3H_5)PHOX]PF_6 as catalyst (2.5 mol%) and an excess of nucleophile (2-3 eq.) in THF at room temperature.[55]



63 **154**

Scheme III.7. Model asymmetric amination reaction

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[55] These are the usual reaction conditions for this transformation involving different *P,N*-ligands as chiral catalysts.

Table III.5 summarizes the results obtained in terms of conversion and enantioselection for two different π-allyl palladium complexes at different reaction times and temperatures.

Table III.5. Amination reaction of **63** with **49a** and **49c** as catalysts

Entry	Catalyst	Rc. Cond.[a]	Time(h)	Conv.(%)[b]	ee154(%)[c,d](*S*)[e]
1	**49a**	24ºC, 2eq. Nu	24	75	50
2	**49a**	45ºC/ MW, 30W, 2eq. Nu	3.5	34	54
3	**49a**	70ºC/ MW, 50W, 2eq. Nu	2	47	42
4	**49a**	24ºC, 3eq. Nu	24	>99	74
5	**49c**	24ºC, 2eq. Nu	24	57	53
6	**49c**	45ºC/ MW, 30W, 2eq. Nu	5	47	63

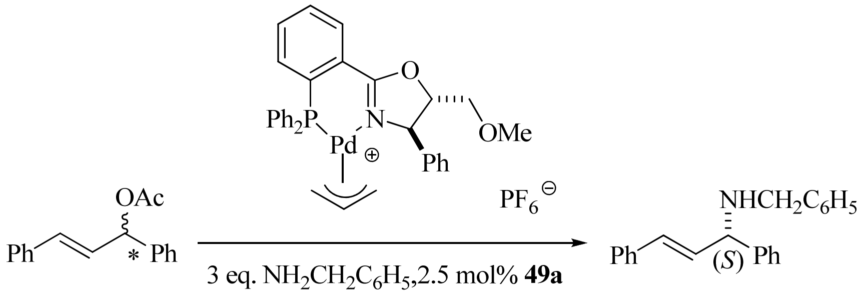
a) general reaction conditions : 2.5 mol % **49**, THF; b) conversion determined by ^{1}H-NMR;[40] c) ee-determined by HPLC using a chiral column (ODH); d) absolute configuration *S*; e)$[\alpha]_D$ = + 16.4 (c = 0.85 in $CHCl_3$)[40] f) 2.3 mol% PHOX$(BH_3)_2$(R=Me), 5.5 mol% DABCO,1.1 mol % $Pd_2(dba)_2CHCl_3$; g) toluene.

The π-allyl palladium complexes **49a** and **49c** mediated the allylic benzylamination of substrate **63** in moderate to good yields depending on the reaction conditions. At room temperature longer reaction times, 24 h, (entries 1 and 5 in Table III.5) were required for obtaining reasonable conversions. Further increasing the amount of nucleophile (up to 3 eq.) allowed full conversions to be achieved. Under all the tested conditions, the observed enantioselectivities were low for both **49a** and **49c**. While an increase in temperature led to an increase in catalytic activity further decreases in the enantioselectivity were recorded.

Results reported by Pfaltz using PHOX **66** (analogue to **49a** with a hydrogen at C-5, 94% ee),[40] indicate that the presence of a substituent at C-5 of the oxazoline ring is detrimental for the enantioselectivity. Several strategies were considered in order to improve our catalysts.

It has been reported that the use of the sodium salt of benzylamine as the nucleophile in the allylic amination has led to increased conversion and enantioselectivity.[56] However, our $[Pd(\eta^3\text{-}C_3H_5)PHOX]PF_6$ complexes are not suitable for this strategy, as a Pd(0) precatalyst is required.[56]

A more attractive option was found in the literature, through the use of BSA-LiOAc[28] or BSA-KOAc[57] combinations as nucleophile activation agents. No explanation was given for the role of BSA-LiOAc/KOAc in the activation of benzylamine in allylic amination. Hou[57] and Sinou[28] simply reported better conversions and enantioselectivities mediated by chiral *P,N*-palladium complexes in the presence of the aforementioned additives. The effect of BSA and acetate salts in the model amination reaction mediated by our catalyst **49a,** are summarized in Table III.6. Aminations were carried out with the usual catalyst loading (2.5 mol%), 3 eq. of BSA and co-catalytic amounts of acetate salts (2.5 mol%).



63 **154**

Scheme III.8. BSA and acetate salts effect in asymmetric amination reactions

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[56] Breeden, S.; Wills, M. *J. Org. Chem.* **1999**, *64*, 9735-9738.
[57] Zheng, W.-H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151-5154.

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Dana Madeleine Popa
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Table III.6. The effect of BSA and acetate salts in the amination reaction

Entry	Activating agent	Salt	T(ºC)	Time (h)	Conv.(%)[a,b]	ee (%)[c](*S*)[d, e]
1	-	-	24	2	>99	65
2	BSA	-	24	2	99	92
3	BSA	KOAc	24	2	98	95
4	BSA	LiOAc	24	2	>99	94
5	BSA	KOAc	0	24	79	97

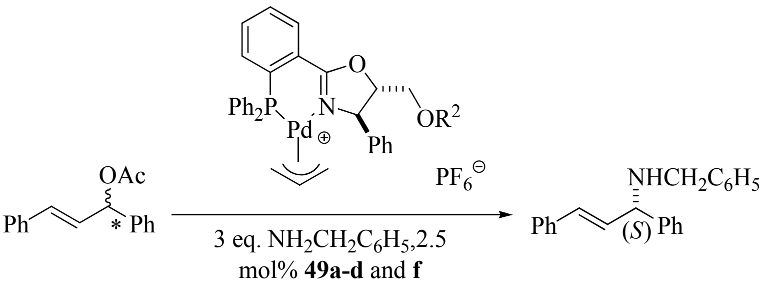
a) general reaction conditions: 2.5 mol% **49a**. 2.5 mol% MOAc 3eq. NH_2CH_2Ph, 3eq. BSA, neat; b) conversion determined by ^{1}H-NMR;[40] c) ee- determined by HPLC using a chiral column (ODH); d) absolute configuration *S*; e)$[\alpha]_D = +16.4$ (c = 0.85 in $CHCl_3$)[40]

The use of BSA (3 eq.) had a significant effect on the enantioselectivity of the reaction, which increases up to 92% ee (*cf.* entries 1 and 2). The use of an acetate salt together with BSA led to a further small increase in enantioselectivity (up to 95% ee in the case of KOAc and 94% ee for LiOAc, entries 3-4). Thus, the acetate ion is important for increasing the enantioselectivity, whereas the cation did not significantly affect the outcome of the reaction. Enantioselectivity increased by lowering the temperature at 0ºC, but conversion was only 79% even after 24 hours (entry 5).

In terms of both yield and enantioselectivity these results, are among the best described in the literature for this Pd-catalyzed transformation using PHOX-type ligands.[40] In addition, the reaction was remarkably fast with near total conversions achieved after 2 h at room temperature.

The role of BSA-KOAc/LiOAc is not fully understood, and given the high pK_a benzylamine it is unlikely that the combined action of BSA/MOAc[28,39] would lead to deprotonation of the nucleophile, as observed with malonic esters (see allylic alkylations with dimethyl malonate in chapter II). Buchwald and co-workers have reported the use of BSA as an activating agent for the ring opening of epoxides with primary aliphatic amines.[58] The primary amine was first silylated by BSA at room temperature; the nucleophilic character of the amine was thus increased and the *N*-silylated amine was capable of performing an epoxide ring-opening in the absence of any other activating agents (*i.e.* Lewis acids). In an analogous way, BSA has been used as an activating agent of primary alkylamines towards several electrophiles (*e.g.* esters,[59] acyl chlorides,[60] and sulphonylisocyanates[61]).

The rest of the library of Pd/PHOX complexes prepared in this work (**49a-d** and **f**) were tested under the same conditions in the model amination reaction (Scheme III.9). The results have been summarized in Table III.7.



63 **154**

Scheme III.9. Model asymmetric amination reactions with **49a-d** and **49f** as catalysts

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[58] Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202-12206.

[59] a)Alibert-Fouet, S.; Mulliez, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 2555-2563; b) Sun, Y.; Martell, A. E.; Welch, M. J. *Tetrahedron* **2000**, *56*, 5093-5103.

[60] Raucher, S.; Jones, D. S. *Synth. Commun.* **1985**, *15*, 1025-31.

[61] Nagasawa, H. T.; Smith, W. E.; Kwon, C. H.; Goon, D. J. W. *J. Org. Chem.* **1985**, *50*, 4993-6.

Table III.7. Amination reaction with **49a-d** and **49f** as catalysts

Entry	Catalyst	Time (h)	Conv.(%) [a, b]	ee (%)[c](*S*)[d]
1	**49a**	2	98	95
2	**49b**	2	>99	84
3	**49c**	2	>99	83
4	**49d**	2	>99	88
5	**49f**	24	97	87

a) general reaction conditions: 2.5 mol% **49a-d** and **f**, 2.5 mol% KOAc 3eq. NH_2CH_2Ph, 3eq. BSA, neat, room temperature; b) conversion determined by ^{1}H-NMR;[40] c) ee- determined by HPLC using a chiral column (ODH); d) absolute configuration *S*; e)$[\alpha]_D$ = +16.4 (c = 0.85 in $CHCl_3$).[40]

Complexes **49a-d** provided almost total conversion after 2 hours (entries 1 to 4). Complex **49f** bearing a triazol ring was the least active catalyst of the series, as 24h were required to achieve full conversion. The best enantioselectivity was obtained with **49a** bearing the least bulky group at C-5 in the oxazoline ring (95% ee), while complexes **49b-d** (entries 2-5) provided enantioselectivities ranging from 83% to 88%.

To conclude with, it should be recalled that the reaction conditions developed in this work for complex **49a** and the model amination are very efficient both in terms of conversion rate and enantioselectivity. Other PHOX ligands[40] have provided lower conversions even after very long reaction times (96h, 97% conversion).

The role of BSA[62] together with several acetates[63] has been described in some cases as essential in the allylic alkylation reaction where malonic esters are used

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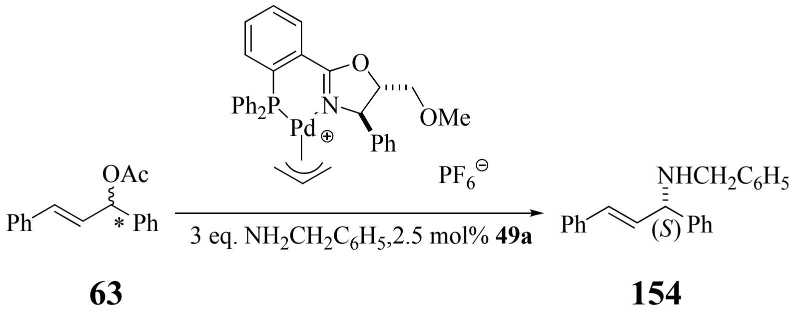
[62] a) Nemoto, T.; Hamada, Y. *Chemical Record* **2007**, *7*, 150-158; b) Chen, Y. Z.; Smith, M. D.; Shimizu, K. D. *Tetrahedron Lett.* **2001**, *42*, 7185-7187; c) Dvorak, D.; Stary, I.; Kocovsky, P. *J. Amer. Chem. Soc.* **1995**, *117*, 6130-6131; d) Widhalm, M.; Mereiter, K.; Bourghida, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2983-2986; e) Bricout, H.; Carpentier, J. F.; Mortreux, A. *Chem. Commun.* **1995**, 1863-1864.

[63] Zhao, D.; Ding, K. *Org. Lett.* **2003**, *5*, 1349-1351.

as the nucleophiles.[64] Tetrabutyl ammonium fluoride (TBAF)[65] and tetrabutyl ammonium bromide (TBAB)[66] have also been used together with BSA to activate the nucleophile by generation of the corresponding carbanion.

As ionic additives have played an important role in allylic alkylation and we have seen that BSA and acetate play an important role in the amination mediated by **49**, we judged as interesting performing the **49a**-mediated benzylamination of **63** in the presence of some catalytic amounts of several anionic additives (F^-, Cl^-, Br^-). Reactions were carried out at room temperature with an excess of 3 eq. of benzylamine and 2.5 mol% of the corresponding additive, results are summarized in Table III.8.



Scheme III.10. Asymmetric amination with BSA and ionic additives

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[64] Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.
[65] Nakano, H.; Okuyama, Y.; Yanagida, M.; Hongo, H. *J. Org. Chem.* **2001**, *66*, 620-625.
[66] Gong, L. Z.; Chen, G. S.; Mi, A. Q.; Jiang, Y. Z.; Fu, F. M.; Cui, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4297-4302.

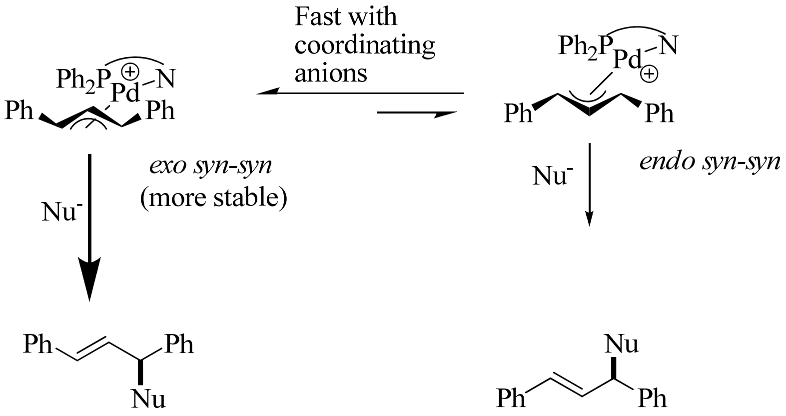
Table III.8. The effect of BSA and ionic additives in the amination reaction

Entry	Activating agent	Salt	Time (h)	Conv.(%) [a, b]	ee (%)[c](*S*)[d, e]
1	BSA	NBu_4Cl	24	96	95
2	BSA	NBu_4BH_4	24	89	88
3	BSA	NBu_4F	24	84	66

a) general reaction conditions: 2.5 mol% **49a**, 2.5 mol% NBu_4X 3eq. NH_2CH_2Ph, 3eq. BSA, neat, room temperature; b) conversion determined by ^1H-NMR;[40] c) ee- determined by HPLC using a chiral column (ODH); d) absolute configuration *S*; e)$[\alpha]_D$ = +16.4 (c = 0.85 in $CHCl_3$)[40]

As have been indicated in a previous section of this chapter (Table III.6, compare entry 1 to 2, 3 and 4 from), the use of BSA and BSA with acetate salts lead to dramatic increase in enantioselectivities. Thus we studied the effect of BSA together with tetrabutyl ammonium salts in the amination reaction. While NBu_4Cl had only a minor effect (with respect to acetate), the use of both NBu_4F and NBu_4BH_4 had a deleterious effect on catalytic activity and enantioselectivity (Table III.8).

While we have no clear explanation for these observations, the effect of several anions in the asymmetric amination reaction mediated by the *P,N*-ligand **171** have been reported.[33] Togni *et al.* showed that the rate of interconversion between 1,3-disubstituted π-allyl palladium complexes might be affected by the nature of the anion.[33]



Scheme III.11. Rationalisation of the effect of the acetate anion in the stereochemical outcome of allylic aminations

These authors suggested that small anions such as acetate, which coordinate directly to the palladium centre, generate a pentacoordinate complex that shifts the *exo-syn-syn/endo-syn-syn* equilibrium towards the more stable and reactive *exo-syn-syn* complex. The enantioselectivity of the amination would thus be increased, as the *exo-syn-syn* complex leads to the major enantiomer and the *endo-syn-syn* to the minor one.[67]

A similar argument could account for the increase in the enantioselectivity in the allylic amination mediated by **49a** in the presence of acetate anion.

As the nature of the anion turned out to have a significant influence on the catalytic activity,[68] a number of palladium-phosphinooxazoline complexes have been described with different anions such as chloride,[69] hexafluoroantimonate

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[67] Only the diastereomers *endo* and *exo*-syn-syn are observed in Togni's ligand **171**[33]

[68] a) Belokon, Y. N.; Maleev, V. I.; North, M.; Usanov, D. L. *Chem. Commun. (Cambridge, U. K.)* **2006**, 4614-4616; b) Hoelscher, M.; Francio, G.; Leitner, W. *Organometallics* **2004**, *23*, 5606-5617; c) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743-7754; d) Lensink, C.; Rijnberg, E.; de Vries, J. G. *J. Mol. Catal. A: Chem.* **1997**, *116*, 199-207; e) Kaellstroem, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194-3200.

[69] a)Kollmar, M.; Helmchen, G. *Organometallics* **2002**, *21*, 4771-4775; b) Markert, C.; Neuburger, M.; Kulicke, K.; Meuwly, M.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5892-5895, S5892/1-S5892/21.

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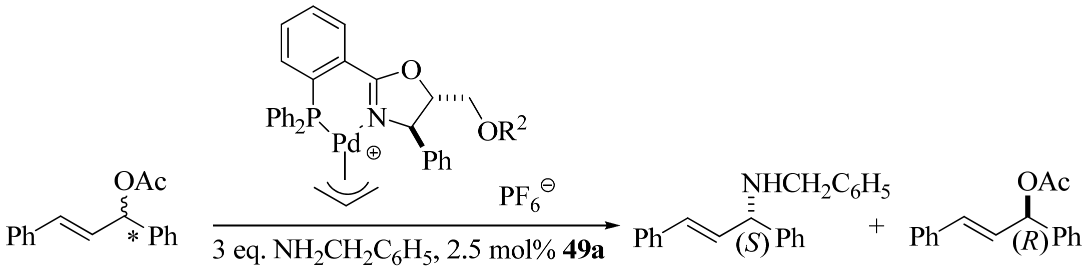
(SbF_6),[70] acetate,[71] tetrafluoroborate (BF_4),[72] perchlorate (ClO_4),[73] and hexafluorophosphate (PF_6).[74] Unfortunately, no comparative study on the activity in allylic aminations has been reported.

A kinetic resolution of the starting allyl acetate was observed throughout the whole optimization study where full conversions were not achieved. Unreacted allyl acetate was recovered with around 20% ee and had *R* configuration.[54e]



63 **154** (*R*)-**63**

Scheme III.12. Asymmetric allylic amination with benzylamine

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[70] Kollmar, M.; Goldfuss, B.; Reggelin, M.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2001**, *7*, 4913-4927.

[71] Suzuka, T.; Kawatsura, M.; Okada, A.; Hayashi, T. *Tetrahedron: Asymmetry* **2003**, *14*, 511-515.

[72] Armstrong, P. B.; Bennett, L. M.; Constantine, R. N.; Fields, J. L.; Jasinski, J. P.; Staples, R. J.; Bunt, R. C. *Tetrahedron Lett.* **2005**, *46*, 1441-1445.

[73] Kollmar, M.; Steinhagen, H.; Janssen, J. P.; Goldfuss, B.; Malinovskaya, S. A.; Vazquez, J.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2002**, *8*, 3103-3114.

[74] a)Liu, S.; Muller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283-293; b) Schaffner, S.; Mueller, J. F. K.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1998**, *81*, 1223-1232; c)Yamagishi, T.; Ohnuki, M.; Kiyooka, T.; Masui, D.; Sato, K.; Yamaguchi, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3275-3279; d) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III *J. Amer. Chem. Soc.* **2007**, *129*, 11876-11877; e) Zehnder, M.; Schaffner, S.; Neuburger, M.; Plattner, D. A. *Inorg. Chim. Acta* **2002**, *337*, 287-298.

Table III.9. Kinetic resolution in the model asymmetric amination reaction with **49a**

Entry	**Rc. Cond.**[a]	**Time(h)**	**Conv.(%)**	**ee 154 (%)(*S*)**	**ee 63 (%) (*R*)**[54]
1	THF, rt, 24ºC	24	99	74	-
2	neat, rt, 24ºC	2	>99	65	-
3	THF, BSA, LiOAc, rt, 24ºC	48	36	93	9
4	THF, BSA, KOAc, rt, 24ºC	21	53	94	15
5	neat, BSA, LiOAc, rt, 24ºC	2	>99	94	-

a) 0.025 mol% **49a**, 3 eq Nu.

The mechanism of kinetic resolution is presumed to be similar as to the one discussed for allylic alkylations (see chapter II, Mechanistic issues). It should be pointed out that the kinetic resolution was only detected when THF was used as the solvent at room temperature with **49a**. Kinetic resolution was not observed under the optimized reaction conditions when total conversion was not reached.

In the following sections we will present the evaluation of the catalytic activity of the new family of [Pd(η^3-C_3H_5)PHOX]PF_6 complexes for the amination of several substrates with different nitrogen-nucleophiles.

III.2. Allylic amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene with different nitrogen nucleophiles

In this study a number of primary and secondary amines have been employed in the asymmetric amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene acetate. Optimal reaction conditions were found for each nitrogen-nucleophile, using the additives that proved to be the most efficient in the amination of the model substrate with benzylamine. The results obtained in the optimization process are presented in the following section.

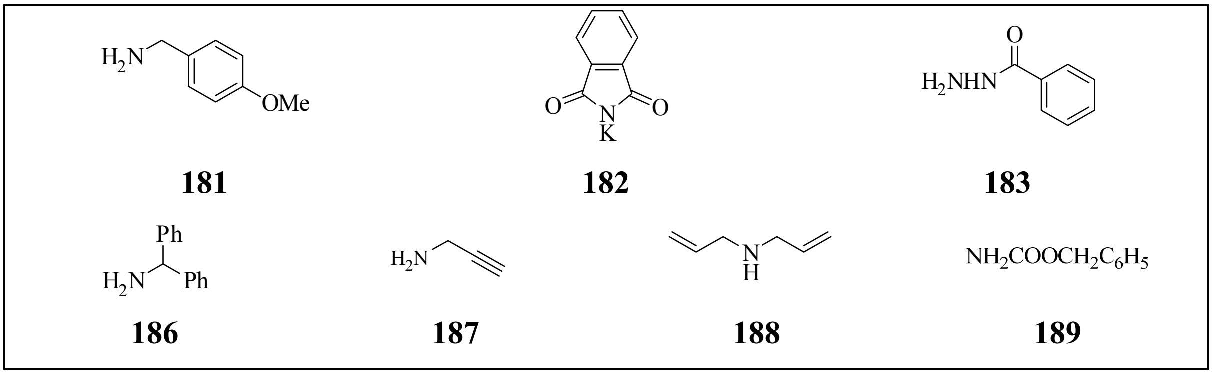
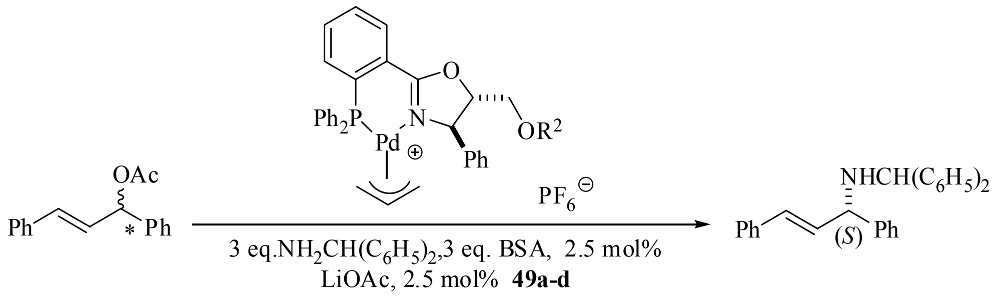


Figure III.3. Primary and secondary nucleophiles employed in the amination of **63**

Figure III.3 shows the differently substituted nitrogen nucleophiles tested in the allylic amination reaction. This set of nucleophiles will allow us to study the effect of the steric and/or electronic properties of the reagent on the amination reaction. In addition, the presence of different functional groups should allow the derivatization of the final products for further applications.

Benzhydrylamine has not been previously used as a nucleophile in the allylic amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene. The activities of the catalysts **49a-d** were studied with this hindered amines in order to examine the effect of the nucleophile size, additives and temperature on enantioselectivity.



63 **190**

Scheme III.13. Allylic amination of **63** with benzhydrylamine

Table III.10. Results of the amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene with benzhydrylamine

Entry	Catalyst	T(ºC)	Time(h)	Conv.(%)^{a,b}	ee (%)^{c,d}(S)^{e}
1	**49a**	24	96	20	95
2	**49a**	40	24	95	94
3	**49b**	24	96	14	86
4	**49b**	40	96	15	83
5	**49c**	24	96	27	87
6	**49c**	40	96	28	84
7	**49d**	24	65	4	84
8	**49d**	40	65	9	81

a) General reaction conditions: 2.5 mol% **49**, 2.5 mol% LiOAc, 3eq. $NH_2CH(C_6H_5)_2$, 3eq. BSA, THF; b) conversion determined by ^{1}H-NMR; c) ee determined by HPLC using a chiral column (ADH); d) absolute configuration *S*; e) $[\alpha]_D = +30.6$ (c = 1.21in $CHCl_3$).

Enantioselectivity and conversions were higher when complex **49a** was used as the catalyst as in the previous studied case of benzylamine (95% ee and 20% conversion, entry 1 in Table 10). With this catalyst high conversions (up to 95%) were easily achieved by raising the temperature to 40ºC, with practically no decrease in the enantioselectivity (entry 2, Table 10).

Lower conversions and enantioselectivities were obtained for the allylic amination of substrate **63** with benzhydrylamine mediated by π-allyl palladium complexes with bulky substituents at C-5 ($R^2 = CH_2Ph, CHPh_2, CPh_3$). However, increasing the temperature was not found to improve conversions for these systems. Catalyst **49b** rendered 86% ee and 14% conversion at room temperature (entry 3, Table 10) and 83% ee with 15% conversion when the temperature was increased to 40ºC (entry 4, Table 10). Complex **49c** afforded enantioselectvities similar to complex **49b** but with higher conversions (entries 5 and 6 in Table 10). The catalyst bearing the bulky trityl substituent at C-5, **49d**, turned out to be the least active catalyst of the series (entry 7 and 8 in Table 10).

With the best catalyst in hand, **49a**, we examined the use of the additives BSA-KOAc/LiOAc (see Table III.11).

Table III.11. Allylic amination with benzhydrylamine. Reaction optimization

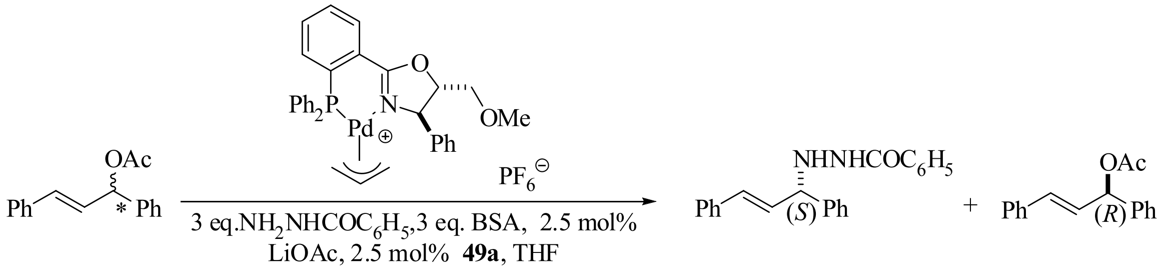
Entry	**Reaction Conditions**	**T(ºC)**	**Time (h)**	**Conv. (%)[a,b]**	**ee for 190 (%)[c,d] (S)[e]**
1	BSA	-20	144	2	91
2	BSA	24	144	9	91
3	BSA, LiOAc	24	96	20	95
4	BSA, LiOAc	40	24	95	94
5	BSA, KOAc, neat	24	24	94	96

a) general reaction conditions: 2.5 mol% **49a**, 2.5 mol % MOAc, 3eq. $NH_2CH(C_6H_5)_2$, 3eq. BSA, THF; b) conversion determined by ^{1}H-NMR; c) ee determined by HPLC using a chiral column (ADH); d) absolute configuration *S*; e) $[\alpha]_D = +30.6$ (c = 1.21 in $CHCl_3$)

In conclusion, neat reaction conditions proved to be the most suitable ones for the amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene with benzhydrylamine (96% ee and 94% conversion, entry 5 in Table III.11). Kinetic resolution of the starting material was not observed in any of the performed amination reactions with benzhydrylamine.

Next, the results obtained with other nitrogen nucleophiles in the amination reaction of the model substrate using the most active catalyst of the family, **49a**, are presented.

The amination of **63** with benzoylhydrazine was performed (Scheme III.14) and the results obtained are presented in Table III.12. The enantioselectivities were high under all studied conditions though high temperatures were required for good conversion. Kinetic resolution of **63** was observed in almost all the cases where total conversion was not obtained.



63 **191** **(*R*)- 63**

Scheme III.14. Allylic amination of **63** with benzoylhydrazine

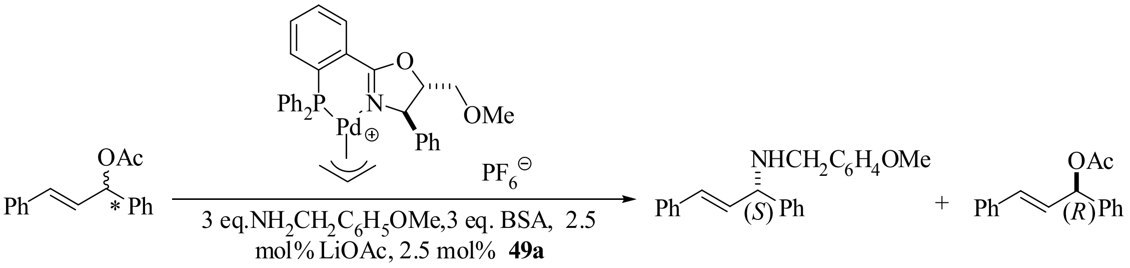
Table III.12. Amination reaction of **63** with benzoylhydrazine as the nucleophile

Entry	Reaction conditions	T(ºC)	Time (h)	Conv. (%)[a,b]	ee 191 (%)[c,d] (*S*)[e]	ee 63 (%) (*R*)[f]
1	BSA, LiOAc	24	115	17	95	15
2	BSA	24	115	2	91	7
3	BSA, LiOAc	50	48	60	90	32
4	BSA	50	48	12	80	2
5	6 eq. BSA, KOAc, neat	24	24	>99	94	-

a) reaction conditions: 2.5 mol% **49a**, 2.5 mol% LiOAc, 3eq. $NH_2NHCOC_6H_5$, 3eq. BSA, THF; b) conversion determined by ^{1}H-NMR;[40]c) ee- determined by HPLC using a chiral column (ADH or OJ); d) absolute configuration *S*; e) $[\alpha]_D = +8.3$ (c = 0.81 in $CHCl_3$);[40] f)ADH column (hexane:iPrOH, 85:15, 0.5ml/min), t_S=11.75 min. t_R=12.29 min;

As observed for other nuclephiles, acetate salts have a positive effect on the allylic amination reaction. We observed that in the absence of LiOAc both the conversion and the enantioselectivities were lower. The best result, total conversion and 94% ee, was achieved under neat conditions at 24ºC (entry 5). These results are similar to those reported by Pfaltz with PHOX ligands,[40] in terms of conversion and enantioselectivity, though reaction times were reduced by a factor of two with our catalyst.

Next, we tested *p*-methoxybenzylamine as a nucleophile in the allylic amination of **63** (Scheme III.15). Results using complex **49a** are summarized in Table III.13. Where low conversions were recorded, kinetic resolution was observed, recovered **63** was found to be of *R* configuration, from which we assigned **(*S*)-192**.



63 **192** **(*R*)- 63**

Scheme III.15. Allylic amination of **63** with *p*-methoxybenzylamine

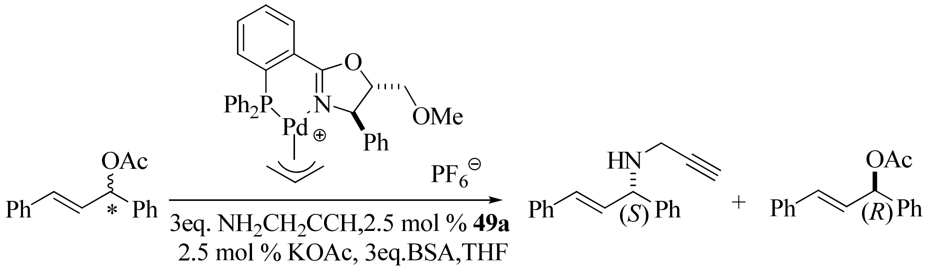
Table.III.13 Allylic amination of **63** with *p*-methoxybenzylamine

Entry	Reaction Conditions	T(ºC)	Time (h)	Conv. (%)[a,b]	ee 192 (%)[c,d] (*S*)[e]	ee 63(%) (*R*)[f]
1	BSA, LiOAc	-20	144	22	96	13
2	BSA, LiOAc	24	48	39	95	13
3	BSA, LiOAc	50	18	>99	92	-
4	BSA, KOAc, neat	24	4	94	94	9

a) general reaction conditions: 2.5 mol% **49a**, 2.5 mol% LiOAc, 3eq. $NH_2CH_2C_6H_5OMe$, 3eq. BSA, THF; b) conversion determined by ^{1}H-NMR; c) ee- determined by HPLC using a chiral column (ADH); d) absolute configuration *S*; e) $[\alpha]_D$ = +28.2 (c = 0.82in $CHCl_3$); f) ADH column (hexane :IPA, 94:6, 0.7 mL/min), t_S=9.9 min. t_R=10.3 min

Conversions were improved by increasing the reaction temperature without negatively affecting the enantioselectivity. The best results (94% ee, and 94% conversion) were obtained at room temperature using BSA and KOAc as additives (entry 4 in Table III.13). Binaphthalene-based chiral *P,N*-ligand **177**[47] is the only example of a PHOX-type ligand described in the literature for this particular reaction and the results presented here are very similar to those reported.

The allylic amination of **63** with propargylamine is of great interest (Scheme III.16). In the first place, propargylamine has not been described before as nucleophile in allylic amination reactions, and, secondly, the resulting substitution products are interesting chiral synthons that can be further functionalized into more complex chiral compounds using several synthetic methodologies, such as the Pauson-Khand[75] reaction.



63 **193** **63**

Scheme III.16. Allylic amination of **63** with propargylamine

Employing catalyst **49a** with BSA and acetate salts as additives, the amination reaction was investigated over a wide range of temperatures (24ºC to 55ºC). The best results in terms of conversion (>99%) and enantioselectivity (97%), were

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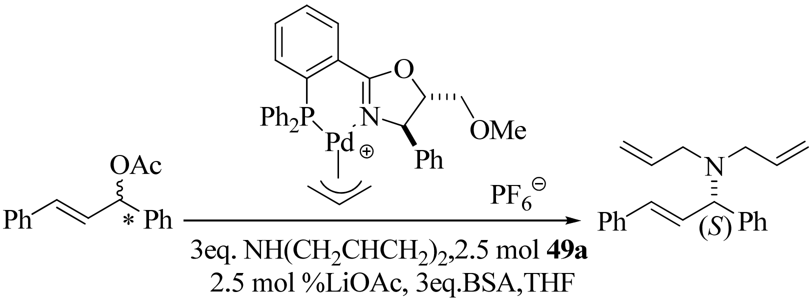
[75] a)Ashfeld, B. L.; Miller, K. A.; Smith, A. J.; Tran, K.; Martin, S. F. *Org. Lett.* **2005**, *7*, 1661-1663; b) Ashfeld, B. L.; Miller, K. A.; Smith, A. J.; Tran, K.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 9018-9031.

achieved at room temperature (2 h, 2.5 mol% **49a**, 2.5 mol% KOAc, 3 eq. BSA and 3 eq. nucleophile).

Another new amination product with possible further applications was obtained with good results from the amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene, **63** with diallylamine. The reactions were carried out at 24ºC and 40ºC employing BSA and acetate salts as additives. The conversions and enantioselectivities recorded in this reactions summarized in the Table III.14.



63 **194**

Scheme III.17. Allylic amination of **63** with diallylamine

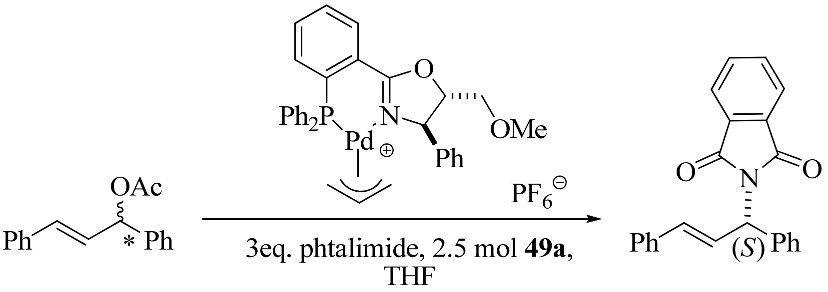
Table.III.14. Amination reaction with diallylamine as nucleophile

Entry	Reaction conditions	T(ºC)	Time (h)	Conv. (%)^{a,b}	ee (%)^{c,d} (*S*)^{e}
1	BSA, LiOAc	24	122	13	86
2	BSA, LiOAc, 5 mol % **49a**	40	168	44	98
3	BSA, KOAc, neat	24	4	>99	>99

a) general reaction conditions: 2.5 mol% **49a**, 2.5 mol% LiOAc 3eq. $NH(CH_2CH=CH_2)_2$, 3eq. BSA, THF; b) conversion determined by ^{1}H-NMR; c) ee determined by HPLC using a chiral column (ADH); d) absolute configuration *S*; e) $[\alpha]_D = +27.6$ (c = 2.20 in $CHCl_3$).

When 2.5 mol % of **49a** was used at room temperature, good enantioselectivity (86%) but low conversion (13%) was obtained (entry 1, Table III.14). Using BSA and KOAc as the additives under solvent free conditions, full conversion and very high enantioselectivity (>99%) were obtained at room temperature (entry 3).

Finally, potassium phthalimide was also tested as a nucleophile in the asymmetric amination of **63** using **49a** as the catalyst.



63 **195**

Scheme III.18. Allylic amination of **63** with phthalimide

This nucleophile proved to be less active than the previously studied ones. In order to react the phthalimide with **63**, higher reaction temperatures (50ºC) were required. Under solvent free conditions (3 eq. BSA, 3 eq. potassium phthalimide, 2.5 mol% KOAc), an enantioselectivity of 92% and 65% conversion were observed.

III.3. Allylic amination of different allylic acetates

After examining and optimizing reaction conditions for the allylic amination of **63** with differing nucleophiles, we turned our attentions to studying the allylic amination of different allylic substrates, using benzylamine and benzhydrylamine as nitrogen sources.

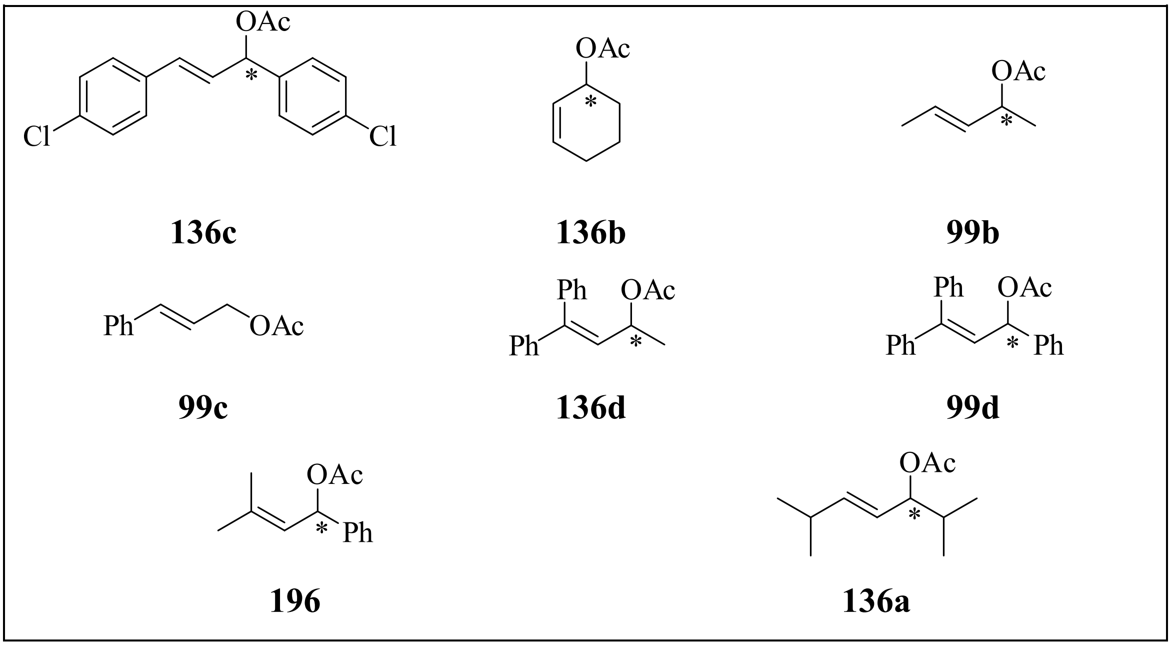


Figure III.4. Substrate expansion[76] for the asymmetric amination reaction

We have evaluated the catalytic activity of **49a** in the asymmetric amination reaction of two relatively unhindered acetates (*E*)-pent-3-en-2-yl acetate, **99b**, and cyclohex-2-enyl acetate, **136b**, with benzylamine. The reactions conditions investigated were carried out with BSA and acetate salts as additives and a temperature range of 0ºC to 45ºC. The results obtained in the amination of **99b** and **136b** with benzylamine are collected in Table III.15.

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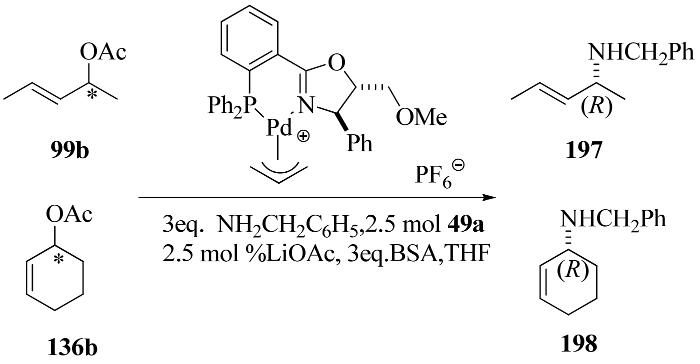
[76] Non commercial allylic acetates have been synthesized in their racemic form as it has been described in chapter II.



Scheme III.19. Allylic amination of (*E*)-pent-3-en-2-yl acetate and cyclohex-2-enyl acetate

Table III.15. Allylic amination of **99b** and **136b** with benzylamine.

Entry	Substrate	T(ºC)	Time (h)	Conv. (%)^{a}	ee (%) (*R*)
1	**99b**	0	90	>99^{b}	69^{c}
2	**99b**	45	48	32^{b}	56^{c}
3	**99b**	24^{d}	4	>99^{b}	63^{c}
4	**136b**	0	90	47^{e}	32^{f}
5	**136b**	45	21	>99^{e}	23^{f}
6	**136b**	24^{d}	4	>99^{e}	37^{f}

a) reaction conditions: 2.5 mol% **49a**, 2.5 mol% LiOAc, 3eq. $NH_2CH_2C_6H_5$, 3eq. BSA, THF; b) conversion determined by ^{1}H-NMR;[77] c) ee determined by HPLC using a chiral column (ODH); absolute configuration *R*; $[\alpha]_D$ = +1.6(c = 1.76 in $CHCl_3$);[78] d) neat conditions, KOAc instead of LiOAc; e) conversion determined by ^{1}H-NMR;[79] f) ee determined by HPLC using a chiral column (OBH); absolute configuration *R*; (OBH column), retention times t_R = 11.0 min, t_S = 12.2 min.[79]

The best observed results were under solvent free "neat" conditions (entries 3 & 6, Table III.15). In the case of substrate **99b** higher enantioselectivities were at 0ºC (69% *vs*. 63%), however, reaction times were significantly increased to 90 h. In the amination of the substrates **99b** and **136b** with benzylamine no kinetic resolution of the starting substrates was observed.

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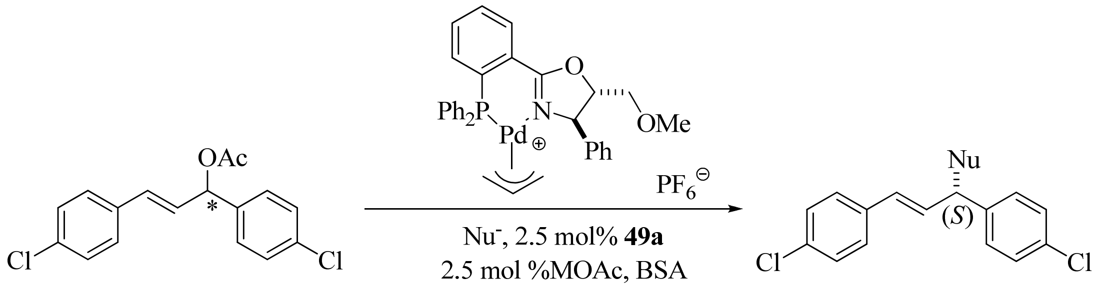
[77] Ohta, T.; Sasayama, H.; Nakajima, O.; Kurahashi, N.; Fujii, T.; Furukawa, I. *Tetrahedron: Asymmetry* **2003**, *14*, 537-542.

[78] Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Amer. Chem. Soc.* **2000**, *122*, 7905-7920.

[79] Zhao, D.; Sun, J.; Ding, K. *Chem. Eur. J.* **2004**, *10*, 5952-5963.

Although the allylic amination of these substrates proceeded with moderate conversions and enantioselectivities, it should be noted that these results are amongst the best reported for PHOX ligands, Pftaltz´s Pd-phosphinooxazoline catalysts achieved similar results in the asymmetric amination of substrate **99b** with benzylamine.[40] on the other hand, PHOX ligands have not been previously reported in the amination of this type of cyclic substrate (**136b**) with benzylamine.

The amination reactions of (*E*)-1,3-bis(4-chlorophenyl)allyl acetate **136c** were also studied with benzylamine and benzhydrylamine as nucleophiles (see Scheme III.21). Good enantioselectivities and conversions could be achieved with our methodology; the optimized reaction conditions are collected in Table III.16.



136c

199, $Nu^-=NH_2CH_2Ph$

200, $Nu^-=NH_2CHPh_2$

Scheme III.20. Allylic amination of **136c** with benzylamine and benzhydrylamine

Table III.18. Allylic amination of **136c** with benzylamine and benzhydrylamine

Entry	Nucleophile	Reaction conditions	T(ºC)	Time (h)	Conv.(%)[a,b]	ee(%)(*S*)
1	6 eq. NH_2CH_2Ph	6 eq. BSA, KOAc, neat	24	1	>99	94[c]
2	3 eq. NH_2CHPh_2	3eq. BSA, LiOAc	40	90	>99	77[d]

a) reaction conditions: 2.5 mol% **49a**, 2.5 mol% LiOAc 3eq. NH_2CH_2Ph, 3eq. BSA, THF; b) conversion determined by ^1H-NMR; c) ee- determined by HPLC using a chiral column (ODH); absolute configuration *S*; $[\alpha]_D = +3.8$ (c = 0.93 in $CHCl_3$);[41] d) ee- determined by HPLC using a chiral column (ADH); absolute configuration *S*; $[\alpha]_D = +10.0$(c = 0.89 in $CHCl_3$).

The amination of **136c** with benzylamine proceeded with similar results as substrate **63**. Under neat conditions with 6 eq. of nucleophile and BSA we were able to achieve full conversion in one hour with 94% ee (entry 1 in Table III.18). Higher temperatures (40ºC) were required to achieve good conversions in the case of benzhydrylamine. Furthermore, moderated enantioselectivities were observed for this bulkier nucleophile (77% ee, entry 2 in Table III.18).

This methodology was also applied to substrate **99c** (see Scheme III.22). However, the reaction proceeded with low regioselectivity for the branched product as literature data also indicates.[80] The best reaction conditions rendered branched substitution product in 69% ee with a branched to linear ratio of 1:71.

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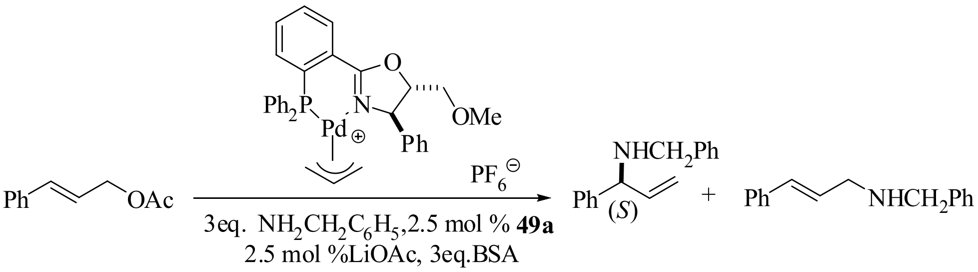
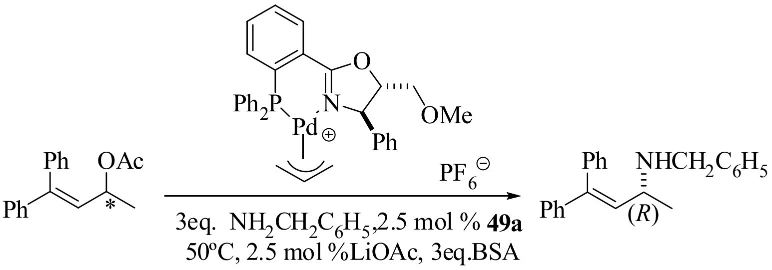
[80] Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585-4593.



99c **201** **202**

Scheme III.21. Allylic amination of cinnamyl acetate with benzylamine

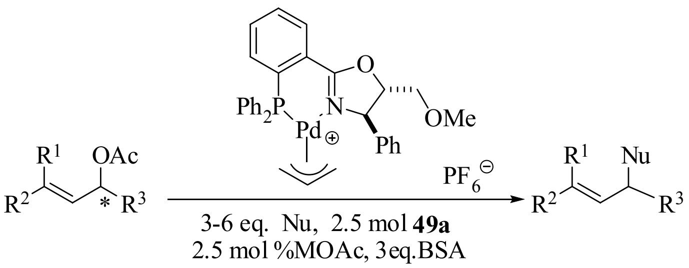
Finally, the asymmetric amination of the trisubstituted allyl substrate **136d** was studied (Scheme III.22). Again, “neat” reaction conditions at 50ºC turned out to be the most efficient: total conversion with good enantioselectivities (89% ee) were observed. No kinetic resolution was observed with substrate **136d**, the results obtained in the amination of this substrate with benzylamine being comparable to the previous reports for PHOX-type ligands.[41]



136d **203**

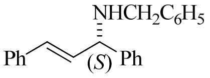
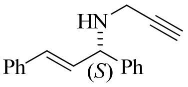
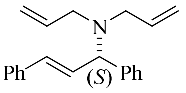
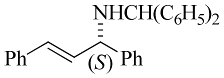
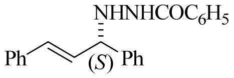
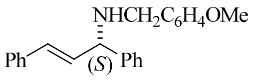
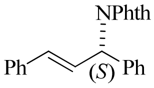
Scheme III.22. Allylic amination of **136d** benzylamine

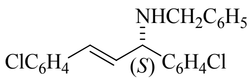
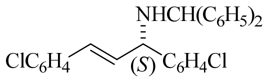
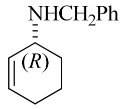
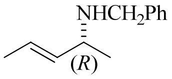
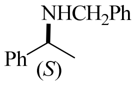
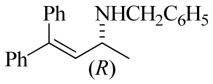
Table III.19 summarizes the results obtained for the amination reaction of the studied substrates with the most efficient [Pd(η^3-C_3H_5)PHOX]PF_6 complex, **49a**, developed in this work.



Scheme III.23. Allylic amination under optimized conditions

Table III.19. Best results obtained in the amination reaction

Entry	Product	Reaction conditions	T(ºC)	Time(h)	Conv.(%)[a]	ee(%)
1	 **154**	BSA, KOAc	24	2	98	95
2	 **193**	BSA, KOAc	24	2	>99	97
3	 **194**	BSA, KOAc	24	4	>99	99.3
4	 **190**	BSA, KOAc	24	24	94	96
5	 **191**	6 eq. BSA, KOAc	24	24	>99	94
6	 **192**	BSA, KOAc	24	4	94	94
7	 **195**	BSA, KOAc	50	48	65	92

Entry	Product	Reaction conditions	T(ºC)	Time(h)	Conv.(%)[a]	ee(%)
8	 **199**	6 eq. Nu, 6 eq. BSA, KOAc	24	1	>99	94
	 **200**	BSA, KOAc	24	48	54	79
10	 **198**	BSA, KOAc	24	4	>99	37
11	 **197**	BSA, KOAc	24	4	>99	63
12	 **201**	BSA, LiOAc,THF	24	40	86	69[b]
13	 **203**	5 eq. Nu, BSA, KOAc	50	15	>99	89

a) general reaction conditions: 2.5 mol% **49a**, 2.5 mol% KOAc, 3eq. nucleophile, 3eq. BSA, neat; b) Branched/Linear : 1:71.

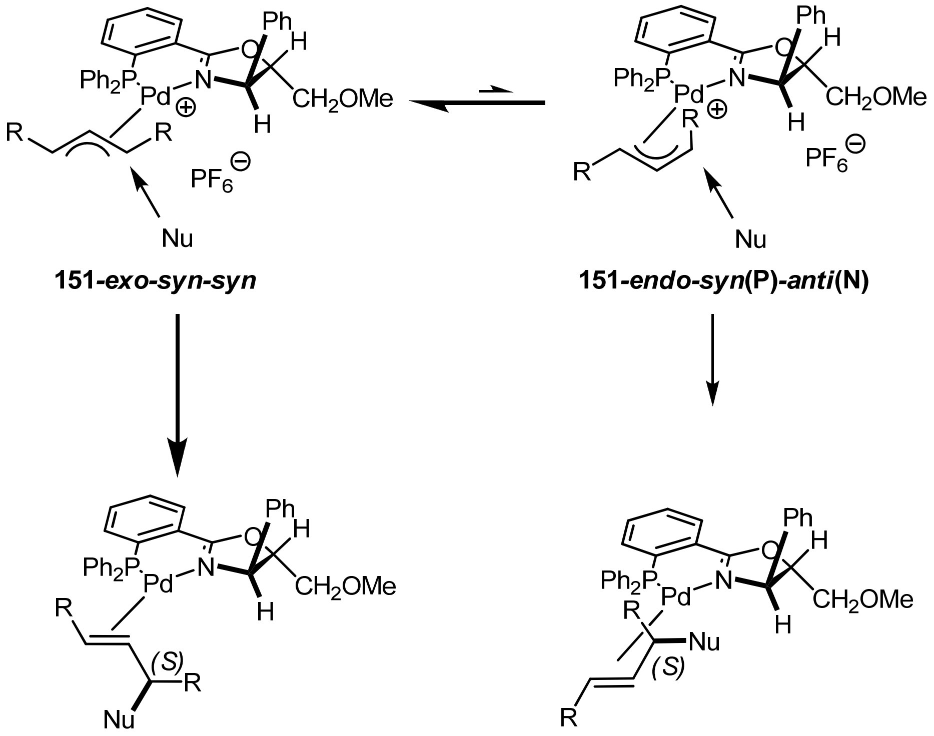
For almost all the substrates and nucleophiles, neat reaction conditions gave the best results with good enantioselectivities and conversions being observed at room temperature, except for hindered substrates and nucleophiles where higher temperatures were required to attain good conversions (entries 7 and 13 in Table III.19).

The model substrate, (*E*)-3-acetoxy-1,3-diphenyl-1-propene, **63**, worked well with all tested nucleophiles (entries 1 to 7), with enantioselectivities ranging from 92% to >99% ee and conversions from 65% to >99%. Longer reaction times for bulkier nucleophiles such as benzhydrylamine (entry 4, 94% conversion and 96%) or higher temperatures and prolonged reaction times such as for phthalimide (entry 7, 50ºC, 48 h, 65% conversion and 92% ee) were required, compared to small unhindered *N*-nucleophiles (entries 1-3 and 6).

The allylic amination of (*E*)-1,3-bis(4-chlorophenyl)allyl acetate worked well with benzylamine, enantioselectivities and conversions being similar to those obtained for the model substrate (total conversion and 94% ee in one hour at room temperature, *cf*. entries 8 and 1). The results obtained in the amination of the (*E*)-1,3-bis(4-chlorophenyl)allyl acetate with benzhydrylamine were worse compared to those for (*E*)-3-acetoxy-1,3-diphenyl-1-propene with the same nucleophile (54% conversion and 79% ee after 48 h at room temperature) (*cf.* entry 9 to entry 4).

The allylic amination of both cyclic and aliphatic alkylic substrates, with benzylamine proceeded with moderate enantioselectivities (37% and 63% respectively) and total conversions in 4 hours time at room temperature (entries 10 and 11). The amination of the cinnamyl acetate substrate proceeded in favor of the linear product (ratio of 1:71 branched to linear) with total conversion in one hour at room temperature (entry 12).

The mechanism of the allylic amination reaction is practically the same as for the asymmetric alkylation with carbon nucleophiles (*vide ante*) and, thus, the stereochemical rationalisation outcome should be very similar. The possible formation of the amination product with *S* configuration results from attack of the nucleophile onto the allyl carbon *trans* to nitrogen in precursors, ***endo-syn-syn*-151** and ***exo-anti*(P)-*syn*(N)-151**, should be discarded as the allyl carbon *trans* to phosphorus is much more reactive towards nucleophiles than the carbon atom *trans* to the nitrogen.



Scheme III.25. Possible reaction pathways leading to *S* amination products

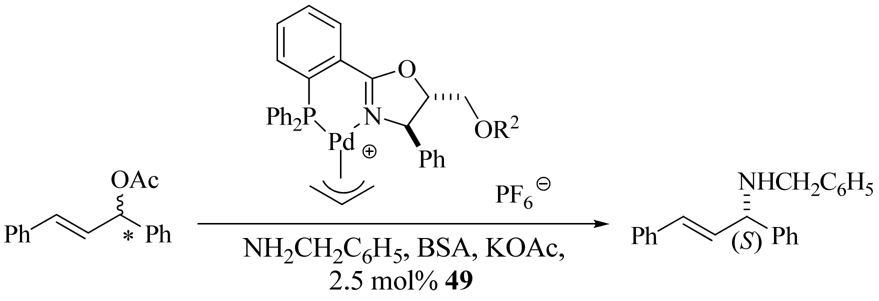
IV. EXPERIMENTAL PROCEDURES

IV.1. Employed procedures

The generally employed procedures together with the material and apparatus used were presented in the experimental section of chapter II.

IV.2. General procedures for palladium-catalyzed allylic amination

P1. Allylic amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene, 63 with benzylamine



63 **154**

A solution of (*E*)-3-acetoxy-1,3-diphenyl-1-propene, **63** (0.25 g, 1.00 mmol) in THF[81] (2.0 mL) was added at room temperature[81] to a solution of phopshinooxazoline-palladium complex **49a-d** (0.02 mmol)[81] in THF[81] (2.0 mL) under argon. Benzylamine (0.32 g, 0.33 mL, 3.00 mmol)[81] and BSA (0.61 g, 0.746 mL, 3.00 mmol)[81] were syringed into the previous solution and a catalytic amount of LiOAc [81] (0.001 g, 0.02 mmol) was lastly added under argon. The mixture was stirred at room temperature for 48 hours.[81] The reaction mixture was then diluted with diethyl ether, and washed with water (2 x 4.0 mL), the organic

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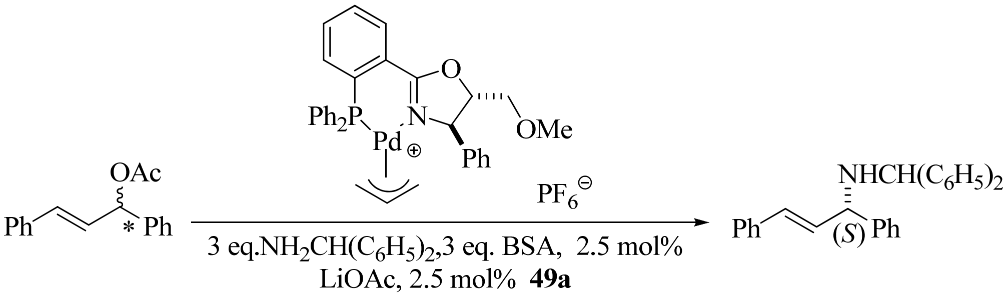
[81] Unless stated otherwise.

phase was dried over anhydrous $MgSO_4$. The drying agent was filtered off. The crude mixture was filtered through a short SiO_2 pad eluting with ethyl acetate. The conversion of the reaction was measured after removing the solvent by ^1H-NMR of the crude mixture.[81]

The enantiomeric excess was determined from the filtered crude by HPLC on ODH column, (0.6 mL min^{-1} *n*- hexane/ *iso*-propanol, 99:1): (*R*)-**154** Rt = 19.5 min, (*S*)-**154** Rt = 20.8 min.

P2. Allylic amination of (E)-1,3-diphenylallyl acetate, 63 with benzhydrylamine

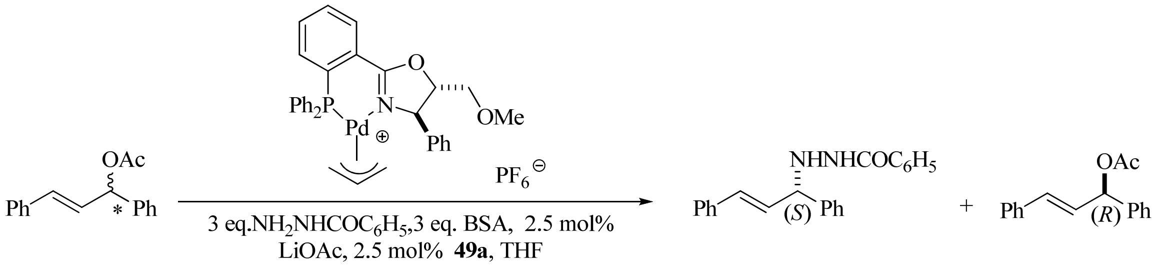


63 **190**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine but using benzhydrylamine as nucleophile. The amination product **190** was identified and characterized[82].

The enantiomeric excess was determined by HPLC on ADH column with precolumn (0.6 mL min^{-1} *n*- hexane/ *iso*-propanol, 98:2): (*R*)-**190** Rt = 9.2 min, (*S*)-**190** Rt = 8.0 min.

P3. Allylic amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene, 63 with benzoylhydrazine

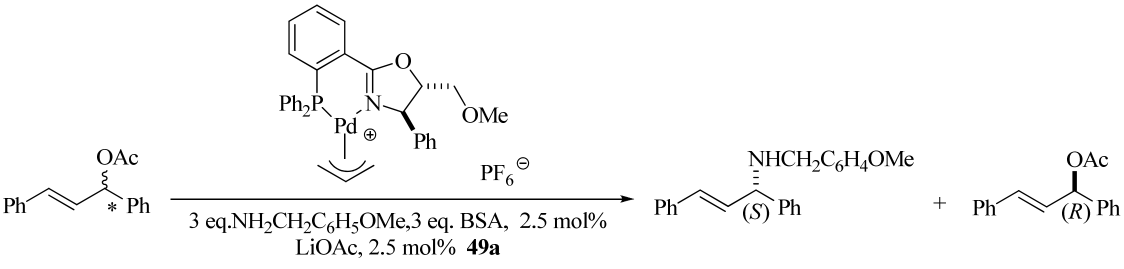


63 **191** **(*R*)- 63**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine, using **49a** as catalyst in all the cases and benzoylhydrazine as nucleophile. The amination product **191** was identified by ^{1}H-NMR.[40]

The enantiomeric excess was determined by HPLC separation method: 1) ADH column, hexane: *iso*-propanol, 85:15, 0.5ml/min. Retention times: (*R*)-**63** Rt = 31.4 min, (*S*)-**63** Rt = 35.9 min; 2) OJ column, hexane: *iso*-propanol, 85:15, 0.5ml/min. Retention times: (*S*)-**63** Rt = 27.7 min, (*S*)-**63** Rt = 31.4 min.

P4. Allylic amination of (E)-1,3-diphenylallyl acetate, 63 with *p*-methoxybenzilamine

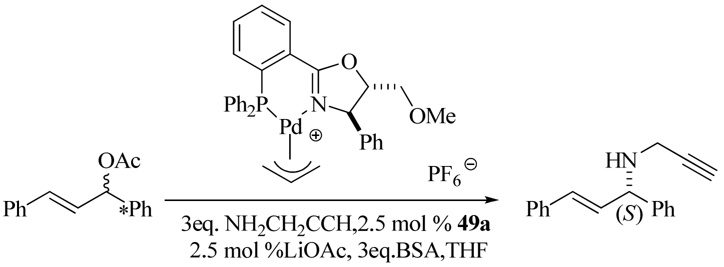


63 **192** **(*R*)- 63**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine but using *p*-methoxybenzilamine as nucleophile. The amination product **192** was identified and characterized.[82]

The enantiomeric excess was determined by HPLC on ADH column with precolumn (0.7 mL min^{-1} *n*- hexane/ *iso*-propanol, 94:6): (*R*)-**192** Rt = 20.9 min, (*S*)-**192** Rt = 18.0 min.

P5. Allylic amination of (*E*)-3-acetoxy-1,3-diphenyl-1-propene, 63 with propargylamine

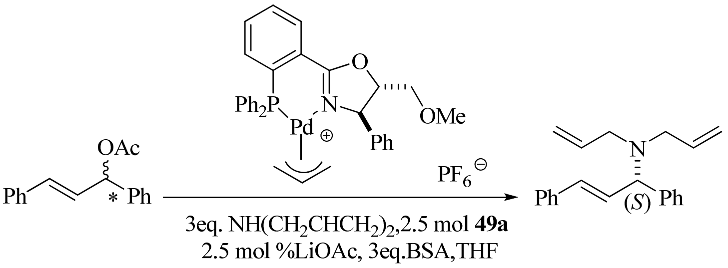


63 **193**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1,3-diphenyl-1-propene with benzylamine using **49a** as catalyst in all the cases and propargylamine as nucleophile. The amination product **193** was identified and characterized.[82]

The enantiomeric excess was determined by HPLC on ADH column with precolumn (0.5mL min^{-1} *n*- hexane/*iso*-propanol, 90:10): (*R*)-**193** Rt = 17.1 min, (*S*)-**193** Rt = 18.4 min.

P6. Allylic amination of (E)-1,3-diphenylallyl acetate, 63 with diallylamine



63 **194**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1,3-diphenyl-1-propene with benzylamine using **49a** as catalyst in all the cases and diallylamine as nucleophile. The amination product **194** was identified and characterized.[82]

The enantiomeric excess was determined by HPLC on ADH column with precolumn (0.4 mL min^{-1}, 0 to 5 min, *n*- hexane/isopropyl alcohol, 100:0; 0.2 mL min^{-1}, 5 to 40 min, *n*- hexane/ *iso*-propanol, 80:20): (*R*)-**194** Rt = 19.2 min, (*S*)-**194** Rt = 20.0 min.

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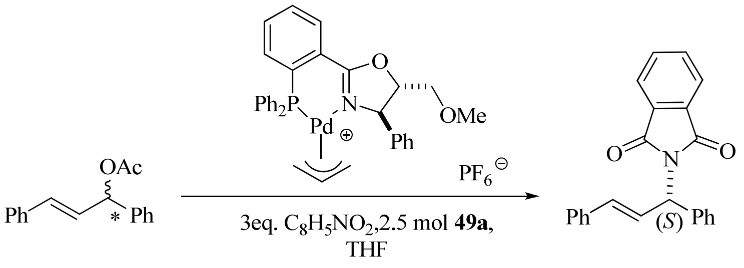
[82] See characterization section.

P7. Allylic amination of (E)-1, 3-diphenylallyl acetate, 63 with pftalimide

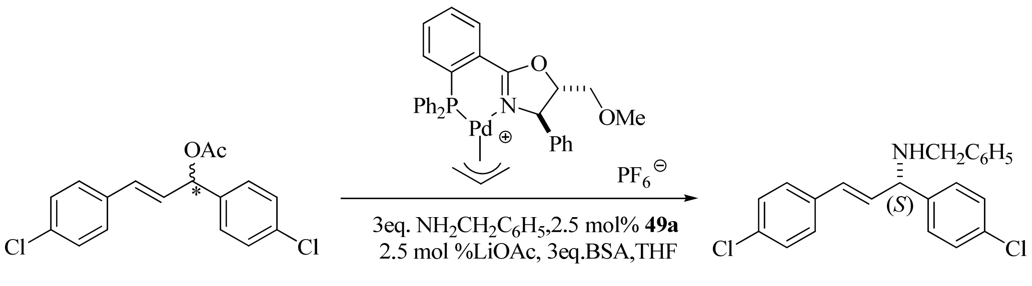


63 **195**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine but using **49b** as catalyst in all the cases and phtalimide as nucleophile. The amination product was identified by ^{1}H-NMR.

The enantiomeric excess was determined by HPLC separation method: OD column, hexane: *iso*-propanol, 98:2, 0.5ml/min. (*R*)-**195** Rt = 31.6 min, (*S*)-**195** Rt = 25.6 min.

P8. Allylic amination of (E)-1,3-bis(4-chlorophenyl)allyl acetate, 136c with benzylamine



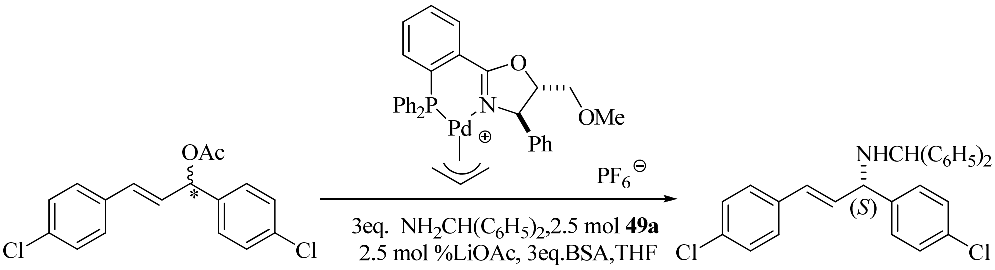
136c **199**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine but employing (*E*)-1,3-bis(4-

chlorophenyl)allyl acetate as substrate using cxOMe as catalyst in all the cases. The amination product was identified by ^{1}H-NMR.[41]

The enantiomeric excess was determined by HPLC separation method: ODH column, hexane: *iso*-propanol, 98:2, 0.7ml/min.: (*R*)-**199** Rt = 13.1 min, (*S*)-**199** Rt = 15.8 min.

P9. Allylic amination of (E)-1,3-bis(4-chlorophenyl)allyl acetate, 136c with benzhydrylamine

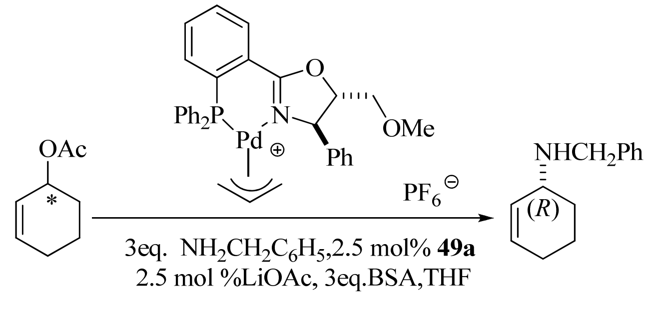


136c **200**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine but using **49a** as catalyst, (*E*)-1,3-bis(4-chlorophenyl)allyl acetate as starting material and benzhydrylamine as nucleophile. The amination product **200** was identified and characterized.[82]

The enantiomeric excesses were determined by HPLC on ADH column with precolumn (0.6 mL min^{-1} *n*- hexane/ *iso*-propanol, 98:2): (*R*)-**200** Rt = 11.7 min, (*S*)-**200** Rt = 10.3 min.

P10. Allylic amination of cyclohex-2-enyl acetate with benzylamine

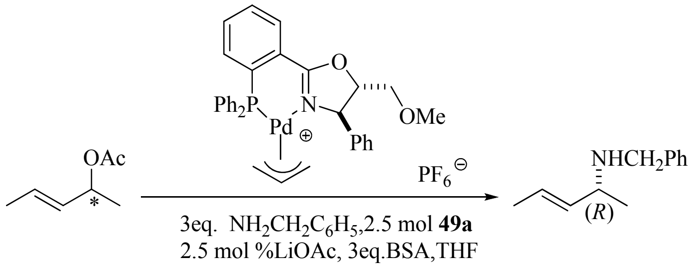


136b **198**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1,3-diphenyl-1-propene with benzylamine but using **49a** as catalyst, cyclohex-2-enyl acetate as starting material. The amination product **198** was identified by ^{1}H-NMR.[79]

The enantiomeric excesses were determined by HPLC on OBH column with precolumn (230 nm, 0.5 mL min^{-1} *n*- hexane/ *iso*-propanol, 98:2): (*R*)-**198** Rt = 11.98 min, (*S*)-**198** Rt = 10.7 min.

P11. Allylic amination of (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine

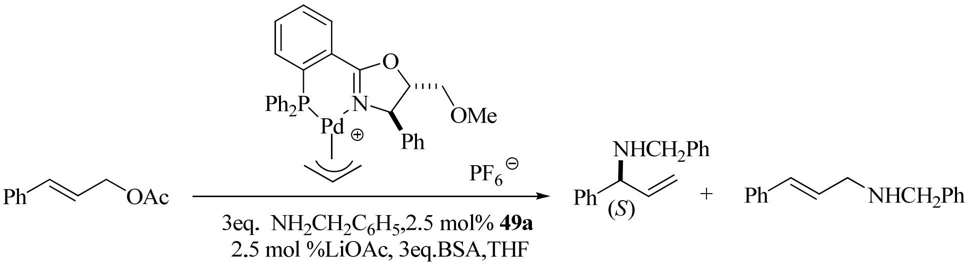


99b **197**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1,3-diphenyl-1-propene with benzylamine but using **49a** as catalyst, cyclohex-2-enyl acetate as starting material. The amination product **197** was identified by ^{1}H-NMR.[77]

The enantiomeric excesses were determined by HPLC on ODH column with precolumn (230 nm, 0.5 mL min^{-1} *n*- hexane 100%): (*R*)- **197** Rt = 36.4 min, (*S*)-**197** Rt = 30.7 min.

P12. Allylic amination of cinnamyl acetate with benzylamine

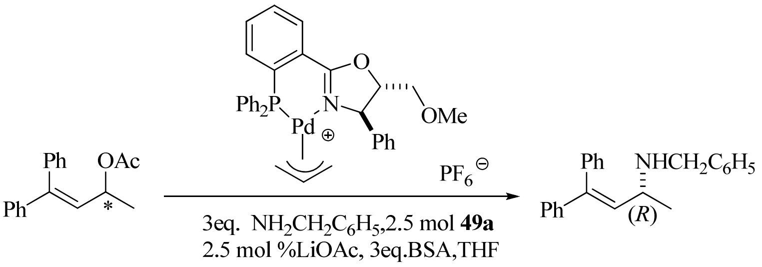


99c **201**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine but using **49a** as catalyst, cinnamyl acetate as starting material. The amination product **201** was identified by ^{1}H-NMR.[6]

The enantiomeric excesses were determined by HPLC on ODH column with precolumn (210 nm, 0.5 mL min^{-1} *n*- hexane/ *iso*-propanol, 99:1): (*R*)-**201** Rt = 10.36 min, (*S*)-**202** Rt = 11.25 min.

P13. Allylic amination of 4, 4-diphenylbut-3-en-2-yl acetate with benzylamine



136d **203**

The amination procedure was analogous to the one described for (*E*)-3-acetoxy-1, 3-diphenyl-1-propene with benzylamine but using **49a** as catalyst, 4,4-diphenylbut-3-en-2-yl acetate as starting material. The amination product **204** was identified by ^{1}H-NMR.[52]

The enantiomeric excesses were determined by HPLC on OJH column with precolumn (254 nm, 0.6 mL min^{-1} *n*- hexane/ *iso*-propanol, 90:10): (*R*)-**204** Rt = 12.4 min, (*S*)-**204** Rt = 18.6 min.

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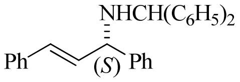
IV.3. Synthesis and characterization of the allylic amination products

E-(*S*)-*N*-benzhydryl-1, 3-diphenylprop-2-en-1-amine, 190



Employing general procedure P9 a solution of (*E*)-3-acetoxy-1, 3-diphenyl-1-propene **63** (0.25 g, 1.00 mmol) in THF[81] (2.0 mL) was added at room temperature[81] to a solution of phopshinooxazoline-palladium **49** (0.02 mmol)[81] in THF[81] (2.0 mL) under argon. Benzhydrylamine (0.56g, 0.53 mL, 3.00 mmol)[81] and BSA (0.60 g, 0.74 mL, 3.00 mmol)[81] were syringed into the previous solution and a catalytic amount of LiOAc[81] (0.001 g, 0.02mmol) was lastly added under argon. The final product **190** was obtained as white solid.

$[\alpha]^{23}_{D}$= +30.6 (c= 1.21 in $CHCl_3$).[83]

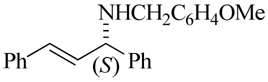
IR(film) ν: 3025, 2925, 2850, 1949, 1810, 1598, 1492, 1180, 966, 914, 745 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75-7.05 (m, 20H, Ph), 6.49(d, *J* = 15.8 Hz, 1H, PhC*H*CH), 6.29 (dd, *J* = 15.8 Hz, *J* = 7.5 Hz, 1H, PhCHC*H*), 4.87 (s, 1H, C*H*Ph_2), 4.28 (d, *J* = 7.2 Hz, 1H, C*H*NHCHPh_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ:144.0 (*C*, Ph), 143.9 (*C*, Ph), 143.0 (*C*, Ph), 137.0 (*C*, Ph), 132.4 (Ph*C*H=CH), 130.6 (PhCH=*C*H), 128.6 (*C*H, Ph), 128.5 (*C*H, Ph), 128.3 (*C*H, Ph), 127.6 (*C*H, Ph), 127.4 (*C*H, Ph), 127.3 (*C*H, Ph), 127.0 (*C*H, Ph), 126.9 (*C*H, Ph), 126.4 (*C*H, Ph), 63.5 (*C*HPh_2), 61.9 (*C*HNH);

HRMS(ESI+ve): Calculated for: $C_{28}H_{25}N$ (M+H): 376.2065, Obtained: 376.2056.

***E*-(*S*)-*N*-(4-methoxybenzyl)-1, 3-diphenylprop-2-en-1-amine, 192**



Employing general procedure P4 a solution of (*E*)-3-acetoxy-1, 3-diphenyl-1-propene **63** (0.25 g, 1.00 mmol) in THF[81] (2.0 mL) was added at room temperature[81] to a solution of phopshinooxazoline-palladium **49a** (0.015g, 0.02 mmol)[81] in THF[81] (2.0 mL) under argon. *Para*-methoxybenzylamine (0.42g, 0.39 mL, 3.00 mmol)[81] and BSA (0.74 mL, 3.00 mmol)[81] were syringed into the previous solution and a catalytic amount of LiOAc[81] (0.001 g, 0.02mmol) was lastly added under argon. The final product **192** was obtained as transparent yellow oil.

$[\alpha]^{23}_{D}$= +28.2 (c= 0.82 in $CHCl_3$).[83]

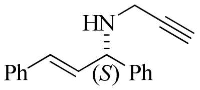
IR(film) ν: 3024, 2832, 1610, 1510, 1492, 1245, 1174, 966, 914, 745 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29-7.17 (m, 12H, Ph), 6.88-6.84 (m, 2H, Ph), 6.56 (d, *J* = 15.8 Hz, 1H, PhC*H*CH), 6.30 (dd, *J* = 15.8 Hz, *J* = 7.5 Hz, 1H, PhCHC*H*), 4.37 (d, *J* = 7.5 Hz,1H, C*H*NH), 3.79 (s, 3H, OMe), 3.75-3.68 (m, 2H, $CH_2C_6H_4OMe$).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 158.7(*C*, Ph), 143.0(*C*, Ph), 137.0 (*C*, Ph),132.7 (*C*, Ph), 132.5(*C*H, Ph), 130.3(*C*H, Ph), 129.4(*C*H, Ph), 128.6(*C*H, Ph), 128.5(*C*H, Ph), 127.5(Ph*C*H=CH), 127.4(*C*H, Ph), 127.3(*C*H, Ph), 126.4(CH=*C*HCHN), 113.8(*C*H, Ph), 64.5(*CH*NH), 55.3(OCH_3), 50.8(NHCH_2);

HRMS (ESI+ve): Calculated for: $C_{23}H_{23}NONa$ (M+Na): 352.1677, Obtained: 352.1666.

E-(*S*)-1, 3-diphenyl-*N*-(prop-2-ynyl)prop-2-en-1-amine, 193



Employing general procedure P5 a solution of (*E*)-3-acetoxy-1, 3-diphenyl-1-propene **63** (0.25 g, 1.00 mmol) in THF[81] (2.0 mL) was added at room temperature[81] to a solution of phopshinooxazoline-palladium **49a** (0.015g, 0.02 mmol)[81] in THF[81] (2.0 mL) under argon. Propargylamine (0.17g, 0.19 mL, 3.00 mmol)[81] and BSA (0.60 g, 0.74 mL, 3.00 mmol)[81] were syringed into the previous solution and a catalytic amount of LiOAc[81] (0.001 g, 0.02mmol) was lastly added under argon. The final product **193** was obtained as yellow oil.

$[\alpha]^{23}_{D}$= +26.6 (c= 1.15 in $CHCl_3$).[83]

IR(film) ν: 3290, 3025, 2832, 1491, 1449, 1330, 1110, 968, 913, 749 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.43-7.12 (m, 10H, Ph), 6.63 (d, *J* = 15.9 Hz, 1H, PhC*H*CH), 6.26 (dd, *J* = 15.9 Hz, *J* = 7.7 Hz, 1H, PhCHC*H*), 4.60 (d, *J* = 7.7 Hz,1H, C*H*NH), 3.43 (dd, *J* = 17.3 Hz, *J* = 2.6 Hz, 1H, C*H*H), 3.34 (dd, *J* = 17.3 Hz, *J* = 2.6 Hz, 1H, CH*H*), 2.24-2.25 (m, 1H, CCH).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 142.0 (*C*, Ph), 136.8 (*C*, Ph), 131.6 (*C*H, Ph), 130.8 (*C*H, Ph), 128.6 (Ph*C*H=CH), 128.5 (*C*H, Ph), 127.5 (*C*H, Ph), 127.4 (*C*H, Ph), 126.4 (PhCH=*C*H), 82.1 (*C*CH), 71.5 (C*C*H), 63.6 (*C*HNH), 35.7 (CH_2).

HRMS (ESI+ve): Calculated for: $C_{18}H_{17}NNa$ (M+Na): 270.1268, Obtained: 270.1259.

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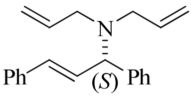
[83] (*S*) configuration was determined in comparison with benzylamine substitution product.

E-(*S*)-*N,N*-diallyl-1, 3-diphenylprop-2-en-1-amine, 194



Employing general procedure P6 a solution of (*E*)-3-acetoxy-1, 3-diphenyl-1-propene **63** (0.25 g, 1.00 mmol) in THF[81] (2.0 mL) was added at room temperature[81] to a solution of phopshinooxazoline-palladium **49** (0.015g, 0.02 mmol)[81] in THF[81] (2.0 mL) under argon. Diallylamine (0.29g, 0.37 mL, 3.00 mmol)[81] and BSA (0.60 g, 0.74 mL, 3.00 mmol)[81] were syringed into the previous solution and a catalytic amount of LiOAc[81] (0.001 g, 0.02mmol) was lastly added under argon. The final product **194** was obtained as transparent yellow oil.

$[\alpha]^{23}_{D}$= +27.26 (c= 2.2 in $CHCl_3$)[83].

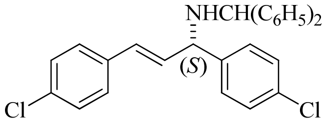
IR(film) ν: 3059, 3025, 2920, 2813, 1739, 1641, 1599, 1492, 1448, 1417, 1229, 1028, 968, 917, 743cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.20 (m, 10H, Ph), 6.54 (d, *J* = 15.7 Hz, 1H, PhC*H*CH), 6.33 (dd, *J* = 15.7 Hz, *J* = 9.1 Hz, 1H, PhCHC*H*), 5.92-5.82 (m, 2H, C*H*=CH_2), 5.19-5.12 (m, 4H, CH=CH_2), 4.43 (d, *J* = 9.1 Hz, 1H, C*H*N), 3.23-3.10 (m, 4H, NCH_2).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 142.2 (*C*, Ph), 137.0 (*C*, Ph), 136.0 (*C*H, Ph), 132.4 (*C*H, Ph), 129.8 (Ph*C*H=CH), 128.6 (*C*H, Ph), 128.5 (*C*H=CH_2), 128.3 (*C*H, Ph), 127.9 (*C*H, Ph), 127.5 (*C*H, Ph), 127.0 (*C*H, Ph), 126.7 (*C*H, Ph), 126.4 (PhCH=*C*H), 117.1 (CH=*C*H_2), 67.1 (*C*HN), 52.6 (*C*H_2N);

HRMS (CI+ve): Calculated for: $C_{21}H_{24}N$ (M+H): 290.1909, Obtained: 290.1917.

E-(*S*)-*N*-benzhydryl-1, 3-bis(4-chlorophenyl)prop-2-en-1-amine, 200



Employing general procedure P9 a solution of (*E*)-3-acetoxy-1, 3-diphenyl-1-propene **63** (0.32g, 1.00 mmol) in THF[81] (2.0 mL) was added at room temperature[81] to a solution of phopshinooxazoline-palladium **49a** (0.015g, 0.01 mmol)[81] in THF[81] (2.0 mL) under argon. Benzhydrylamine (0.564g, 0.530 mL, 3.0 mmol)[81] and BSA (0.61 g, 0.74 mL, 3.00 mmol)[81] were syringed into the previous solution and a catalytic amount of LiOAc[81] (0.001 g, 0.02mmol) was lastly added under argon. The final product **200** was obtained as a yellow- white solid.

$[\alpha]^{23}_{D}$= +10.0 (c= 0.89 in $CHCl_3$).[83]

IR(film) ν: 3060, 3025, 2924, 2885, 1489, 1453, 1090, 1013, 968, 829, 744 cm^{-1}.

1H-NMR (400 MHz, $CDCl_3$) δ: 7.68-6.98 (m, 18H, Ph), 6.35(dd, *J* = 15.9 Hz, *J* = 1.2 Hz, 1H, ClPhCHCH), 6.14 (dd, *J* = 15.9 Hz, *J* = 7.3 Hz, 1H, PhCHCH), 4.72 (s, 1H, $CHPh_2$), 4.17 (d, *J* = 7.3 Hz, 1H, $CHNHCHPh_2$).

13C-NMR (100.6 MHz, $CDCl_3$) δ: 144.9 (*C*, Ph), 143.7 (*C*, Ph), 143.4 (*C*, Ph), 141.1 (*C*, Ph), 135.2 (*C*, Ph), 133.2 (*C*, Ph), 132.5 (Ph*C*H=CH), 129.7 (PhCH=*C*H), 128.8 (*C*H, Ph), 128.7 (*C*H, Ph), 128.6 (*C*H, Ph), 128.5 (*C*H, Ph), 128.4 (*C*H, Ph), 128.3 (*C*H, Ph), 128.0 (*C*H, Ph), 127.7 (*C*H, Ph), 127.6 (*C*H, Ph), 127.5 (*C*H, Ph), 127.4 (*C*H, Ph), 127.2 (*C*H, Ph), 127.1 (*C*H, Ph), 126.7 (*C*H, Ph), 63.6 (*C*HPh2), 61.3 (*C*HNH).

HRMS (ESI+ve): Calculated for: $C_{28}H_{24}NCl_2$ (M+H): 444.1286, Obtained: 444.1289.

CHAPTER IV

A CHIRAL FLUOROEPOXIDE AS A NEW DERIVATIZING AGENT FOR DETERMINING THE OPTICAL PURITY OF α-CHIRAL AMINES AND AS A CHIRON FOR THE SYNTHESIS OF FLUOROPEPTIDOMIMETICS

A CHIRAL FLUOROEPOXIDE AS A NEW DERIVATIZING AGENT FOR DETERMINING THE OPTICAL PURITY OF α-CHIRAL AMINES AND AS A CHIRON FOR THE SYNTHESIS OF FLUOROPEPTIDOMIMETICS

I. DEVELOPMENT OF A NEW CHIRAL DERIVATIZATION AGENT FOR DETERMINING THE OPTICAL PURITY OF α-CHIRAL AMINES

Some of the most important properties (chemical, physical or biological) of chiral compounds from many areas of chemistry, pharmacy, biology are determined by their absolute stereochemistry: One enantiomer of a compound with biological activity may act very differently with respect to the other.[1] Since the interest in enantiopure compounds and their properties has increased significantly[2] accurate, reliable, and convenient methods of measuring the enantiomeric purity of organic compounds are still required.

In the assay of the enantiomeric purity of scalemic mixtures, chiral chromatographic methods (HPLC, GC) have simplified and quickened the analysis of many products.[3] Even so, these techniques have the disadvantage of the expensive chiral stationary phases and their relative sensitivity to chemical and physical agents.

NMR based techniques constitutes an interesting alternative for the determination of the enantiomeric composition of compounds.

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[1] Parker, D. *Chem. Rev.* **1991**, *91*, 1441-57.
[2] Ikunaka, M. *Chem.--Eur. J.* **2003**, *9*, 378-388.
[3] Davankov, V. A. *Pure Appl. Chem.* **1997**, *69*, 1469-1474.

The two enantiomers of a scalemic mixture cannot be differentiated by NMR in an achiral medium. If the enantiomers can be transformed into a diasteromeric mixture, then their differentiation by NMR should be possible.

Several strategies have been envisaged for this purpose:

1. Chiral lanthanide shift reagents (CLRs)[4] form "in situ" diastereomeric complexes with the organic substrate, these complexes being in fast equilibrium exchange with the unbound substrate on the NMR time scale.

2. Chiral solvating agents (CSAs)[5] form diastereomeric solvation complexes, through rapidly reversible equilibrium between the solvent and the enantiomers of the solute.

3. Chiral derivatizing agents (CDA) form by covalent bonding distinct diastereoisomers with the compound to be analysed. In the determination of the enantiomeric composition of a compound by NMR techniques, CDAs are by far the most widely employed agents.

Since the first fluorine-containing CDA reported by Mosher[6] (1969), many new efficient derivatizing agents have been designed.[7] In order to be general and efficient, a derivatizing agent has mainly to fulfil two requirements: Firstly, it should show a clean and fast reaction with both enantiomers of the substrate (absence of kinetic resolution) and, secondly, it should be easily accessible.

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[4] Whitesides, G. M.; Lewis, D. W. *J. Amer. Chem. Soc.* **1970**, *92*, 6979-80.
[5] Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263-331.
[6] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-49.
[7] Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915-2925.

NMR active nuclei other than ^{1}H have been normally introduced in the structure of CDA. Fluorine groups were considered to be very attractive for this purpose, as ^{19}F is a sensitive nucleus with a receptivity almost as high as ^{1}H. Many CDAs containing fluorine groups have been developed: MTPA (α -methoxy- α -(trifluoromethyl)phenyl-acetic acid) [8,9] has been the most common one and is commercially available in enatiomerically pure form. The acid can be easily converted into the acid chloride and, as there is no hydrogen substituted in the alpha position to the COOH group, racemization is thus not possible. MTPA has been successfully employed for determining the optical purity of primary and secondary alcohols and amines by ^{1}H and ^{19}F-NMR analysis.[10] Some other fluorine-containing derivatizing agents, such as (*R*)-2-fluoro acetic acid devatives,[8] (*R*)-2-fluoro-2-phenylethylamine,[9] α-cyano-α-fluorophenylacetic acid (CFPA), [11]α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA),[12] α-cyano-α-fluoro-2-naftylacetic acid (CFNA),[13] (*R*)-2-fluorophenylacetic acid (AFPA),[14] α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetic acid (ATEA),[15] trifluorolactic acid (TFLA) have been depicted in the Figure IV.1.[16]

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[8] Takeuchi, Y.; Ogura, H.; Ishii, Y.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1721-5.

[9] Hamman, S. *J. Fluorine Chem.* **1989**, *45*, 377-87.

[10] Dale, J. A.; Mosher, H. S. *J. Amer. Chem. Soc.* **1973**, *95*, 512-19;Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-7.

[11] Takeuchi, Y.; Itoh, N.; Note, H.; Koizumi, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **1991**, *113*, 6318-20.

[12] Takeuchi, Y.; Konishi, M.; Hori, H.; Takahashi, T.; Kometani, T.; Kirk, K. L. *Chem. Commun. (Cambridge)* **1998**, 365-366.

[13] Takahashi, T.; Fukushima, A.; Tanaka, Y.; Segawa, M.; Hori, H.; Takeuchi, Y.; Burchardt, A.; Haufe, G. *Chirality* **2000**, *12*, 458-463.

[14] Apparu, M.; Tiba, Y. B.; Leo, P. M.; Hamman, S.; Coulombeau, C. *Tetrahedron: Asymmetry* **2000**, *11*, 2885-2898.

[15] Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239-46.

[16] Chambers, R. D.; Gray, W. K.; Sandford, G.; Vaughan, J. F. S. *J. Fluorine Chem.* **1999**, *94*, 213-215.

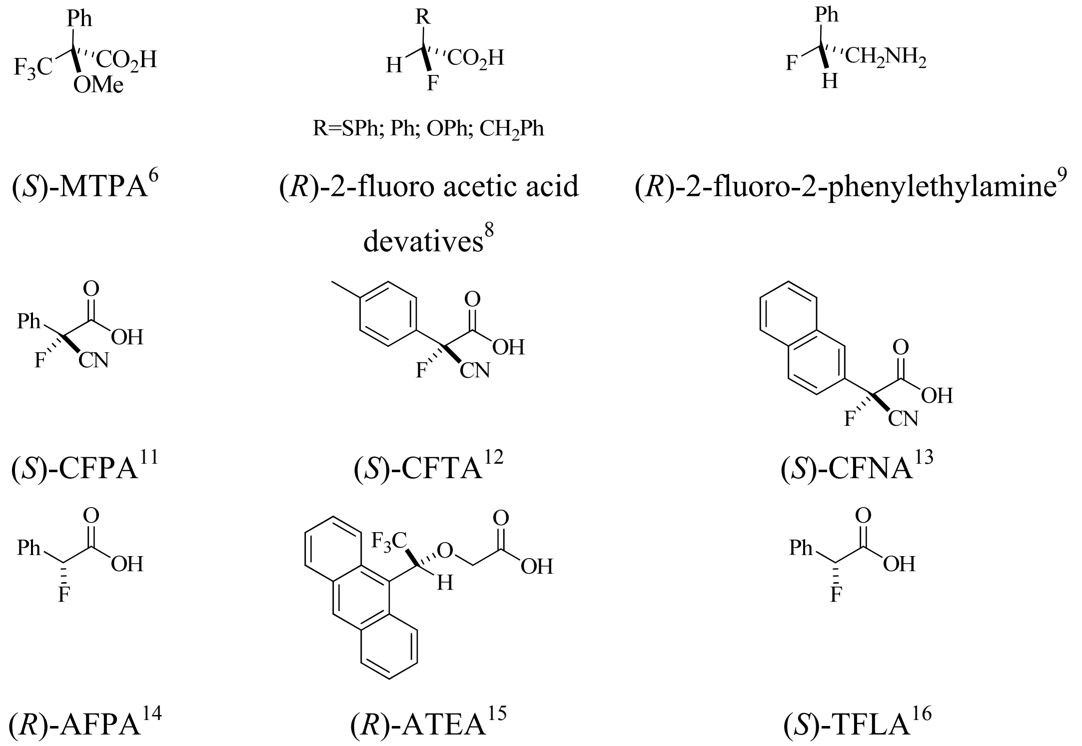

Figure.IV.1. Fluorine-containing CDAs.

Other NMR active nuclei have been introduced in the structure of CDAs. Phosphorous , [17,18,19] silicon,[20] platinum,[21] or selenium[22] containing derivatizing agents have been designed, prepared and widely used (Figure.IV.2.).

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[17] Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304-5.

[18] Kato, N. *J. Am. Chem. Soc.* **1990**, *112*, 254-7.

[19] Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 437-40.

[20] Chan, T. H.; Peng, Q. J.; Wang, D.; Guo, J. A. *J. Chem. Soc., Chem. Commun.* **1987**, 325-6.

[21] Salvadori, P.; Uccello-Barretta, G.; Bertozzi, S.; Settambolo, R.; Lazzaroni, R. *J. Org. Chem.* **1988**, *53*, 5768-70.

[22] Silks, L. A., III; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979-82.

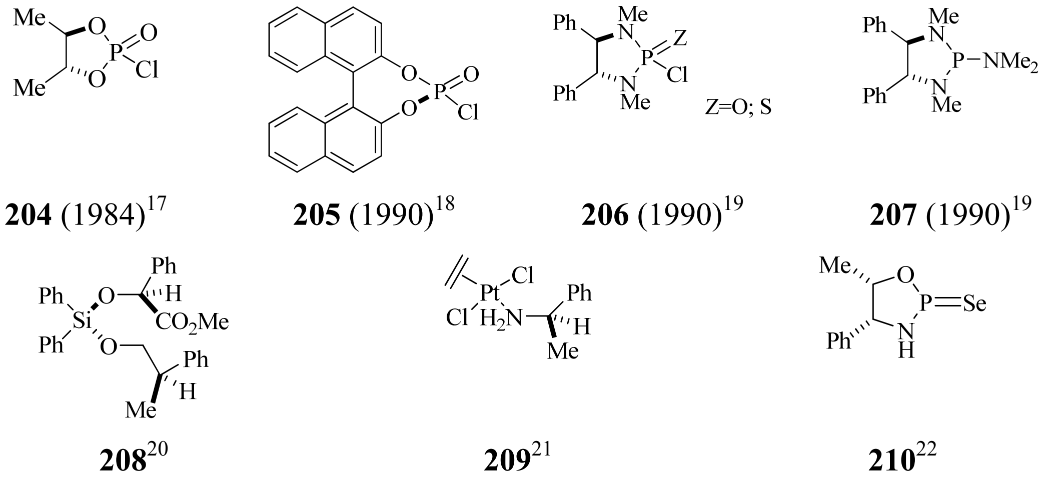
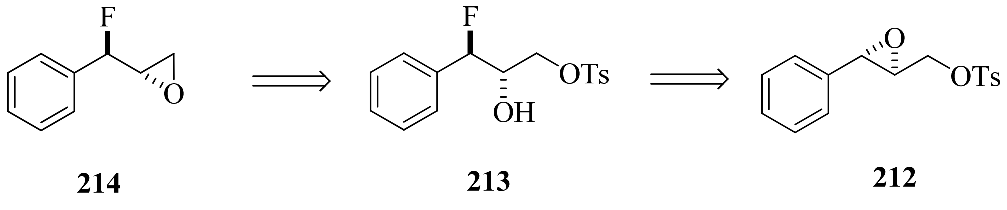


Figure.IV.2. CDA containing different NMR-active nuclei

A new chiral derivatizing agent, (*S*)-2-[(*R*)-fluoro(phenyl)methyl]oxirane, **214,**[23] for chiral amines has been envisaged, prepared and tested within the scope of the present PhD Thesis. Our approach involves that the formed diastereomers should arise by ring-opening of the epoxide by the analyte, i.e. chiral amines.

Our derivatizing agent for chiral amines should be easily available from the tosylate of enantiomerically pure phenyl glycidol, **212**, as indicated in Scheme IV.1.



Scheme IV.1. Retrosynthetic path for chiral derivatizing agent **214**

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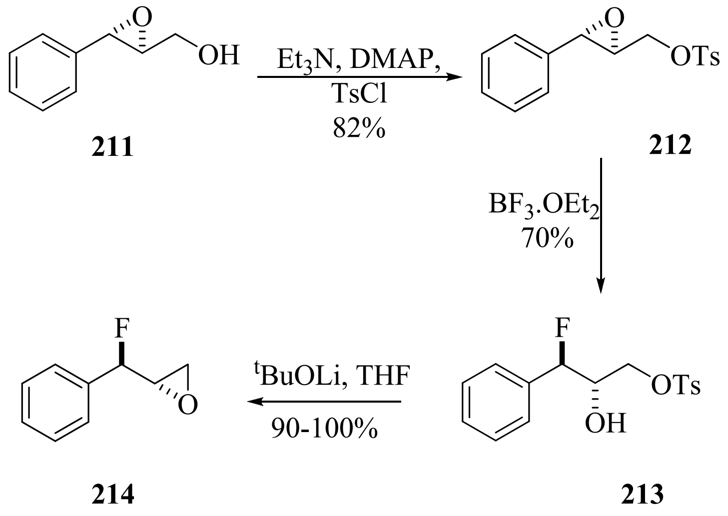
[23] Rodriguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericas, M. A. *Org. Lett.* **2005**, *7*, 3829-3832;Pericas, M. A.; Jimeno, C.; Rodriguez-Escrich, S.; Vidal-Ferran, A.; Popa, D. *Eur. Pat. Appl.* **2007**, 28pp. EP 1750119.

The newly designed CDA contained a UV- active aromatic group and a fluorine heteroatom, both of which should allow distinguishing and analyzing the formed diastereomers through several techniques: *e.g.* HPLC, ^{19}F-NMR, ^{1}H-NMR, ^{13}C-NMR.[24]

Enantiopure phenylglycidol, **211**, was prepared through Sharpless epoxidation of cinnamyl alcohol [25] and the protection of the hydroxyl group in **211** as the tosylate afforded (2*S*,3*S*)-phenylglycidol tosylate, **212**. Regioselective and stereospecific ring-opening of **212** with BF_3 at low temperature (-35ºC), yielded (2*S*,3*R*)-3-fluoro-2-hydroxy-3-phenylpropyl *p*-toluenesulfonate **213**. The desired (*S*)-2-[(*R*)-fluoro(phenyl)methyl]oxirane, **214** was obtained in quantitative yield by intramolecular cyclization mediated by lithium *tert*-butoxide (Scheme IV.2.). The described reaction pathway allows the easy preparation of the enantiopure **214** on multigram scale.[23]



Scheme IV.2. Preparation of resolution reagent, **214**

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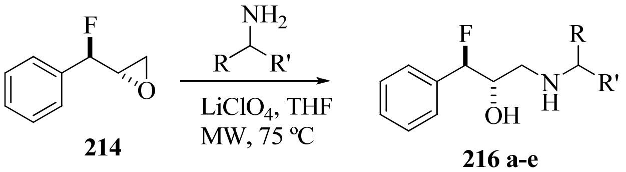
[24] It has to be mentioned that the present investigation project for the new CDA was done in collaboration with Sergi Rodriguez-Escrich. Part of the results presented in this chapter are also discussed in his PhD thesis.

[25] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-6.

With fluoroepoxide **214** in hand, its reactivity towards chiral amines was next tested. To the best of our knowledge, **214** is the first CDA which may derivatise the analyte (*i.e.* chiral amines) by an epoxide ring-opening reaction. This transformation onto **214** took place with *rac*-α-methylamine in excellent yields and with complete regioselectivity using $LiClO_4$ as a promoter[26] both by conventional heating or by microwave irradiation (Scheme IV.3.). Microwave irradiation consistently afforded higher yields, and few decomposition by-products were observed compared to the thermal reaction, therefore this activation method was preferentially used thereafter.



Scheme IV.3. Epoxide ring-opening of **214** with chiral amines

The determination of the diastereomeric composition of the products resulted in the epoxide ring-opening with racemic amines was done by ^{1}H-, ^{13}C-, and ^{19}F-NMR.

Very interestingly, all three distinct nuclei present at the fluorine bearing chiral center were differentially perturbed by the chiral center α to nitrogen, which is located four bounds away, and originated different sets of signals for each diastereomer (Figure.IV.3.).

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[26] Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221-7.

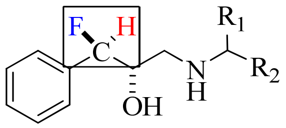
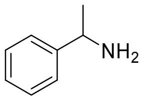
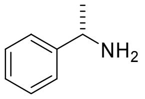
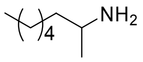
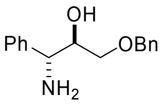
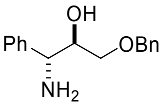
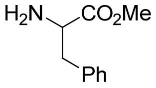
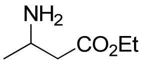


Figure.IV.3. Suitable nuclei for diastereomeric analysis in **216**.

Table.IV.1. Yields and main NMR signals associated to the CHF group of the diastereomers obtained by reaction of chiral amines with derivatizing reagent **214**

Entry	Starting amine		Product (yield [%]^a)		δ [ppm]
1	*rac*-**215a**		**216a** (92)	^{19}F: ^{1}H: ^{13}C:	-186.8; -188.8 5.38; 5.33 95.8; 95.7
2	(*S*)-**215a**		**(*S*)-216a** (92)	^{19}F: ^{1}H: ^{13}C:	-186.8 5.33 95.7
3	*rac*-**215b**		**216b** (50)	^{19}F: ^{1}H: ^{13}C:	-187.6; -187.7 5.30^b 95.80; 95.78
8	*rac*-**215c**		**216c** (74)	^{19}F: ^{1}H: ^{13}C:	-183.5; -186.0 5.43; 5.33 95.8; 95.4
9	(1*R*, 2*R*)-**215c**		**(1*R*, 2*R*) -216c** (75)	^{19}F: ^{1}H: ^{13}C:	-186.5 5.33 95.8
11	*rac*-**215d**		**216d** (70)	^{19}F: ^{1}H: ^{13}C:	-188.9; -189.1 5.31; 5.22 95.4; 95.3
12	*rac*-**215e**		**216e** (72)	^{19}F: ^{1}H: ^{13}C:	-187.0; -187.1 5.38; 5.37 95.9; 95.8

[a] Isolated yield after flash chromatography. [b] No signal separation. [c] 10 mol% $Cu(BF_4)_2.6H_2O$, acetonitrile, 2h, 75 ºC (MW)

^{19}F-NMR was superior in all cases, since only two sets of clearly separated signals, remote from those due to the initial fluoroepoxide, appeared in the spectra. These signals allowed easy integration and, hence, a simple evaluation of diastereomeric (enantiomeric) composition. As mentioned above, the ^{1}H- and ^{13}C-NMR spectra also presented sets of signals corresponding to the methyne moiety showing good line separation and making their integration feasible.

Table IV.1 contains a summary of the studied amines (**215a-e**) and the chemical shifts for the ^{19}F, ^{1}H, and ^{13}C signals corresponding to the considered center in the two diastereomers formed by the ring-opening reaction. As an example of signal separation, the regions of the the ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra of interest for analytical purposes of **216a** obtained from racemic **215a** and from (*S*)-**215a** are shown in Figure.IV.4.

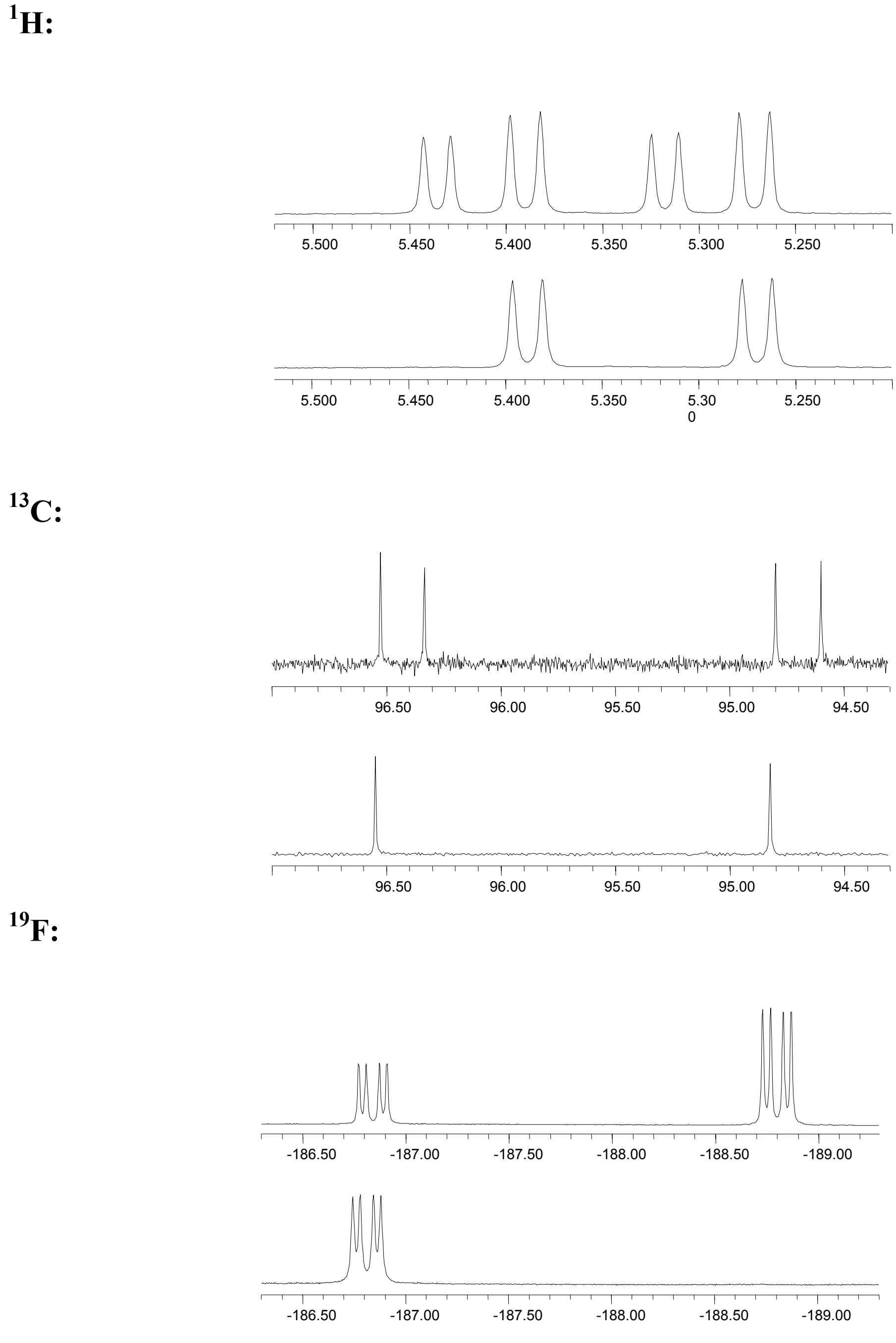


Figure.IV.4. NMR spectra of the CHF region of derivatised α-methyl benzylamine compound, **216a** (partially resolved after flash chromatography) and (*S*)-**216a**.

From a preparative point of view, the reaction worked nicely for acyclic, **215a** primary amines, somewhat lower yields being recorded with long-chain amines **215b**. Even a more functionalised substrate like **215c**, also containing an alcohol and ether functions[27] could be successfully used in the ring-opening of **214.** Phenylalanine methyl ester and β-amino butanoic acid methyl ester (products **216d** and **216e)** were suitable as well. In this way, the enantiomeric composition of a wide variety of nitrogen-containing compounds could be analyzed using the present method.

To ensure that no kinetic resolution happened while the reaction was in course, the reaction crudes were analyzed at different conversion levels for α-methyl benzylamine. In all cases, the ring-opening product was a perfect 1:1 mixture of diastereomers. In addition, the use of either enantiopure or racemic amines led to the same yields of ring-opening products under identical conditions.

It must be pointed out that other NMR signals are also suitable for the determination of the diastereomeric (enantiomeric) composition, but the CHF signals already discussed are in general more separated, appear in a cleaner zone of the spectra, and were much easier to assign.

In practice, the analytical use of **214** involves greatly simplified working conditions. Once it was established that no kinetic resolution was taking place during the ring opening of **214** by primary amines, and since the diagnostic ^{19}F-NMR signals of the diastereomeric amines **215** occured in a clean spectral region, it was not necessary to use stoichiometric amounts of fluoroepoxide **214** with respect to the amine to be analyzed. When 20 mol % of fluoroepoxide is used, the chiral derivatising reagent is completely consumed within 15 min and the reaction crude can be directly submitted to ^{19}F-NMR analysis, without any intermediate purification. In this way, enantiomeric purities up to 95% on **216a**

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[27] Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *Journal of Organic Chemistry* **1999**, *64*, 7902-7911.

have been easily determined with less than 1% error, as shown in Figure.IV.5. and Table.IV.2.

In addition to the NMR-based determinations of diastereomeric composition, it is also generally possible to separate the diastereomers of **216a-e** by HPLC, using a commercial Zorbax-Sil column and a UV-Vis detector.

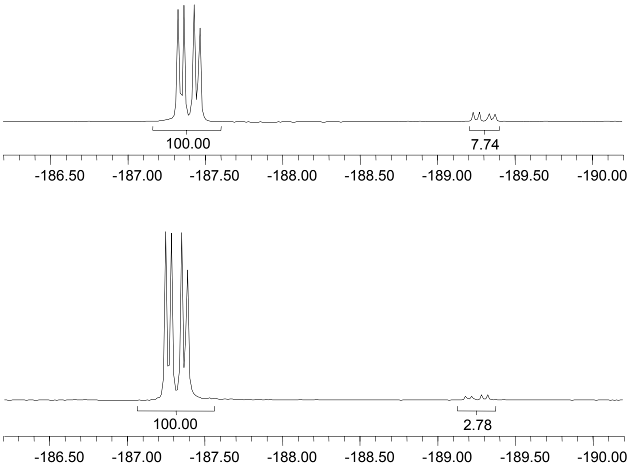


Figure.IV.5. ^{19}F-NMR spectra of **216a** obtained from 85% (top) and 95% ee (bottom) (*S*)-α-methyl benzylamine, **215a**.

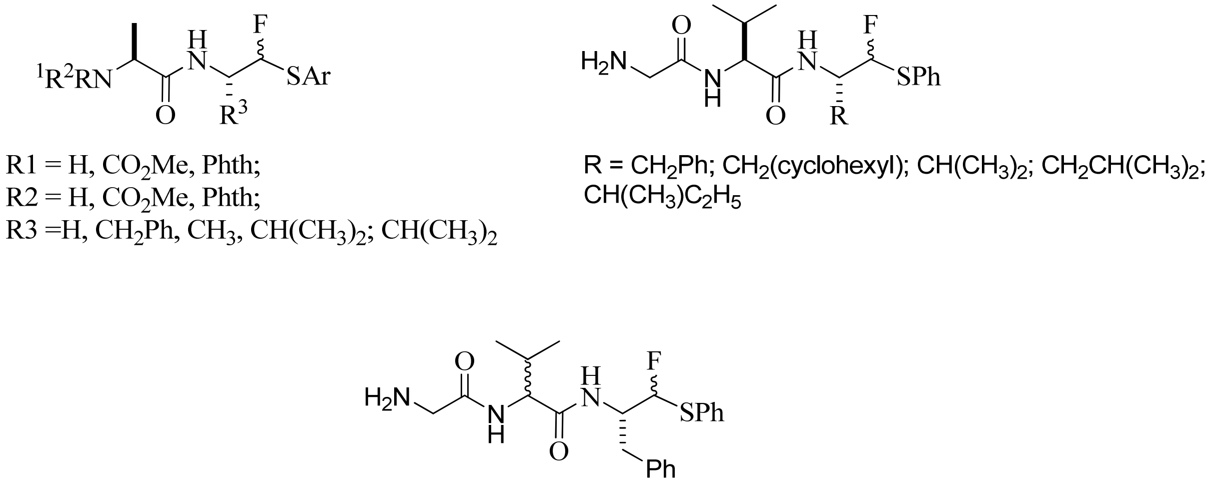
Table.IV.2. Comparison of analysis methods

Entry	Method	95% ee	85% ee
1	weighting (α-methylbenzylamine)	95.7	86.6
2	GC[a] (α-methyl benzylamine)	96.0	87.3
3	mean	**95.9**	**87.0**
4	HPLC[b] (**216a**)	95.7	85.0
5	^{19}F-NMR (**216a**)	**95.2**	**85.3**
6	mean	94.6	85.6

To conclude with, we have described a new chiral derivatising agent for the reliable and easy determination of the enantiomeric excesses of α-chiral primary amines. The clear and easy differentiation of the corresponding enantiomers by different techniques (NMR and HPLC) makes the reagent a useful analytic tool.

II. A CHIRAL FLUOROEPOXIDE AS A CHIRON FOR THE SYNTHESIS OF FLUOROPEPTIDOMIMETICS

Peptides have a great potential either as drugs themselves or as drug targets. At present, peptide drugs represent a small but growing number of pharmaceutical molecules. Among them, the peptidomimetics present a great interest as they can have similar biological effects as their natural peptide counterparts with the potential added advantages of their higher metabolic stability and improved pharmacokinetic proprieties.[28] Particularly, fluoropeptidomimetics, have been designed for the use as protease inhibitors[29] (see Figure IV.6).



R1 = H, CO_2Me, Phth;
R2 = H, CO_2Me, Phth;
R3 =H, CH_2Ph, CH_3, $CH(CH_3)_2$; $CH(CH_3)_2$

R = CH_2Ph; CH_2(cyclohexyl); $CH(CH_3)_2$; $CH_2CH(CH_3)_2$; $CH(CH_3)C_2H_5$

Figure.IV.6. Literature described fluoropeptidomimetics.

(*S*)-2-[(*R*)-fluoro(phenyl)methyl]oxirane might be regarded as an ideal starting material (chiron) for the preparation of a new class of fluorine-containing

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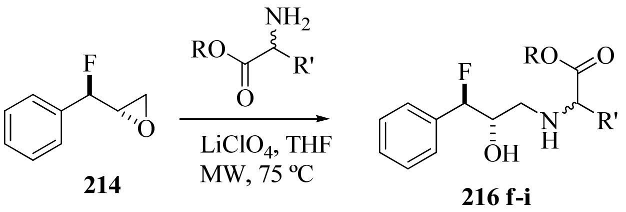
[28] Clynen, E.; Baggerman, G.; Husson, S. J.; Landuyt, B.; Schoofs, L. *Expert Opin. Drug Discovery* **2008**, *3*, 425-440;Brennan, M. P.; Cox, D.; Chubb, A. J. *Front. Drug Des. Discovery* **2007**, *3*, 395-432;Benedetti, E.; Pedone, C.; Saviano, M. *Front. Drug Des. Discovery* **2007**, *3*, 539-558.

[29] Annedi, S. C.; Li, W.; Samson, S.; Kotra, L. P. *J. Org. Chem.* **2003**, *68*, 1043-1049;Annedi, S. C.; Majumder, K.; Wei, L.; Oyiliagu, C. E.; Samson, S.; Kotra, L. P. *Bioorg. Med. Chem.* **2005**, *13*, 2943-2958.

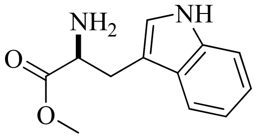
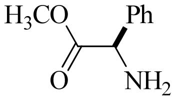
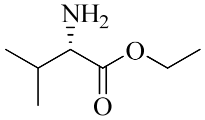
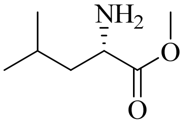
peptidomimetics by epoxide ring-opening in fluoroepoxide **214** with the esters derived from enantiopure amino acids. The ring-opening of fluoroepoxide **214** with the methyl ester of triptophane (**215f**), methyl ester of phenylglicine (**215g**), ethyl ester of valine (**215h**) and methyl ester of leucine (**215i**) has been studied (See scheme IV.4.) and the corresponding compounds could be easily prepared.



Scheme IV.4. Epoxide ring opening of **214** with functionalised enantiopure α-amino acids.

The epoxide ring-opening proceeded smoothly under the reaction conditions already developed for the analysis of the optical purity of several amines by derivatisation with **214** (See previous section in this chapter). $LiClO_4$, was used as the mediator under microwave irradiation conditions and the ring-opening fully proceeded in 3.5 hours at 75ºC. The desired compounds could be easily isolated with good yields (Table IV.3).

Table IV.3. Results obtained by reaction of **215 f-i** with reagent **214**

Entry	Starting amino-esters		Product	yield [%]
1	(*S*)-**215f**		**216f**	60
2	(*R*)-**215g**		**216g**	76
3	(*S*)-**215h**		**216h**	63
4	(*S*)-**215i**		**216i**	67

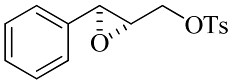
The size of the amino ester substituent has proved to have a slightly detrimental effect in the yield. Thus, *L*-tryptophan methyl ester and *L*-valine ethyl ester rendered the fluorine-containing derivatives in slightly lower yields (see entries 1 and 3 from Table IV.3).

The evaluation of the chemical stability of the new fluoropeptidomimetics and their activity as protease inhibidors will be carried out in the near future in our group.

III. EXPERIMENTAL PROCEDURES

III.1. Synthesis of (S)-2-((R)-Fluoro(phenyl)methyl)oxirane (214)

III.1.1. Synthesis of (2S,3S)-3-Phenyl-2-tosyloxymethyloxirane[30]



Tosyl chloride (2.79 g, 14.65 mmols) dissolved in 60 mL of anhydrous CH_2Cl_2 was added over a mixture of triethylamine (3.3 mL, 22.6 mmol), and 4-DMAP (0.19 g, 1.55 mmol). Over the reaction mixture cooled at -20ºC, (2S, 3S)-3-phenyl-2, 3-epoxipropan-1-ol (2.00 g, 13.30 mmol) dissolved in 4 mL of anhydrous CH_2Cl_2 was added and the stirring was maintained for 16 h. The reaction was quenched with a tartaric acid solution 10% (3 x 5 mL), then with a saturated solution of $NaHCO_3$ (3 x 5 mL) and brine (3 x 5 mL). The organic phases were dried over anhydrous $MgSO_4$ and the solvent eliminated under reduced pressure. The crude was purified by flash chromatography, Si_2O, hexane: ethyl acetate 1:0 to 4:1. The final product was obtained as a white solid (3.33 g) in 82 % yield.

^{1}H-RMN (200 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 8.4 Hz, 2H, Ph), 7.37-7.19 (m, 7H, Ph), 4.33 (d x d, *J* = 11.4 Hz, *J* = 3.6 Hz, 1H, C*H*HOSO$_2$), 4.14 (d x d, *J* = 11.4 Hz, *J* = 5.8 Hz, 1H, CH*H*OSO$_2$), 3.75 (d, *J* = 2.2 Hz, 1H, CH-Ph), 3.24 (d x d x d, *J* = 5.8 Hz, *J* = 3.6 Hz, *J* = 2.2 Hz, 1H, CH-O), 2.45 (s, 3H, CH_3) ppm.

^{13}C-RMN (50 MHz, $CDCl_3$) δ: 145.2 (C, Ph), 135.5 (C, Ph), 132.6 (C, Ph), 130.0 (CH, Ph), 128.6 (CH, Ph), 128.5 (CH, Ph), 128.0 (CH, Ph), 125.7 (CH, Ph), 69.4 (CH_2), 58.5 (CH-O), 56.4 (CH-O), 21.7 (CH_3) ppm.

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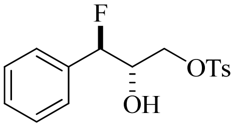
[30] Cristina Puigjaner, Doctoral Thesis **2000**.

III.1.2. Synthesis of (2S,3R)-3-Fluoro-2-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (213)[30]



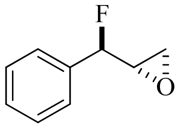
Over a solution of the epoxide (213) (3.49 g, 11.5 mmol) in 35 mL of anhydrous CH_2Cl_2 cooled to -35ºC was added drop wise $BF_3.Et_2O$ (0.49 mL, 3.83 mmol) and next the mixture was stirred for one hour. The reaction was quenched with 75 mL of a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 75 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuum. Purification by column chromatography on silica gel with hexane: ethyl acetate 9:1 to 4:1) yielded the desired product (0.096 g) in 92 % yield.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 7.66 (d x d, *J* = 6.6 Hz, *J* = 1.8 Hz, 2H, Ph), 7.26-7.14 (m, 7H, Ph), 5.35 (d x d, J_{H-F} = 46.5 Hz, *J* = 5.1 Hz, 1H, CH-F), 4.06-3.94 (m, 2H, CH_2), 3.84-3.77 (m, 1H, CH-OH), 2.34 (s, 3H, CH_3) ppm.

^{13}C-RMN (50 MHz, CD Cl_3) δ: 145.1 (C, Ph), 135.3 (d, J_{C-F} = 20.0 Hz, *C*HF), 132.2 (C, Ph), 129.9 (CH, Ph), 129.1 (d, J_{C-F} = 1.8 Hz, Ph-*C*HF), 128.7 (CH, Ph), 128.0 (CH, Ph), 126.1 (d, J_{C-F} = 7.3 Hz, Ph-*C*HF), 93.1 (d, J_{C-F} = 174.7 Hz, *C*H-F), 72.2 (d, J_{C-F} = 23.7 Hz, *C*H-OH), 69.2 (d, J_{C-F} = 6.4 Hz, CH_2), 21.6 (CH_3) ppm.

^{19}F -RMN (282 MHz, $CDCl_3$) δ: -193.1 (d x d, J_{H-F} = 46.4 Hz, J_{H-F} = 19.3 Hz, CHF) ppm.

III.1.3. Synthesis of (S)-2-((R)-Fluoro(phenyl)methyl)oxirane (214)



Monotosylated fluorodiol (3.24 g, 10.0 mmol) was dissolved in 10 mL of anhydrous THF in a flame-dried flask, and treated with 10 mL of 1 M lithium *tert*-butoxide in THF. After 30 minutes, the reaction was quenched with 20 mL of water and extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were dried (Na_2SO_4), and solvents removed *in vacuo* to afford **215** (1.52 g) as oil in quantitative yield.

$[\alpha]^{27}_{D}$ =-20.9 (c = 1.01, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.45: (5H, m, Ph), 5.13 (1H, d x d, $^3J_{HH}$ = 6,3 Hz, $^2J_{HF}$ = 47,2 Hz, C*H*F), 3.35 (1H, m, C*H*O), 2.89 (1H, d x d x d, $^4J_{HF}$ = 4.2 Hz, $^3J_{HH}$ = 4.2 Hz, $^2J_{HH}$ = 4.7 Hz, C*H*HO), 2.88 (1H, d x d x d, $^4J_{HF}$ = 1.6 Hz, $^3J_{HH}$ = 2.6 Hz, $^2J_{HH}$ = 4.8 Hz, CH*H*O) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 136,04 (d, $^2J_{CF}$ = 21.2 Hz, C, Ph), 129.07 (d, $^4J_{CF}$ = 2.2 Hz, CH, Ph), 128.66 (CH, Ph), 126.00 (d, $^3J_{CF}$ = 6.6 Hz, CH, Ph), 94.62 (d, $^1J_{CF}$ = 175.7 Hz, CHF), 53.62 (d, $^2J_{CF}$ = 27.9 Hz, *C*HO), 44.18 (d, $^3J_{CF}$ = 8.1 Hz, CH_2) ppm.

^{19}F NMR ($CDCl_3$, 470.5 MHz): δ -180,96 (d, $^2J_{FH}$ = 46.8 Hz) ppm.

MS (EI+): m/z 152 (35%, M^+), 109 (100%, C_7H_6F).

III.2. Synthesis and characterization of compounds 216 a-i

III.2.1. General procedures

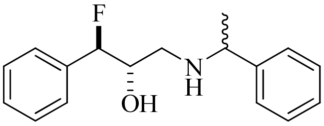
Fluoroepoxide **214** (0.082 g 0.530 mmol) and $LiClO_4$ (0.059 mg 0.54 mmol) were weighed in a microwave reactor vessel, the reagents were dissolved in 5 mL of dry THF, and purged with argon. Then the amine (0.38 mmol) was added via syringe. The mixture was heated at 75 ºC in the microwave reactor (CEM Discovery) for 1.5-3 hours. After cooling down to r.t., water was added to the vessel, and the mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried (Na_2SO_4), and the solvents removed *in vacuo*. The resulting crude was purified by flash chromatography using silica gel and eluting with hexanes: ethyl acetate mixtures of increasing polarity (9:1 to 2:1) to afford the corresponding amino alcohol.

III.2.2. Characterization

* Indicates a signal corresponding to the other diastereomer.

+* Indicates a signal that corresponds to both diastereomers (signal not separated)

III.2.1. Synthesis and characterization of (1R,2S)-1-Fluoro-1-phenyl-3-((RS)-1-phenylethylamino)propan-2-ol (216a, diastereomeric mixture)



Following the general procedure described in the anterior paragraph of these chapter, were employed *rac*-α-methylbenzylamine (50 μL, 0.38 mmol) to give the desired product (0.096 g) 92 % yield.

^{1}H NMR (CDCl$_3$, 500MHz): δ 7.2-7.4(+*) (20H, m, Ph), 5.38 (1H, d x d, $^3J_{\mathrm{HH}}$ = 5.6 Hz, $^2J_{HF}$ = 47.2 Hz, C*H*F), 5,33* (1H, d x d, $^3J_{\mathrm{HH}}$ = 6.2 Hz, $^2J_{\mathrm{HF}}$ = 47.5 Hz, C*H*F), 3.96* (1H, m, C*H*OH), 3.85 (1H, m, C*H*OH), 3.68 (1H, q, $^3J_{\mathrm{HH}}$ = 6.6 Hz, C*H*CH3), 3.66* (1H, q, $^3J_{\mathrm{HH}}$ = 6,7 Hz, C*H*CH$_3$), 2.55 (1H, d x d, $^2J_{\mathrm{HH}}$ = 12.3 Hz, $^3J_{\mathrm{HH}}$ = 6.7 Hz, CH*H*), 2.50 (1H, d x d, $^2J_{\mathrm{HH}}$ = 12.3 Hz, $^3J_{\mathrm{HH}}$ = 4.0 Hz, C*H*H), 2.49* (1H, d x d, $^2J_{\mathrm{HH}}$ = 12.3 Hz, $^3J_{\mathrm{HH}}$ = 4.0 Hz, C*H*H), 2.40* (1H, d x d, $^2J_{\mathrm{HH}}$ = 12.3 Hz, $^3J_{\mathrm{HH}}$ = 7.1 Hz, CH*H*), 2.18 (2H, s, N*H*, O*H*), 1.33* (3H, d, $^3J_{\mathrm{HH}}$ = 6.7 Hz, C*H*$_3$), 1.31 (3H, d, $^3J_{\mathrm{HH}}$ = 6.6 Hz, C*H*$_3$) ppm.

^{13}C NMR (CDCl$_3$, 125 MHz): δ 145.06 (*C*, Ph), 144.84* (*C*, Ph), 136.71 (d, $^2J_{\mathrm{CF}}$ = 20.3 Hz, *C*, Ph), 136.55* (d, $^2J_{\mathrm{CF}}$ = 20.3 Hz, *C*, Ph), 128.81 (d, $^4J_{\mathrm{CF}}$ = 1.6 Hz, *C*H, Ph); 128.74* (d, $^4J_{\mathrm{CF}}$ = 1.5 Hz, *C*H, Ph), 128.49* (d, $^3J_{\mathrm{CF}}$ = 5.1 Hz, *C*H, Ph), 128.44 (d, $^3J_{\mathrm{CF}}$ = 4.9 Hz, *C*H, Ph), 127.08 (*C*H, Ph), 126.55*(*C*H, Ph), 126.50(*C*H, Ph), 126.46*(*C*H, Ph), 126.40(*C*H, Ph), 126.33(*C*H, Ph), 126.27*(*C*H, Ph), 95.82 (d, $^1J_{\mathrm{CF}}$ = 173.0 Hz, ***C***HF); 95.68* (d, $^1J_{\mathrm{CF}}$ = 173.6 Hz, ***C***HF), 72.78 (d, $^2J_{\mathrm{CF}}$ = 22.6 Hz, ***C***HOH), 72.60* (d, $^2\mathrm{J}_{\mathrm{CF}}$ = 21.4 Hz, ***C***HOH), 58.44(*C*HCH$_3$), 58.13*58.44(*C*HCH$_3$), 48.63 (d, $^3J_{\mathrm{CF}}$ = 5.2 Hz, *C*H$_2$), 48.26* (d, $^3J_{\mathrm{CF}}$ = 5.5 Hz, *C*H$_2$), 24.20* (*C*H$_3$), 23.88 (*C*H$_3$) ppm.

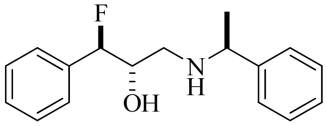
^{19}F NMR (CDCl$_3$, 470.5 MHz): δ -186.84* (d x d, $^2J_{FH}$ = 47.3 Hz, $^3J_{FH}$ = 17.2 Hz), -188.80 (d x d, $^2J_{\mathrm{FH}}$ = 47.0 Hz, $^3J_{\mathrm{FH}}$ = 18.3 Hz) ppm.

HRMS (EI+): m/z found: 273.1524 (M+), calculated for C17H20NOF: 273.1529.

HPLC (column Zorbax RX-SIL, eluent hexane: 2-propanol (0.1% Et2NH) 99:1, flow

1.0 ml/min), tR$_{\text{diastereomer “3R”}}$= 14.6 min; tR$_{\text{diastereomer “3S”}}$= 16.6 min.

*III.2.2. Synthesis and characterization of (1R,2S)-1-Fluoro-1-phenyl-3-((S)-1-phenylethylamino)propan-2-ol (**216a**)*



Following the general procedure described in the anterior paragraph of these chapter, were employed *(S)*-α-methylbenzylamine (50 µL, 0.38 mmol) to give the desired product (0.096 g) 92 % yield.

$[\alpha]^{27}_D$ =-56.5 (c = 0.39, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400MHz) δ: 7.20-7.34 (10H, m, Ph), 5.33 (1H, d x d, $^3J_{HH}$ = 6.2 Hz, $^2J_{HF}$ = 47.5 Hz, C*H*F), 3.97 (1H, m, C*H*OH), 3.66 (1H, q, $^3J_{HH}$ = 6.6 Hz, C*H*CH3), 2.50 (1H, d x d, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.0 Hz, C*H*H), 2.40 (1H, d x d, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 7.1 Hz, CH*H*), 2.27 (2H, bs, N*H*, O*H*), 1.33 (3H, d, $^3J_{HH}$ = 6.6 Hz, CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.66 (*C*, Ph) , 136.48 (d, $^2J_{CF}$ = 20.4 Hz, *C*, Ph), 128.77 (d, $^4J_{CF}$ = 2.0 Hz, *C*H, Ph), 128.44 (d, $^3J_{CF}$ = 5.1 Hz, *C*H, Ph), 127.08 (*C*H, Ph), 126.52 (*C*H, Ph), 126.41 (*C*H, Ph), 126.34 (*C*H, Ph), 95.74 (d, $^1J_{CF}$ = 173.5 Hz, ***C***HF), 72.52 (d, $^2J_{CF}$ = 22.7 Hz, ***C***HOH), 58.12 (*C*HCH_3), 48.21 (d, $^3J_{CF}$ = 5.3 Hz, *C*H_2), 24.12 (*C*H_3) ppm.

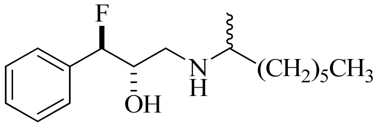
^{19}F NMR ($CDCl_3$, 470.5 MHz) δ: -186,84 (d x d, $^2J_{FH}$ = 47.4 Hz, $^3J_{FH}$ = 17.0 Hz) ppm.

IR (neat, ATR) ν : 3299, 3148, 2915, 2863 (cm^{-1}).

HRMS (EI$^+$): m/z found: 273.1519 (M$^+$), calculated for $C_{17}H_{20}NOF$: 273.1529.

HPLC (column Zorbax RX-SIL, eluent hexane: 2-propanol (0.1% Et2NH) 99:1, flor 1.0 ml/min), t_R= 17.0 min.

*III.2.3. Synthesis and characterization of (1R, 2S)-1-fluoro-3-(2'-octylamino)-1-phenylpropan-2-ol (**216b**, diastereomeric mixture)*



Following the general procedure described in the anterior paragraph of these chapter, were employed *rac*-2-octanamine (64 µL, 0.38 mmol) to give the desired product (0.053 g) 50 % yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.18(+*) (10H, m, Ph), 5.30(+*) (2H, d x d, $^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 5.84 Hz C*H*F), 3.89(+*) (2H, m, C*H*OH), 2.51(+*) (10H, m, CH_2NHC*H*, O*H*), 1.17(+*) (20H, m (CH_2)$_5$), 0.9* (3H, d, $^3J_{HH}$ = 6.43 Hz, CH_3CH), 0.89 (3H, d, $^3J_{HH}$ H = 6.43 Hz, CH_3CH), 0.83(+*) (6H, m, C$H_3$$CH_2$) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ:136.74 (*C*, Ph), 136.57* (*C*, Ph), 128.77 (*C*H, Ph), 128.47(+*) (*C*H, Ph), 126.36 (*C*H, Ph), 126.31* (*C*H, Ph), 95.80* (d, $^1J_{CF}$ = 174.1Hz, ***C***HF) , 95.78 (d, $^1J_{CF}$ = 174 Hz, ***C***HF), 72.4* (d, $^2J_{CF}$ = 23.5 Hz, ***C***HOH), 72.03 (d, $^2J_{CF}$ = 22.7 Hz, ***C***HOH), 53.50 (*C*HCH_3), 53.08* (*CH*CH_3), 47.75*(d, $^3J_{CF}$ = 5.5 Hz, *C*H_2), 47.46(d, $^3J_{CF}$ = 5.5 Hz, *C*H_2), 37.03* (*C*H_2), 36.80 (*C*H_2), 31.80(+*) (*C*H_2), 29.38(+*) (*C*H_2), 25.95* (*C*H_2), 25.85 (*C*H_2), 22.58(+*) (*C*H_2), 20.33* (*C*H_2), 20.06 (*C*H_2), 14.05(+*) (*C*H_2) ppm.

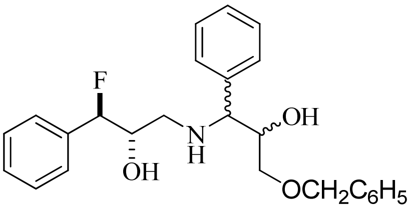
^{19}F NMR ($CDCl_3$, 470.5 MHz) δ:-187.63* (d x d, $^2J_{HF}$ = 46.3 Hz, $^3J_{HF}$ = 17.7 Hz), -187.72 (d x d, $^2J_{HF}$ = 46.3 Hz, $^3J_{HF}$ = 17.7 Hz) ppm.

IR ν: 3500, 3176, 3033, 2925, 2854, 1454, 1085, 1073 cm^{-1}

HRMS (CI+): m/z found: 281.2148(M^+), calculated for $C_{17}H_{28}FNO$: 281,2155.

HPLC (column Zorbaz RX-SIL, eluent hexane: 2-propanol (0.1% Et2NH, 99:1, flow 1,0 ml/min), $tR_{(rac)}$= 15 min.

*III.2.4. Synthesis and characterization of 3-(3’-benzyloxy-2’-hydroxy-1’-phenylpropyl-1’-amino)-(1R, 2S)-1-fluoro-1- phenylpropan-2-ol (**216c**, diastereomeric mixture)*



Following the general procedure described in the anterior paragraph of these chapter, were employed 1-amino-3-benzoyloxy-1-phenyl-2-propanol (0.098 g, 0.38 mmol) to give the desired product (0.115 g) 74 % yield.

^{1}H NMR (CDCl$_3$, 500 MHz) δ : 7.35-7.19(+*) (30H, m, Ph), 5.28* (1H, d x d, $^2J_{HF}$ = 47.37 Hz, $^3J_{HH}$ = 6.11 Hz C*H*F), 5.42 (1H, d x d, $^2J_{HF}$ = 47 Hz, $^3J_{HH}$ = 6 Hz C*H*F), 4.43* (2H, s, OCH_2Ph), 4.45 (2H, s, OCH_2Ph), 4.0* (1H, m, *CH*OH(CF)), 3.97(+*) (2H, q, $^3J_{HH}$ = 5.13 Hz C*H*OH(CHPh)), 3.9 (1H, m, C*H*OH(CF)), 3.75(+*) (2H, m, C*H*NHPh), 3.35(+*) (4H, m, CH_2OCH$_2$Ph), 2.5(+*) (4H, m, CH_2NH) ppm.

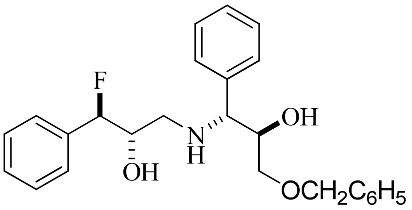
^{13}C NMR (CDCl$_3$, 125 MHz) δ : 139.24 (*C*, Ph), 139* (*C*, Ph), 137.8(+*) (*C*, Ph), 136.42(+*)(d, $^2J_{CF}$ =20.21 Hz, *C*, Ph), 128.9*(*C*H, Ph), 128.80 (*C*H, Ph), 128.51(+*) (*C*H, Ph), 128.46(+*) (*C*H, Ph), 128.41(+*) (*C*H, Ph), 127.74(+*) (*C*H, Ph), 127.68(+*) (*C*H, Ph), 127.51(+*) (*C*H, Ph), 126.44* (*C*H, Ph), 126.39* (*C*H, Ph), 126.35 (*C*H, Ph), 126.3 (*C*H, Ph), 95.8* (d, $^1J_{CF}$ = 172.75 Hz, ***C**H*F), 95.4 (d, $^1J_{CF}$ = 173.64 Hz, ***C**H*F), 73.5(+*) (O*C*H_2Ph), 73.39 (d, $^2J_{CF}$ =22.58 Hz, *CH*OH(CF)), 72.80* (d, $^2J_{CF}$ = 22.58 Hz, *CH*OH(CF)), 72.58(+*) (C*H*OH(CHPh)), 71.42(+*) (*C*H_2Ph), 65.38(+*) (*CH*Ph), 64.81(+*) (*CH*Ph), 48.52 (d, $^3J_{CF}$ = 5.4 Hz, *C*H_2NH), 48.27* (d, $^3J_{CF}$ = 5.5 Hz, *C*H_2NH) ppm.

^{19}F NMR (CDCl$_3$, 470.5 MHz) δ: -185.9* (d x d, $^2J_{HF}$ = 48.5 Hz, $^3J_{HF}$ = 17.8 Hz), -183.51 (d x d, $^2J_{HF}$ = 47.5 Hz, $^3J_{HF}$ = 17 Hz) ppm.

HRMS (ES+): m/z found (M+H): 410.2126, calculated for $C_{25}H_{29}FNO_3$: 410.2131.

HPLC (column Zorbaz RX-SIL, eluent hexane: 2-propanol (0,1% Et_2NH) 90:10 to 99:1 and 20 min isocratic, flow 1,0 ml/min,) $tR_{(\text{ diastereomer R})}$=12.6, $tR_{(\text{diastereomer S})}$ = 16.0 min.

III.2.5. Synthesis and characterization of 3-(3'-benzyloxy-2'-hydroxy-1'-phenylpropyl-1'-amino)-(1R, 2S)-1-fluoro-1-phenylpropan-2-ol, (1R, 2R), ***216c***



Following the general procedure described in the anterior paragraph of these chapter, were employed (1R, 2R)-1-amino-3-benzoyloxy-1-phenyl-2-propanol (0.098 g, 0.38 mmol) to give the desired product (0.117 g) 75 % yield.

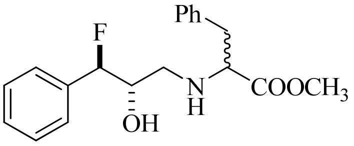
$[\alpha]^{25}_{D}$ = -31.43(c = 0.51, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.34-7.19 (15H, m, Ph), 5.28 (1H, d x d, $^2J_{HF}$ = 47.4 Hz, $^3J_{HH}$ = 6.11 Hz C*H*F), 4.43 (2H, d x d, $^2J_{HH}$ = 11.5 Hz, OC*H₂*Ph), 4.01 (1H, m, C*H*OH(CF)), 3.975 (1H, q, $^3J_{HH}$ = 5.13 Hz C*H*OH(CHPh)), 3.75 (1H, d, $^3J_{HH}$ =4.89 Hz, C*H*NH), 3.34 (2H, m, C*H₂*NH), 2.5 (1H, d x d, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 7.5 Hz, C*H*HOCH₂Ph), 2.38 (1H, d x d, $^2J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 3.6 Hz, CH*H*OCH₂Ph) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 139 (*C*, Ph), 137.8 (*C*, Ph), 136.4 (d, $^2J_{CF}$ = 20.21 Hz, *C*, Ph), 128.93 (*C*H, Ph), 128.53 (*C*H, Ph), 128.46 (*C*H, Ph),128.4 (*C*H, Ph), 127.80 (*C*H, Ph), 127.74 (*C*H, Ph), 127.61 (*C*H, Ph), 126.5 (*C*H, Ph), 126.4 (*C*H, Ph), 95.80 (d, $^1J_{CF}$ = 173.64 Hz, ***C***HF), 73.52 (O*C*H₂Ph), 72.8 (d, $^2J_{CF}$

= 22.58 Hz, *C*HOH(CF)), 72.51 (CHOH(CHPh)), 71.4 (*C*H_2Ph), 64.81 (*C*HPh), 48.27(d, $^3J_{CF}$ = 5.51 Hz, *C*H_2NH).
^{19}F NMR ($CDCl_3$, 470,5 MHz) δ: -185.51 (d x d, $^2J_{HF}$ = 48.5 Hz, $^3J_{HF}$ = 17.7 Hz) ppm.
IR (neat, ATR) ν:3375, 3305, 3030, 1452, 1260cm^{-1}.
HRMS (ES+): m/z found: 410.2135(M+H), calculated for $C_{25}H_{29}FNO_3$: 410.2131.
HPLC (column Zorbaz RX-SIL, eluent hexane: 2-propanol (0,1% Et_2NH) 90:10 to 99:1 and 20 min isocratic, flow 1,0 ml/min,) tR$_{\text{(diastereomer R)}}$=12.6 min.

*III.2.6. Synthesis and characterization of (2S,3R)-1N-((DL)-phenylalaninate methyl ester)-3-fluoro-3-phenylpropan-2-ol (**216d**, diastereomeric mixture)*



Following the general procedure described in the anterior paragraph of these chapter, were employed DL-phenylalaninate methyl ester (0.068 g, 0.38 mmol) to give the desired product (0.088 g) 70 % yield.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.3-7.05 (+*) (20H, m, Ph), 5.31* (1H, d x d, $^2J_{HF}$ = 47.6 Hz, $^3J_{HH}$ = 6.1 Hz C*HF*), 5.22 (1H, d x d, $^2J_{HF}$ = 47.1 Hz, $^3J_{HH}$ = 5.3 Hz C*H*F), 3.79 (+*) (2H, m, C*H*OH), 3.59* (3H, s, CH_3), 3.57 (3H, s, CH_3), 3.38* (1H, t, $^3J_{HH}$ = 7.3 Hz, CHNH), 3.29 (1H, t, $^3J_{HH}$ = 7.9 Hz CHNH) 2.94 (+*) (m, 8H, CH2) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174.7*(*C*=O), 174.53 (*C*=O), 137.42 (*C*, Ph), 137.05* (*C*, Ph), 136.54* (d, $^2J_{CF}$ = 22.0 Hz, *C*, Ph), 136.5 (d, , $^2J_{CF}$ = 19.8 Hz, *C*, Ph), 129.1* (*C*H, Ph), 129.25 (*C*H, Ph), 128.78* (*C*H, Ph), 128.74 (*C*H, Ph), 128.49* (*C*H, Ph), 128.43 (*C*H, Ph), 128.86* (*C*H, Ph), 126.82, (+*)(*C*H, Ph), 126.32 (*C*H, Ph), 126.26 (*C*H, Ph), 126.25 (*C*H, Ph), 95.36* (d, $^1J_{CF}$ = 174.8 Hz,

*C*HF), 95.25 (d, $^{1}J_{CF}$ = 174.1 Hz, ***C***HF), 73.28 (d, $^{2}J_{CF}$ = 22.8 Hz, *C*HOH), 72.07* (d, $^{2}J_{CF}$ = 24.2 Hz, *C*HOH), 63.39 (*C*HNH), 62.69* (CHNH), 51.83 (*C*H_3), 51.79* (*C*H_3), 49.04 (d, $^{3}J_{CF}$ = 6.6 Hz, *C*H_2), 48.68(d, $^{3}J_{CF}$ = 6.0 Hz, *C*H_2), 39.74* (*C*H_2), 39.7 (*C*H_2) ppm.

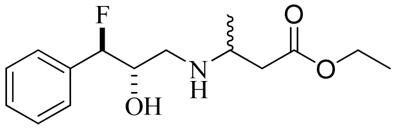
^{19}F NMR ($CDCl_3$, 470.73 MHz): δ -188.9* (d x d, $^{2}J_{FH}$ = 47.1 Hz, $^{3}J_{FH}$ = 16.3 Hz), -189.08 (dd, $^{2}J_{FH}$ = 47.8 Hz, $^{3}J_{FH}$ = 19.2 Hz) ppm.

IR (neat, ATR) ν : 3400, 2875, 2750, 1495cm^{-1}

HRMS (ES+): m/z found: 332.165 (M+H); calculated for $C_{19}H_{23}NO_3F$: 332.166.

HPLC/MASS (column Waters Atlantis dC18, 3um, 2.1*150mm, eluent MeOH/H2O; 5% to 100% in 30 min hold for 15 min, flow 0.2ml/min, injection volume 10ul, MS detection +ve ESI, extracted ion : (M+Na) tR$_{\text{(diastereomer R.)}}$= 25.38 min, tR$_{\text{(diastereomer S.)}}$= 25.98 min.

*III.2.7. Synthesis and characterization of (2S,3R)-1-N-(ethyl 3'-aminobutanoate)-3-fluoro-3-phenylpropan-2-ol (**216e**, diastereomeric mixture)*



Following the general procedure described in the anterior paragraph of these chapter, were employed 3-aminobutanoate (0.050 g, 0.38 mmol) to give the desired product (0.078 g) 72 % yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.4-7.26 (+*) (10H, m, Ph), 5.38* (1H, d x d, $^{2}J_{HF}$ = 46.9 Hz, $^{3}J_{HH}$ = 5.9 Hz C*H*F), 5.37 (1H, d x d, $^{2}J_{HF}$ = 47.7 Hz, $^{3}J_{HH}$ = 5.9 Hz C*H*F), 4.12* (2H, q, $^{3}J_{HH}$ = 7.1 Hz, C*H*$_2$CH$_3$), 4.11 (2H, q, $^{3}J_{HH}$ = 7.1 Hz, C*H*$_2$CH$_3$), 3.94 (+*) (m, 2H, C*H*OH), 3.03 (+*) (m, 2H, $^{3}J_{HH}$ = 6.4 Hz C*H*NH), 2.57 (+*) (m, 4H, C*H*$_2$CO), 2.34 (+*) (m, 8H, C*H*$_2$NH, N*H*, O*H*), 1.25* (t, 3H,

$^3J_{HH}$ = 7.0 Hz CH_3CH$_2$,), 1.24 (t, 3H, $^3J_{HH}$ = 7.2 Hz CH_3CH$_2$), 1.07* (d, 3H, $^3J_{HH}$ = 6.3 Hz CH_3CHNH), 1.05 (d, 3H, $^3J_{HH}$ = 5.7 Hz CH_3CHNH) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz) δ: 172.19 (*C*=O), 172.16* (*C*=O), 136.87 (*C*, Ph), 136.67* (*C*, Ph), 128.76 (+*) (*C*H, Ph), 128.47 (+*) (*C*H, Ph), 126.42 (*C*H, Ph), 126.35* (*C*H, Ph), 95.85 (d, $^1J_{CF}$ = 174.1 Hz, *C*HF), 95.75* (d, $^1J_{CF}$ = 173.5 Hz, *C*HF), 72.76 * (d, $^2J_{CF}$ = 22.8 Hz, *C*HOH), 72.33 (d, $^2J_{CF}$ = 22.8 Hz, *C*HOH), 60.4 (+*) (*C*H$_2$CH$_3$), 50.56* (*C*HNH), 50.04 (*C*HNH), 47.86* (d, $^3J_{CF}$ = 5.6 Hz, *C*H$_2$NH), 47.61 (d, $^3J_{CF}$ = 5.6 Hz, *C*H$_2$NH), 41.68 (*C*H$_2$CO), 41.51* (*C*H$_2$CO), 20.54* (*C*H$_3$), 20.27 (*C*H$_3$), 14.19* (*C*H$_3$), 14.18 (*C*H$_3$) ppm.

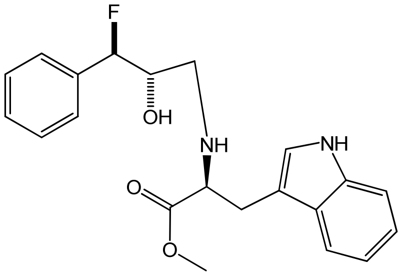
^{19}F NMR (CDCl$_3$, 376.47 MHz) δ: -186.95 (d x d, $^2J_{FH}$ = 47.3 Hz, $^2J_{FH}$ = 16.7 Hz), -187.1* (d x d, $^2J_{FH}$ = 47.3 Hz, $^2J_{FH}$ = 16.8. Hz) ppm.

HRMS (ES+): m/z found: 284.165 (M+H); calculated for $C_{15}H_{23}NO_3F$: 284.166.

HPLC (column Zorbaz RX-SIL, eluent hexane: 2-propanol (0.1% Et$_2$NH) 99:1, flow

1,0 mL/min, tR$_{(diastereomers)}$ = 22.8 min, 23.6 min.

*III.2.8. Synthesis and characterization of (S)-methyl 2-((2S,3R)-3-fluoro-2-hydroxy-3-phenylpropylamino)-3-(1H-indol-3-yl)propanoate (**216f**)*

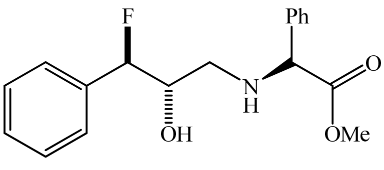


Following the general procedure described in the anterior paragraph of these chapter, were employed L-tryptophan methyl ester (0.86g, 3.95 mmol) to give the desired product (0.85 g) 60 % yield.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 8.25 (1H, bs, NH), 7.55-6.94 (10H, m, Ph), 5.27 (1H, d x d, $^3J_{HH}$ = 6.3 Hz, $^2J_{HF}$ = 46.3 Hz, C*H*F), 3.89-3.80 (1H, m, C*H*OH), 3.61 (3H, s, CH3), 3.54 (1H, dxd, $^3J_{HH}$ = 5.59 Hz, $^3J_{HH}$ = 5.94 Hz, C*H*NH), 3.15 (1H, d x d, $^2J_{HH}$ = 13 Hz, $^3J_{HH}$ = 5.0 Hz, C*H*H), 3.03 (1H, d x d, $^2J_{HH}$ = 13 Hz, $^3J_{HH}$ = 7.1 Hz, CH*H*), 2.70 (2H, bs, N*H*, O*H*), 2.64 (1H, d x d, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 7.8 Hz, C*H*H), 2.44 (1H, d x d, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 4.5 Hz, CH*H*) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz) δ: 175 (*CO*), 136.4 (d, $^2J_{CF}$ = 20.21 Hz, *C*, Ph), 136.1 (2*C*, Ph), 128.7 (*C*H, Ph), 128.4 (*C*, Ph), 12.4 (*C*H, Ph), 126.2 (d, $^3J_{CF}$ = 7.1 Hz *C*H, Ph), 122.8 (*C*H, Ph), 121.9 (*C*H, Ph), 119.3 (*C*H, Ph), 118.4 (*C*H, Ph), 111.2 (*C*H, Ph), 110.8 (*C*H, Ph), 95.40 (d, $^1J_{CF}$ = 174.29 Hz, ***C***HF), 72.0 (d, $^2J_{CF}$ = 24.3 Hz, *C*HOH(CF)), 71.7 (*C*HN), 51.8 (*C*H_3), 48.73 (d, $^3J_{CF}$ = 5.33 Hz, *C*H_2), 29.19 (CH_2) ppm.

HRMS (HRMS): m/z found: 371.1762 (M+H); calculated for $C_{21}H_{24}N_2O_3F$: 371.1771.

*III.2.9. Synthesis and characterization of (R)-methyl 2-((2S,3R)-3-fluoro-2-hydroxy-3-phenylpropylamino)-2-phenylacetate (**216g**)*



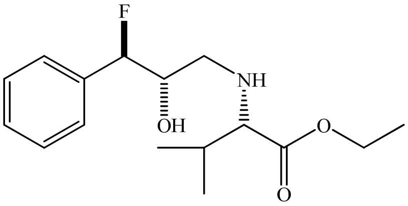
Following the general procedure described in the anterior paragraph of these chapter, were employed L-Ph-glycine- me ester (0.32g, 0.054 mmol) to give the desired product (0.079 g) 76 % yield.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 7.30-7.16 (10H, m, Ph), 5.30 (1H, d x d, $^3J_{HH}$ = 6.3 Hz, $^2J_{HF}$ = 46.3 Hz, C*H*F), 4.22 (1H, CH), 3.89-3.80 (1H, m, C*H*OH), 3.61

(3H, s, CH3), 3.54 (1H, dxd, $^3J_{HH}$ = 5.59 Hz, $^3J_{HH}$ = 5.94 Hz, C*H*NH), 3.82-3.93 (1H, m, CHOH), 3.58 (3H, s, OMe), 2.57-2.43 (2H, CH_2) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 173.2 (*CO*), 136.6 (d, $^2J_{CF}$ = 20.2 Hz, *C*, Ph), 128.8 (*C*H, Ph), 128.5 (*CH*, Ph), 128.2 (*C*H, Ph), 127.4 (*C*H, Ph), 127.3 (*C*H, Ph), 126.36 (d, $^3J_{CF}$ = 7Hz *C*H, Ph), 95.52 (d, $^1J_{CF}$ = 173.9 Hz, ***C***HF), 72.9 (d, $^2J_{CF}$ = 22.9 Hz, *C*HOH(CF)), 65.47 (CHN), 52.3 (CH_3), 48.62 (CH_2) ppm.

*III.2.10. Synthesis and characterization of (S)-ethyl 2-((2S,3R)-3-fluoro-2-hydroxy-3-phenylpropylamino)-3-methylbutanoate (**216h**)*



Following the general procedure described in the anterior paragraph of these chapter, were employed L-valine ethyl ester (0.14g, 0.99 mmol) to give the desired product (0.185 g) 63 % yield.

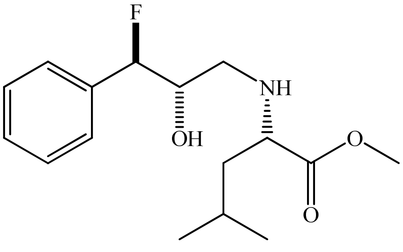
$[\alpha]^{25}_D$ = -11.20. (c = 0.51, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400MHz) δ: 7,38-7,26(m,5H,Ar), 5,42(1H,dxd, $^2J_{HF}$ =46,69, $^3J_{HF}$ =5,23,C-F), 4,21(m, 2H,CH2NH), 3,98(m,1H, CHOH) 2,91(d,1H,CH-NH), 2,77(dxd,1H,J=7,4, J=12,4,CH2(CH3)), 2,42(dxd, 1H, CH2(CH3), 1,93 (m,1H, CH((CH3)2),1,261(t,3H,J=7,14,J=7,12, CH3(CH2)), 0,92(d, 3H, J=6,7, CH3), 0,90(d, J=6,8,3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174,5(*C*=O), 136,7(d, 1C, J=20,507, *C*Ar-CF), 128,6, 128,6, 128,4, 126,2, 126,1 (5*C*, Ph) 96,2(d, J=174,707, *C*-F), 71,7(d,J=22,779, *C*-OH), 66,9(*C*H-NH), 60,4(*C*H_2-NH), 49,0(*C*H_2-(CH_3)), 31,4(*C*H-((CH_3)$_2$), 19,3(*C*H_3-(CH_2)), 18,3(*C*H_3-(CH)), 14,2(*C*H_3-(CH)). ppm.

HRMS (HRMS): m/z found: 298.1818 (M+H); calculated for $C_{16}H_{25}NO_3$ F 298.1810.

*IV.2.11. Synthesis and characterization of (S)-methyl 2-((2S,3R)-3-fluoro-2-hydroxy-3-phenylpropylamino)-4-methylpentanoate (**216i**)*



$[\alpha]^{25}_{D}$ = -10.7 (c = 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400MHz) δ: 7.397-7.236(m, 5H, Ar) 5.408(dxd, $^3J_{HF}$ =5,47, $^2J_{HF}$ =46,91, 1H, CH-F), 3,978(m, 1H, CH-OH), 3,679(s,3H, O-CH3) 3,235(dxd, $^3J_{HH}$ =6,61, $^3J_{HH}$ =7,89, 1H, CH-NH), 2,707(dxd, J=7,42, J=12,391, 1H, CH2-NH), 2,446(dxd, J=4,1, J=12,359, 1H, CH2-NH), 1,754(m, 1H, CH-(Me)2, 1,482(m, 2H, CH2-CHMe2), 0,908(dxd, J=6,65, J=6,14, 6H, 2xMe) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ:175,9(*C*=O), 136,7(d, 1C, J=19.8, *C*Ar-CF), 128,7, 128,6, 128,4, 126,3 (5*C*, Ph), 96,5(d, J=174,82, *C*-F), 72,3(d, J=22,68, *C*-OH), 59.7 (*C*H-NH), 48.8 (*C*H-((CH_3)$_2$), 42.69 (*C*H_2-NH), 24.8 (O *C*H_3) 22.7 (*C*H_3-(CH)), 22.1(*C*H_3-(CH))ppm.

HRMS (HRMS): m/z found: 298.1818 (M+H); calculated for $C_{16}H_{25}NO_3$ F 298.1819.

CONCLUSIONS

1. A new family of phosphinooxazolines and their π-allyl palladium complexes derived from modular, enantiopure β-amino alcohols has been prepared. These palladium complexes have been prepared according to the following synthetic steps: i) Aminolysis of Sharpless epoxyethers followed by *N*-acylation, ii) *O*-Mesylation followed by base-mediated cyclization; iii) Nucleophilic displacement of the fluorine group with potassium diphenylphosphide and iv) formation of the corresponding π-allyl palladium complexes. The $[Pd(\eta^3\text{-allyl})(PHOX)]PF_6$ have been fully characterized and NMR studies have revealed that a π–σ–π isomerization process takes place by selective dissociation of the Pd-C *trans* to phosphorous. Furthermore, the synthetic methodology developed in this PhD thesis paves the way to the preparation of polymer bound chiral phosphinooxazolines.

2. The $[Pd(\eta^3\text{-allyl})(PHOX)]PF_6$ complexes prepared in this work have turned out to be very efficient catalysts in the asymmetric alkylation of several allyl acetates with malonic ester-derived nucleophiles. The alkoxymethyl moiety in the $[Pd(\eta^3\text{-allyl})(PHOX)]PF_6$ complexes (the substituent at C5 of the oxazoline ring) has turned out to be key in determining the stereoselectivity of the allylic alkylation. The optimal ligand, among those in the studied series, bears a non bulky methoxy substituent. The degree of stereoinduction achieved with the catalytic systems developed in this work was amongst the highest with respect to the ones collected in the literature for phosphinooxazolines.

3. Microwave activated allylic alkylation reaction has turned out to be extremely efficient in terms of conversion and selectivity in the case of hindered substrates and should be considered as the method of choice. From a practical point of view, the “lead catalysts” presents a very

attractive temperature-selectivity profile, thus allowing performing the reaction over a broad range of temperatures in extremely short reaction times.

4. Our library of Pd-PHOX complexes has turned out to be very efficient in the asymmetric amination of several allylic substrates with a number of *N*-nucleophiles. Again, best results in terms of enantioselectivity were achieved with the [Pd(η^3-allyl)(PHOX)]PF_6 complex bearing a non bulky methoxymethyl substuent at C5 of the oxazoline ring. The degree of stereoinduction achieved with the lead catalyst was amongst the highest with respect to the ones collected in the literature for phosphinooxazolines.

5. “Neat” amination reaction conditions (*i.e.* 3 eq. BSA, the corresponding *N*-nucleophile, catalytic amounts of [Pd(η^3-allyl)(PHOX)]PF_6 and lithium or potassium acetate) turned out to be extremely efficient in terms of rate, conversion and selectivity for all substrates tested and should be considered as the method of choice.

6. We have described also a new, synthetic, yet enantiopure, chiral resolution reagent, (*S*)-2-[(*R*)-fluoro(phenyl)methyl]oxirane, readily obtained from enantiopure (*2S,3S*) phenylglycidol, that reacts with a variety of α-chiral primary and secondary amines in a straightforward manner through a regioselective ring-opening. Diastereomeric products are easily identified and quantified by ^{19}F, ^{1}H, and ^{13}C NMR and by HPLC, which makes this fluorinated compound a most versatile reagent for the analysis of scalemic mixtures of amines.

7. (*S*)-2-[(*R*)-fluoro(phenyl)methyl]oxirane was employed successfully for the preparation of a new class of fluorine-containing peptidomimetics by

epoxide ring-opening in fluoroepoxide **214** with the esters derived from enantiopure amino acids.

ANNEXE

1. X-Ray Structure for **49a**

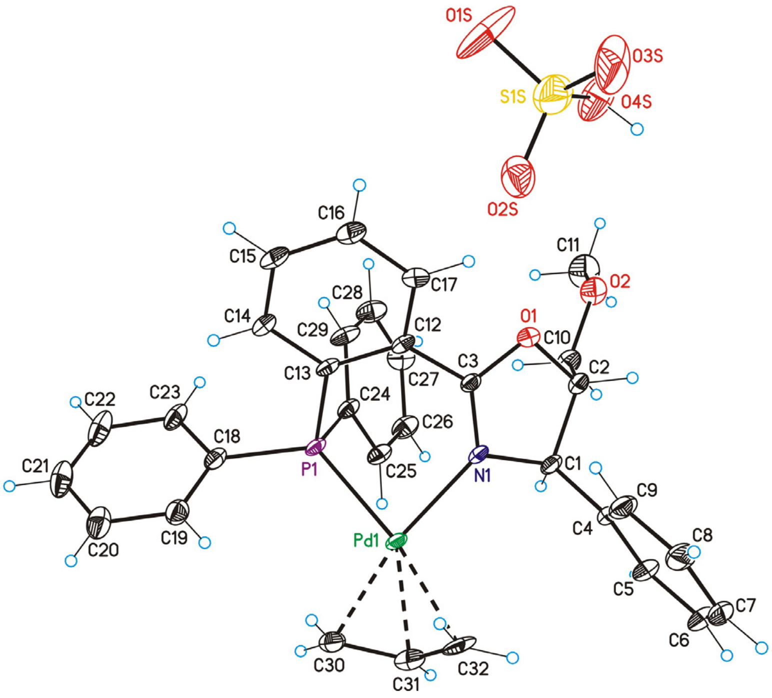


Table 1. Crystal data and structure refinement for **49a**.

Identification code	**49a**	
Empirical formula	C32 H32 N O6 P Pd S	
Formula weight	696.02	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.4197(11) Å	α= 90°.
	b = 16.032(2) Å	β= 96.836(2)°.
	c = 10.0162(12) Å	γ = 90°.
Volume	1501.9(3) Å^3	
Z	2	
Density (calculated)	1.539 Mg/m^3	
Absorption coefficient	0.786 mm^{-1}	
F(000)	712	
Crystal size	0.20 x 0.05 x 0.02 mm^3	

Theta range for data collection	2.81 to 39.06°.
Index ranges	-14<=h<=16, -19<=k<=27, -12<=l<=17
Reflections collected	28292
Independent reflections	14475 [R(int) = 0.0412]
Completeness to theta = 39.06°	96.5 %
Absorption correction	SADABS (Bruker-Nonius)
Max. and min. transmission	0.9844 and 0.8586
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	14475 / 13 / 400
Goodness-of-fit on F^2	1.099
Final R indices [I>2sigma(I)]	R1 = 0.0637, wR2 = 0.1653
R indices (all data)	R1 = 0.0756, wR2 = 0.1750
Absolute structure parameter	0.04(3)
Largest diff. peak and hole	4.541 and -4.060 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for DP122b_0m.

Pd(1)-N(1)	2.109(3)
Pd(1)-C(30)	2.125(4)
Pd(1)-C(31)	2.137(7)
Pd(1)-C(31')	2.206(8)
Pd(1)-C(32)	2.217(7)
Pd(1)-C(32')	2.225(8)
Pd(1)-P(1)	2.2892(8)
N(1)-C(3)	1.296(4)
N(1)-C(1)	1.487(4)
P(1)-C(18)	1.818(4)
P(1)-C(24)	1.831(3)
P(1)-C(13)	1.843(4)
O(1)-C(3)	1.345(4)
O(1)-C(2)	1.467(4)
C(1)-C(4)	1.515(4)
C(1)-C(2)	1.549(5)
O(2)-C(10)	1.411(5)
O(2)-C(11)	1.420(5)
C(2)-C(10)	1.509(5)
C(3)-C(12)	1.480(4)
C(4)-C(5)	1.395(5)
C(4)-C(9)	1.395(6)

C(5)-C(6)	1.414(6)
C(6)-C(7)	1.362(9)
C(7)-C(8)	1.401(7)
C(8)-C(9)	1.402(6)
C(12)-C(17)	1.398(5)
C(12)-C(13)	1.408(5)
C(13)-C(14)	1.397(4)
C(14)-C(15)	1.408(5)
C(15)-C(16)	1.394(7)
C(16)-C(17)	1.403(5)
C(18)-C(19)	1.399(6)
C(18)-C(23)	1.406(5)
C(19)-C(20)	1.398(6)
C(20)-C(21)	1.401(7)
C(21)-C(22)	1.377(8)
C(22)-C(23)	1.402(7)
C(24)-C(29)	1.396(5)
C(24)-C(25)	1.404(4)
C(25)-C(26)	1.393(5)
C(26)-C(27)	1.396(6)
C(27)-C(28)	1.405(6)
C(28)-C(29)	1.391(5)
C(30)-C(31)	1.411(10)
C(30)-C(31')	1.495(11)
C(31)-C(32)	1.389(15)
C(31')-C(32')	1.417(12)
S(1S)-O(3S)	1.421(6)
S(1S)-O(2S)	1.438(5)
S(1S)-O(1S)	1.480(4)
S(1S)-O(4S)	1.550(4)
N(1)-Pd(1)-C(30)	168.38(13)
N(1)-Pd(1)-C(31)	130.0(3)
C(30)-Pd(1)-C(31)	38.7(3)
N(1)-Pd(1)-C(31')	132.8(3)
C(30)-Pd(1)-C(31')	40.3(3)
C(31)-Pd(1)-C(31')	28.3(4)
N(1)-Pd(1)-C(32)	103.8(3)
C(30)-Pd(1)-C(32)	67.6(3)

C(31)-Pd(1)-C(32)	37.1(4)
C(31')-Pd(1)-C(32)	29.7(4)
N(1)-Pd(1)-C(32')	99.8(2)
C(30)-Pd(1)-C(32')	70.1(2)
C(31)-Pd(1)-C(32')	34.1(4)
C(31')-Pd(1)-C(32')	37.3(3)
C(32)-Pd(1)-C(32')	12.6(3)
N(1)-Pd(1)-P(1)	84.86(8)
C(30)-Pd(1)-P(1)	104.58(11)
C(31)-Pd(1)-P(1)	138.9(3)
C(31')-Pd(1)-P(1)	140.5(2)
C(32)-Pd(1)-P(1)	169.6(3)
C(32')-Pd(1)-P(1)	172.2(3)
C(3)-N(1)-C(1)	108.0(3)
C(3)-N(1)-Pd(1)	129.3(2)
C(1)-N(1)-Pd(1)	120.9(2)
C(18)-P(1)-C(24)	107.59(17)
C(18)-P(1)-C(13)	105.00(16)
C(24)-P(1)-C(13)	102.92(15)
C(18)-P(1)-Pd(1)	123.72(12)
C(24)-P(1)-Pd(1)	108.71(10)
C(13)-P(1)-Pd(1)	106.96(10)
C(3)-O(1)-C(2)	106.3(3)
N(1)-C(1)-C(4)	112.4(3)
N(1)-C(1)-C(2)	102.8(2)
C(4)-C(1)-C(2)	114.2(3)
C(10)-O(2)-C(11)	111.3(4)
O(1)-C(2)-C(10)	109.1(3)
O(1)-C(2)-C(1)	104.2(2)
C(10)-C(2)-C(1)	111.3(3)
N(1)-C(3)-O(1)	117.2(3)
N(1)-C(3)-C(12)	127.1(3)
O(1)-C(3)-C(12)	115.7(3)
C(5)-C(4)-C(9)	119.5(3)
C(5)-C(4)-C(1)	119.7(3)
C(9)-C(4)-C(1)	120.8(3)
C(4)-C(5)-C(6)	119.6(4)
C(7)-C(6)-C(5)	120.7(4)
C(6)-C(7)-C(8)	120.2(4)

C(7)-C(8)-C(9)	119.7(5)
C(4)-C(9)-C(8)	120.3(4)
O(2)-C(10)-C(2)	109.3(3)
C(17)-C(12)-C(13)	120.0(3)
C(17)-C(12)-C(3)	117.9(3)
C(13)-C(12)-C(3)	121.9(3)
C(14)-C(13)-C(12)	119.5(3)
C(14)-C(13)-P(1)	121.2(3)
C(12)-C(13)-P(1)	119.3(2)
C(13)-C(14)-C(15)	120.0(4)
C(16)-C(15)-C(14)	120.7(3)
C(15)-C(16)-C(17)	119.1(4)
C(12)-C(17)-C(16)	120.7(4)
C(19)-C(18)-C(23)	119.4(4)
C(19)-C(18)-P(1)	118.3(3)
C(23)-C(18)-P(1)	122.3(3)
C(20)-C(19)-C(18)	120.3(4)
C(19)-C(20)-C(21)	119.7(4)
C(22)-C(21)-C(20)	120.3(4)
C(21)-C(22)-C(23)	120.5(4)
C(22)-C(23)-C(18)	119.8(4)
C(29)-C(24)-C(25)	119.7(3)
C(29)-C(24)-P(1)	121.4(2)
C(25)-C(24)-P(1)	118.8(2)
C(26)-C(25)-C(24)	119.9(3)
C(25)-C(26)-C(27)	120.4(3)
C(26)-C(27)-C(28)	119.6(3)
C(29)-C(28)-C(27)	120.0(4)
C(28)-C(29)-C(24)	120.3(3)
C(31)-C(30)-C(31')	42.8(6)
C(31)-C(30)-Pd(1)	71.1(4)
C(31')-C(30)-Pd(1)	72.8(4)
C(32)-C(31)-C(30)	119.4(9)
C(32)-C(31)-Pd(1)	74.5(5)
C(30)-C(31)-Pd(1)	70.2(3)
C(32')-C(31')-C(30)	118.2(8)
C(32')-C(31')-Pd(1)	72.1(5)
C(30)-C(31')-Pd(1)	66.9(3)
C(31)-C(32)-Pd(1)	68.3(4)

C(31')-C(32')-Pd(1)	70.6(4)
O(3S)-S(1S)-O(2S)	113.5(5)
O(3S)-S(1S)-O(1S)	110.3(4)
O(2S)-S(1S)-O(1S)	110.8(4)
O(3S)-S(1S)-O(4S)	109.5(4)
O(2S)-S(1S)-O(4S)	108.2(3)
O(1S)-S(1S)-O(4S)	104.1(3)

Symmetry transformations used to generate equivalent atoms:

Table 3. Torsion angles [°] for DP122b_0m.

C(30)-Pd(1)-N(1)-C(3)	175.1(7)
C(31)-Pd(1)-N(1)-C(3)	-173.9(5)
C(31')-Pd(1)-N(1)-C(3)	-136.1(5)
C(32)-Pd(1)-N(1)-C(3)	-143.8(4)
C(32')-Pd(1)-N(1)-C(3)	-156.1(4)
P(1)-Pd(1)-N(1)-C(3)	30.3(3)
C(30)-Pd(1)-N(1)-C(1)	11.9(9)
C(31)-Pd(1)-N(1)-C(1)	22.9(5)
C(31')-Pd(1)-N(1)-C(1)	60.8(5)
C(32)-Pd(1)-N(1)-C(1)	53.0(4)
C(32')-Pd(1)-N(1)-C(1)	40.8(4)
P(1)-Pd(1)-N(1)-C(1)	-132.9(2)
N(1)-Pd(1)-P(1)-C(18)	-170.57(17)
C(30)-Pd(1)-P(1)-C(18)	16.3(2)
C(31)-Pd(1)-P(1)-C(18)	37.9(4)
C(31')-Pd(1)-P(1)-C(18)	-6.4(5)
C(32)-Pd(1)-P(1)-C(18)	-24.2(14)
C(32')-Pd(1)-P(1)-C(18)	62.4(17)
N(1)-Pd(1)-P(1)-C(24)	61.86(16)
C(30)-Pd(1)-P(1)-C(24)	-111.25(19)
C(31)-Pd(1)-P(1)-C(24)	-89.6(4)
C(31')-Pd(1)-P(1)-C(24)	-134.0(5)
C(32)-Pd(1)-P(1)-C(24)	-151.8(14)
C(32')-Pd(1)-P(1)-C(24)	-65.1(17)
N(1)-Pd(1)-P(1)-C(13)	-48.64(14)
C(30)-Pd(1)-P(1)-C(13)	138.25(18)
C(31)-Pd(1)-P(1)-C(13)	159.9(4)

C(31')-Pd(1)-P(1)-C(13)	115.5(5)
C(32)-Pd(1)-P(1)-C(13)	97.7(14)
C(32')-Pd(1)-P(1)-C(13)	-175.6(17)
C(3)-N(1)-C(1)-C(4)	117.8(3)
Pd(1)-N(1)-C(1)-C(4)	-75.9(3)
C(3)-N(1)-C(1)-C(2)	-5.5(4)
Pd(1)-N(1)-C(1)-C(2)	160.9(2)
C(3)-O(1)-C(2)-C(10)	106.6(3)
C(3)-O(1)-C(2)-C(1)	-12.3(3)
N(1)-C(1)-C(2)-O(1)	10.6(3)
C(4)-C(1)-C(2)-O(1)	-111.4(3)
N(1)-C(1)-C(2)-C(10)	-106.8(3)
C(4)-C(1)-C(2)-C(10)	131.2(3)
C(1)-N(1)-C(3)-O(1)	-2.6(4)
Pd(1)-N(1)-C(3)-O(1)	-167.5(2)
C(1)-N(1)-C(3)-C(12)	177.1(3)
Pd(1)-N(1)-C(3)-C(12)	12.2(5)
C(2)-O(1)-C(3)-N(1)	10.0(4)
C(2)-O(1)-C(3)-C(12)	-169.7(3)
N(1)-C(1)-C(4)-C(5)	135.6(4)
C(2)-C(1)-C(4)-C(5)	-107.8(4)
N(1)-C(1)-C(4)-C(9)	-46.3(5)
C(2)-C(1)-C(4)-C(9)	70.3(4)
C(9)-C(4)-C(5)-C(6)	0.1(6)
C(1)-C(4)-C(5)-C(6)	178.2(4)
C(4)-C(5)-C(6)-C(7)	-0.6(7)
C(5)-C(6)-C(7)-C(8)	0.9(7)
C(6)-C(7)-C(8)-C(9)	-0.8(7)
C(5)-C(4)-C(9)-C(8)	0.0(6)
C(1)-C(4)-C(9)-C(8)	-178.1(4)
C(7)-C(8)-C(9)-C(4)	0.3(7)
C(11)-O(2)-C(10)-C(2)	-178.9(3)
O(1)-C(2)-C(10)-O(2)	65.7(4)
C(1)-C(2)-C(10)-O(2)	-179.8(3)
N(1)-C(3)-C(12)-C(17)	146.0(4)
O(1)-C(3)-C(12)-C(17)	-34.2(4)
N(1)-C(3)-C(12)-C(13)	-38.0(5)
O(1)-C(3)-C(12)-C(13)	141.7(3)
C(17)-C(12)-C(13)-C(14)	-0.1(5)

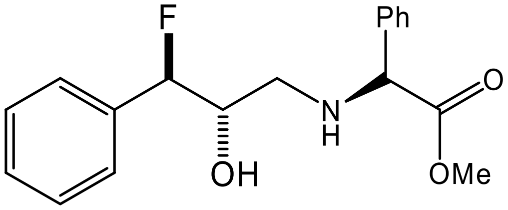
C(3)-C(12)-C(13)-C(14)	-176.0(3)
C(17)-C(12)-C(13)-P(1)	177.3(2)
C(3)-C(12)-C(13)-P(1)	1.4(4)
C(18)-P(1)-C(13)-C(14)	-4.9(3)
C(24)-P(1)-C(13)-C(14)	107.6(3)
Pd(1)-P(1)-C(13)-C(14)	-138.0(2)
C(18)-P(1)-C(13)-C(12)	177.8(2)
C(24)-P(1)-C(13)-C(12)	-69.7(3)
Pd(1)-P(1)-C(13)-C(12)	44.7(3)
C(12)-C(13)-C(14)-C(15)	-0.4(5)
P(1)-C(13)-C(14)-C(15)	-177.7(3)
C(13)-C(14)-C(15)-C(16)	0.8(5)
C(14)-C(15)-C(16)-C(17)	-0.7(5)
C(13)-C(12)-C(17)-C(16)	0.2(5)
C(3)-C(12)-C(17)-C(16)	176.2(3)
C(15)-C(16)-C(17)-C(12)	0.2(5)
C(24)-P(1)-C(18)-C(19)	157.2(3)
C(13)-P(1)-C(18)-C(19)	-93.7(3)
Pd(1)-P(1)-C(18)-C(19)	29.2(3)
C(24)-P(1)-C(18)-C(23)	-24.1(4)
C(13)-P(1)-C(18)-C(23)	85.1(3)
Pd(1)-P(1)-C(18)-C(23)	-152.1(3)
C(23)-C(18)-C(19)-C(20)	0.7(6)
P(1)-C(18)-C(19)-C(20)	179.5(3)
C(18)-C(19)-C(20)-C(21)	-0.2(7)
C(19)-C(20)-C(21)-C(22)	0.4(7)
C(20)-C(21)-C(22)-C(23)	-1.1(8)
C(21)-C(22)-C(23)-C(18)	1.6(7)
C(19)-C(18)-C(23)-C(22)	-1.4(6)
P(1)-C(18)-C(23)-C(22)	179.8(3)
C(18)-P(1)-C(24)-C(29)	83.0(3)
C(13)-P(1)-C(24)-C(29)	-27.6(3)
Pd(1)-P(1)-C(24)-C(29)	-140.7(3)
C(18)-P(1)-C(24)-C(25)	-100.3(3)
C(13)-P(1)-C(24)-C(25)	149.1(3)
Pd(1)-P(1)-C(24)-C(25)	35.9(3)
C(29)-C(24)-C(25)-C(26)	0.0(6)
P(1)-C(24)-C(25)-C(26)	-176.8(3)
C(24)-C(25)-C(26)-C(27)	-0.6(7)

C(25)-C(26)-C(27)-C(28)	0.6(7)
C(26)-C(27)-C(28)-C(29)	0.1(7)
C(27)-C(28)-C(29)-C(24)	-0.7(7)
C(25)-C(24)-C(29)-C(28)	0.7(6)
P(1)-C(24)-C(29)-C(28)	177.4(3)
N(1)-Pd(1)-C(30)-C(31)	13.6(10)
C(31')-Pd(1)-C(30)-C(31)	-45.1(6)
C(32)-Pd(1)-C(30)-C(31)	-30.1(6)
C(32')-Pd(1)-C(30)-C(31)	-16.8(6)
P(1)-Pd(1)-C(30)-C(31)	157.2(5)
N(1)-Pd(1)-C(30)-C(31')	58.7(10)
C(31)-Pd(1)-C(30)-C(31')	45.1(6)
C(32)-Pd(1)-C(30)-C(31')	15.0(5)
C(32')-Pd(1)-C(30)-C(31')	28.3(5)
P(1)-Pd(1)-C(30)-C(31')	-157.7(4)
C(31')-C(30)-C(31)-C(32)	-26.6(7)
Pd(1)-C(30)-C(31)-C(32)	58.1(7)
C(31')-C(30)-C(31)-Pd(1)	-84.7(6)
N(1)-Pd(1)-C(31)-C(32)	53.7(7)
C(30)-Pd(1)-C(31)-C(32)	-129.9(9)
C(31')-Pd(1)-C(31)-C(32)	-54.5(8)
C(32')-Pd(1)-C(31)-C(32)	21.1(5)
P(1)-Pd(1)-C(31)-C(32)	-164.7(5)
N(1)-Pd(1)-C(31)-C(30)	-176.5(3)
C(31')-Pd(1)-C(31)-C(30)	75.4(8)
C(32)-Pd(1)-C(31)-C(30)	129.9(9)
C(32')-Pd(1)-C(31)-C(30)	151.0(9)
P(1)-Pd(1)-C(31)-C(30)	-34.8(7)
C(31)-C(30)-C(31')-C(32')	28.1(7)
Pd(1)-C(30)-C(31')-C(32')	-52.5(7)
C(31)-C(30)-C(31')-Pd(1)	80.6(6)
N(1)-Pd(1)-C(31')-C(32')	-33.8(8)
C(30)-Pd(1)-C(31')-C(32')	132.7(8)
C(31)-Pd(1)-C(31')-C(32')	63.6(8)
C(32)-Pd(1)-C(31')-C(32')	-18.5(6)
P(1)-Pd(1)-C(31')-C(32')	167.9(5)
N(1)-Pd(1)-C(31')-C(30)	-166.4(2)
C(31)-Pd(1)-C(31')-C(30)	-69.1(8)
C(32)-Pd(1)-C(31')-C(30)	-151.1(10)

C(32')-Pd(1)-C(31')-C(30)	-132.7(8)
P(1)-Pd(1)-C(31')-C(30)	35.2(7)
C(30)-C(31)-C(32)-Pd(1)	-56.0(6)
N(1)-Pd(1)-C(32)-C(31)	-140.5(6)
C(30)-Pd(1)-C(32)-C(31)	31.2(6)
C(31')-Pd(1)-C(32)-C(31)	51.0(8)
C(32')-Pd(1)-C(32)-C(31)	-67.5(16)
P(1)-Pd(1)-C(32)-C(31)	74.1(17)
C(30)-C(31')-C(32')-Pd(1)	50.1(6)
N(1)-Pd(1)-C(32')-C(31')	155.5(6)
C(30)-Pd(1)-C(32')-C(31')	-30.4(6)
C(31)-Pd(1)-C(32')-C(31')	-49.2(7)
C(32)-Pd(1)-C(32')-C(31')	46.0(16)
P(1)-Pd(1)-C(32')-C(31')	-78.3(19)

Symmetry transformations used to generate equivalent atoms:

2. X-Ray Structure for: 216g



Crystallization: By slow evaporation of methanol at room temperature

Measured Crystal: colorless translucent needle

Comments: Compound crystallizes in the chiral space group $P2_1$. A confirmation of the absolute configuration by high angle measurements was not done due to the small size of the crystals available. The shortest contact in the crystal packing is N1A···O1B with 2.792 Å (see figure 2). In this hydrogen bonding every molecule is contacting the next one (bidirectional and mono linear). Also a light contact is localized at: F1A···C12B: 3.214 Å.

Figures

Figure 1. Ortep-Plot (50 %) with labeling scheme.

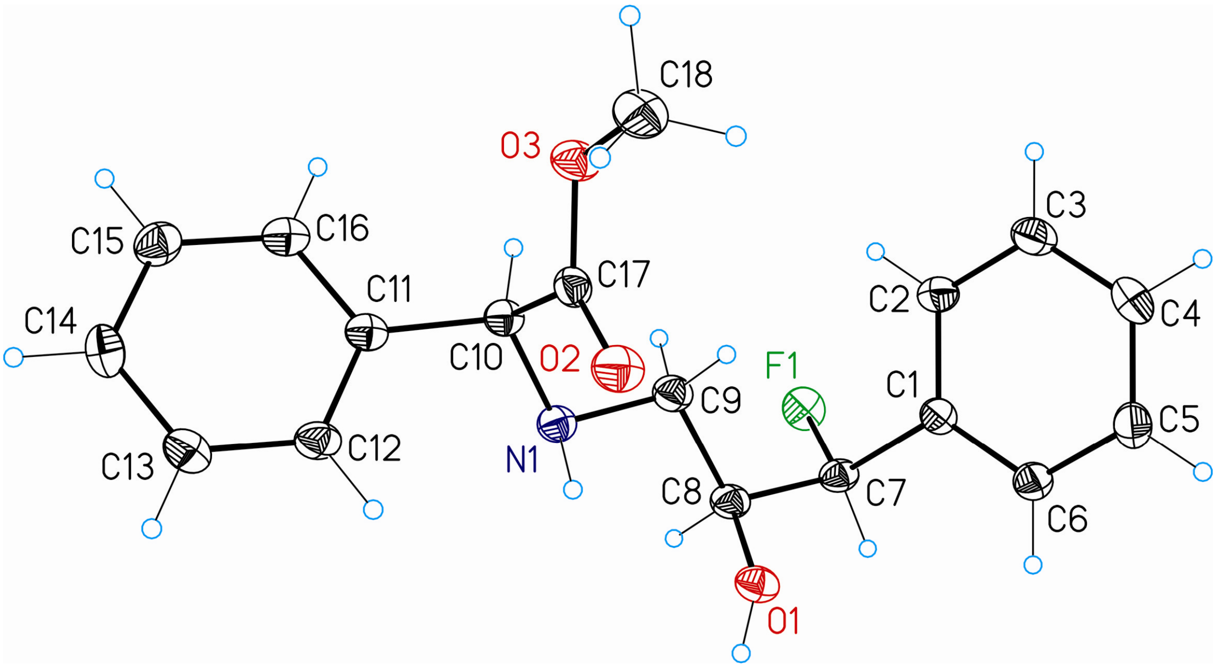


Figure 2. Ortep-Plot (50 %) showing the shortest intermolecular contacts (N1A···O1B: 2.792 Å and F1A···C12B: 3.214 Å).

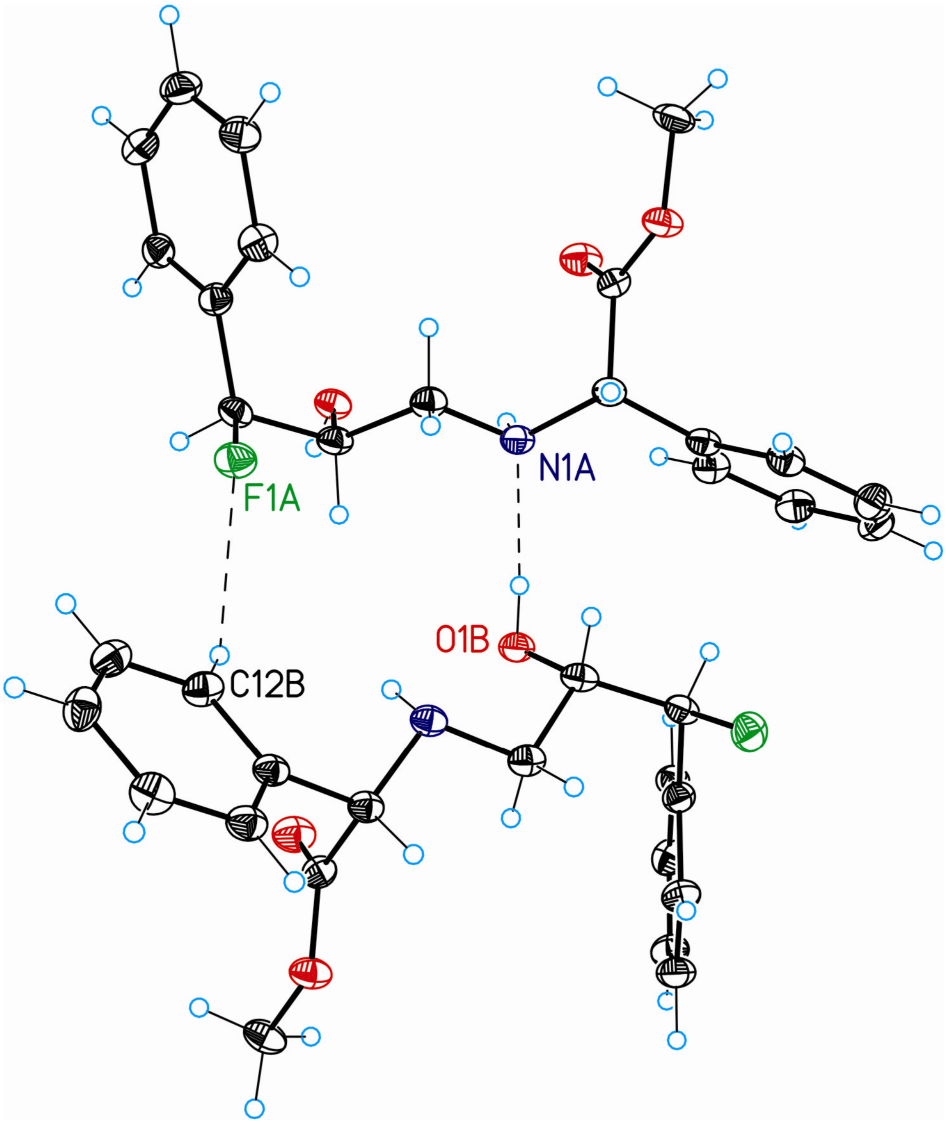
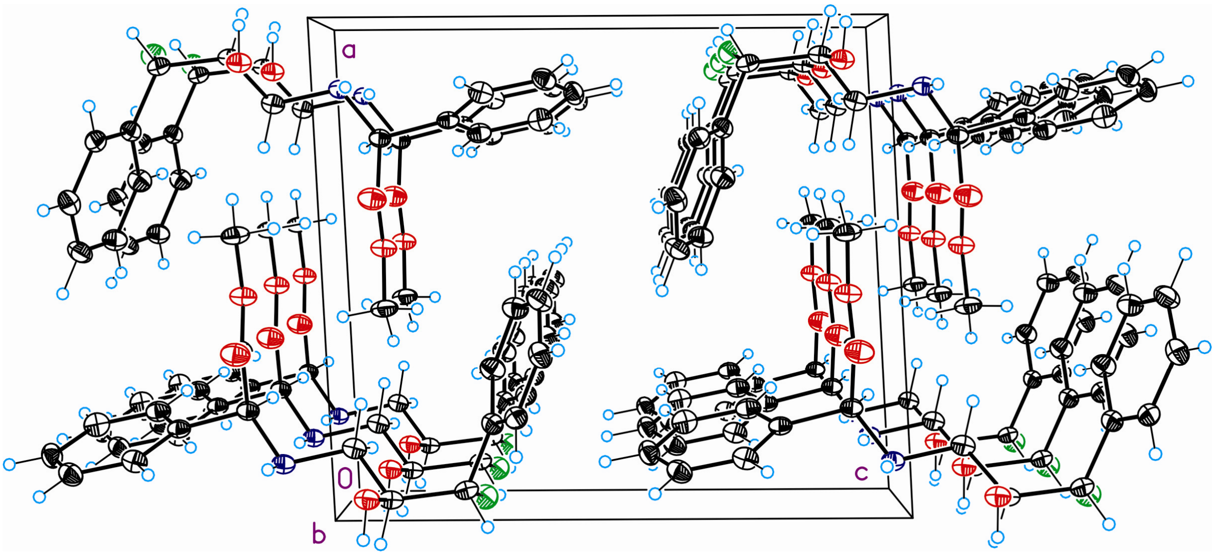


Figure 3. Crystal packing with view along the b-axis.



Experimental

Crystal structure determination was carried out using a Bruker-Nonius diffractometer equipped with a APPEX 2 4K CCD area detector, a FR591 rotating anode with $Mo_{K\alpha}$ radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = 100 K). Fullsphere data collection omega and phi scans. Programs used: Data collection Apex2 V. 1.0-22 (Bruker-Nonius 2004), data reduction Saint + Version 6.22 (Bruker-Nonius 2001) and absorption correction SADABS V. 2.10 (2003). Crystal structure solution was achieved using direct methods as implemented in SHELXTL Version 6.10 (Sheldrick, Universtität Göttingen (Germany), 2000) and visualized using XP program. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL Version 6.10 (Sheldrick, Universtität Göttingen (Germany), 2000). All non hydrogen atoms were refined including anisotropic displacement parameters.

Tables

Table 1. Crystal data and structure refinement for DP117x_0m.

Identification code	dp117x_0m	
Empirical formula	C18 H20 F N O3	
Formula weight	317.35	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.834(3) Å	a= 90°.
	b = 5.9980(12) Å	b= 92.713(8)°.
	c = 12.450(3) Å	g = 90°.
Volume	808.2(3) Å^3	
Z	2	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	336	
Crystal size	0.20 x 0.05 x 0.01 mm^3	
Theta range for data collection	3.77 to 30.53°.	
Index ranges	$-15 \leq h \leq 6$, $-7 \leq k \leq 8$, $-17 \leq l \leq 15$	
Reflections collected	5445	
Independent reflections	3649 [R(int) = 0.0474]	
Completeness to theta = 30.53°	89.8 %	
Absorption correction	SADABS (Bruker-AXS)	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3649 / 1 / 214	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0589, wR2 = 0.1435	
R indices (all data)	R1 = 0.0792, wR2 = 0.1551	
Absolute structure parameter	-0.1(11)	
Largest diff. peak and hole	0.541 and -0.427 e.Å^{-3}	

Table 2. Bond lengths [Å] and angles [°] for DP117x_0m.

C(1)-C(6)	1.381(4)	O(2)-C(17)	1.198(3)	C(10)-C(11)	1.523(4)
C(1)-C(2)	1.403(4)	C(3)-C(4)	1.381(4)	C(10)-C(17)	1.539(3)
C(1)-C(7)	1.514(3)	O(3)-C(17)	1.329(3)	C(11)-C(16)	1.392(4)
O(1)-C(8)	1.411(3)	O(3)-C(18)	1.457(3)	C(11)-C(12)	1.400(4)
F(1)-C(7)	1.416(3)	C(4)-C(5)	1.385(4)	C(12)-C(13)	1.382(4)
N(1)-C(10)	1.462(3)	C(5)-C(6)	1.399(3)	C(13)-C(14)	1.396(4)
N(1)-C(9)	1.479(4)	C(7)-C(8)	1.538(4)	C(14)-C(15)	1.398(4)
C(2)-C(3)	1.394(3)	C(8)-C(9)	1.512(4)	C(15)-C(16)	1.386(5)

C(6)-C(1)-C(2)	119.9(2)	C(9)-C(8)-C(7)	113.7(2)
C(6)-C(1)-C(7)	119.8(2)	N(1)-C(9)-C(8)	110.3(2)
C(2)-C(1)-C(7)	120.3(2)	N(1)-C(10)-C(11)	113.81(19)
C(10)-N(1)-C(9)	110.56(19)	N(1)-C(10)-C(17)	110.8(2)
C(3)-C(2)-C(1)	119.3(3)	C(11)-C(10)-C(17)	106.4(2)
C(4)-C(3)-C(2)	120.6(2)	C(16)-C(11)-C(12)	118.7(3)
C(17)-O(3)-C(18)	115.1(2)	C(16)-C(11)-C(10)	119.8(2)
C(3)-C(4)-C(5)	120.1(2)	C(12)-C(11)-C(10)	121.5(3)
C(4)-C(5)-C(6)	119.8(3)	C(13)-C(12)-C(11)	120.5(3)
C(1)-C(6)-C(5)	120.3(2)	C(12)-C(13)-C(14)	120.5(3)
F(1)-C(7)-C(1)	108.9(2)	C(13)-C(14)-C(15)	119.3(3)
F(1)-C(7)-C(8)	106.9(2)	C(16)-C(15)-C(14)	119.8(3)
C(1)-C(7)-C(8)	116.0(2)	C(15)-C(16)-C(11)	121.1(3)
O(1)-C(8)-C(9)	109.2(2)	O(2)-C(17)-O(3)	125.9(2)
O(1)-C(8)-C(7)	109.5(2)	O(2)-C(17)-C(10)	123.0(2)

O(3)-C(17)-C(10)	111.1(2)

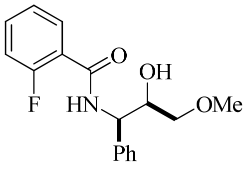
Table 3. Torsion angles [°] for DP117x_0m.

C(6)-C(1)-C(2)-C(3)	-0.6(5)
C(7)-C(1)-C(2)-C(3)	178.6(3)
C(1)-C(2)-C(3)-C(4)	0.6(5)
C(2)-C(3)-C(4)-C(5)	0.2(5)
C(3)-C(4)-C(5)-C(6)	-0.8(5)
C(2)-C(1)-C(6)-C(5)	-0.1(5)
C(7)-C(1)-C(6)-C(5)	-179.2(3)
C(4)-C(5)-C(6)-C(1)	0.8(5)
C(6)-C(1)-C(7)-F(1)	-143.1(3)
C(2)-C(1)-C(7)-F(1)	37.7(4)
C(6)-C(1)-C(7)-C(8)	96.3(3)
C(2)-C(1)-C(7)-C(8)	-82.9(4)
F(1)-C(7)-C(8)-O(1)	174.88(16)
C(1)-C(7)-C(8)-O(1)	-63.4(3)
F(1)-C(7)-C(8)-C(9)	-62.6(2)
C(1)-C(7)-C(8)-C(9)	59.1(3)
C(10)-N(1)-C(9)-C(8)	171.7(2)
O(1)-C(8)-C(9)-N(1)	-62.0(3)
C(7)-C(8)-C(9)-N(1)	175.3(2)
C(9)-N(1)-C(10)-C(11)	166.9(2)
C(9)-N(1)-C(10)-C(17)	-73.3(3)
N(1)-C(10)-C(11)-C(16)	-135.4(2)
C(17)-C(10)-C(11)-C(16)	102.3(3)
N(1)-C(10)-C(11)-C(12)	47.2(3)
C(17)-C(10)-C(11)-C(12)	-75.1(3)
C(16)-C(11)-C(12)-C(13)	-0.6(4)
C(10)-C(11)-C(12)-C(13)	176.8(2)
C(11)-C(12)-C(13)-C(14)	0.6(4)
C(12)-C(13)-C(14)-C(15)	0.1(4)
C(13)-C(14)-C(15)-C(16)	-0.7(4)
C(14)-C(15)-C(16)-C(11)	0.7(4)
C(12)-C(11)-C(16)-C(15)	0.0(4)

C(10)-C(11)-C(16)-C(15)	-177.5(2)
C(18)-O(3)-C(17)-O(2)	-0.6(5)
C(18)-O(3)-C(17)-C(10)	177.8(2)
N(1)-C(10)-C(17)-O(2)	-34.3(4)
C(11)-C(10)-C(17)-O(2)	89.9(4)
N(1)-C(10)-C(17)-O(3)	147.3(2)
C(11)-C(10)-C(17)-O(3)	-88.5(3)

3. Selected NMR-spectra

2-fluoro-N-((1R,2R)-2-hydroxy-3-methoxy-1-phenylpropyl)benzamide, 53a.



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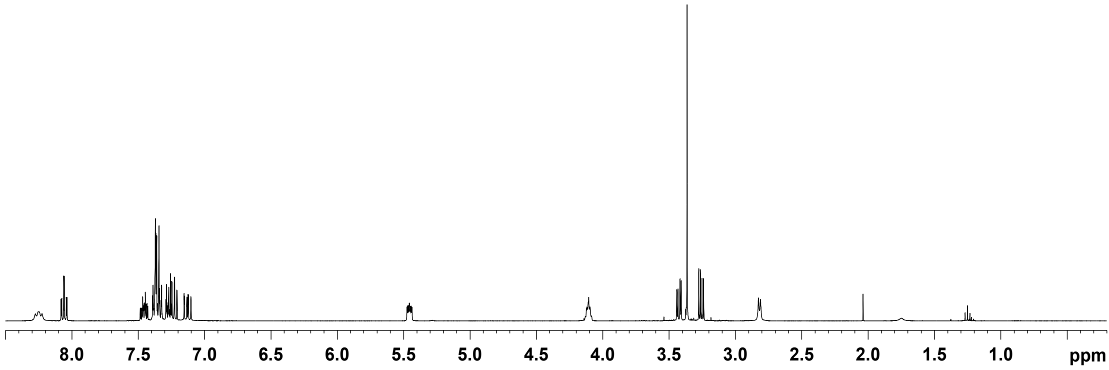

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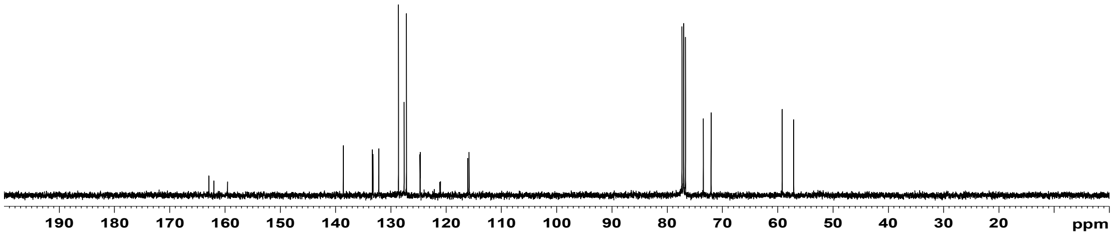
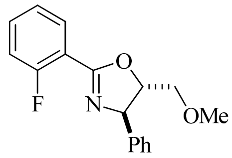


(4R,5S)-2-(2-fluorophenyl)-5-(methoxymethyl)-4-phenyl-4,5-dihydrooxazole,48a



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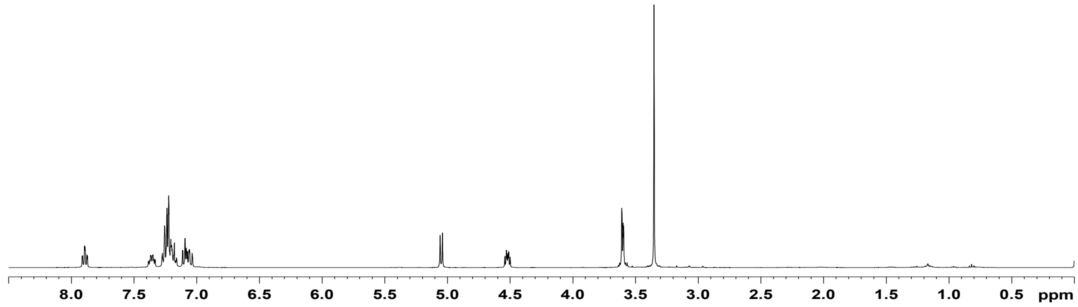

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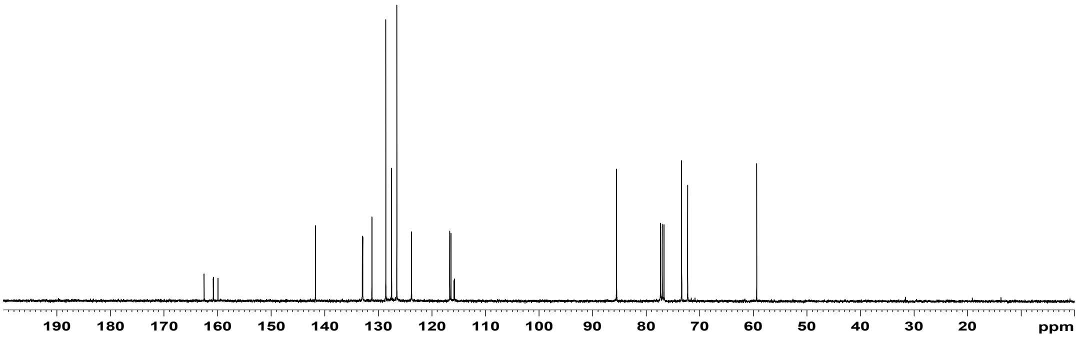
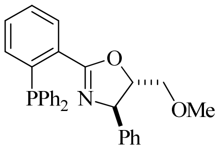


(4R,5S)-2-(2-(diphenylphosphino)phenyl)-5-(methoxymethyl)-4-phenyl-4,5-dihydrooxazole, 55a



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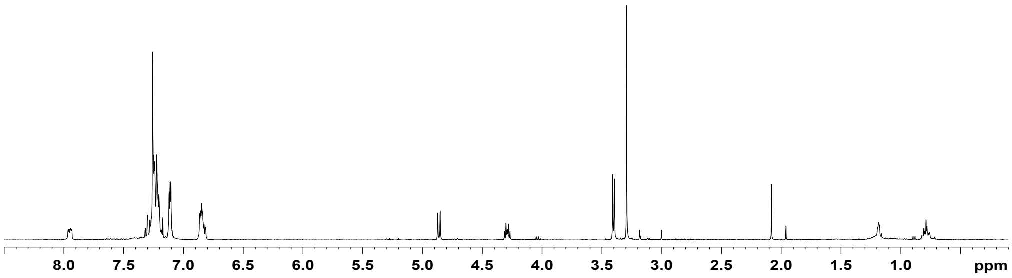
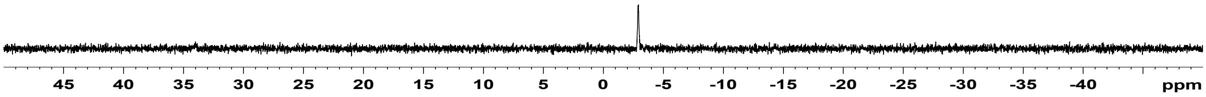
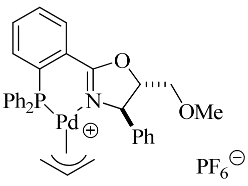


31P-RMN



(η^3–allyl)[(4R,5S)-2-(2-(diphenylphosphino)phenyl)-5-(methoxymethyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49a



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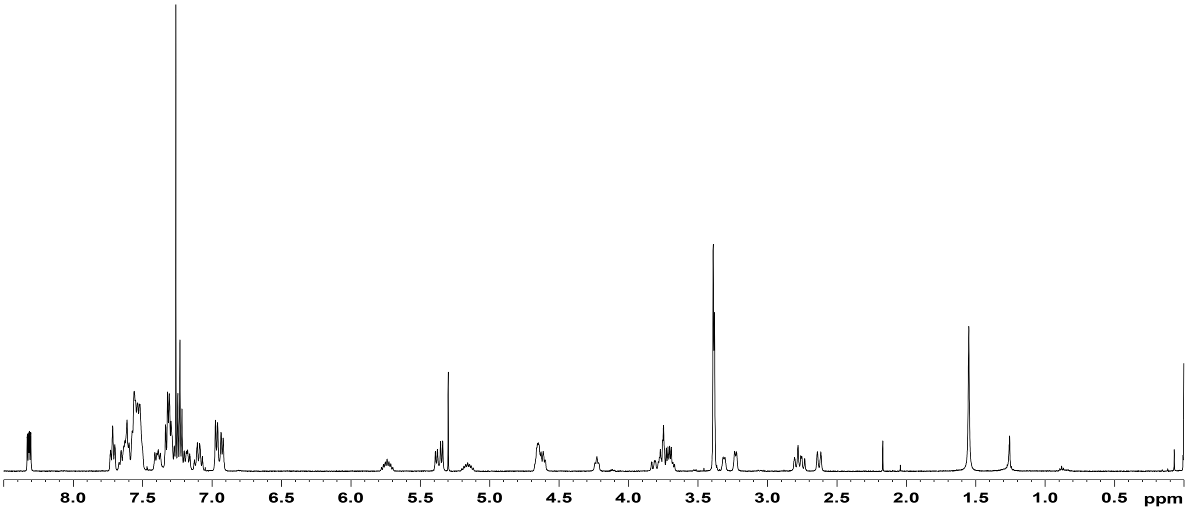

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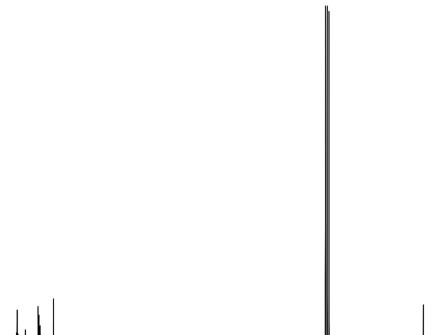

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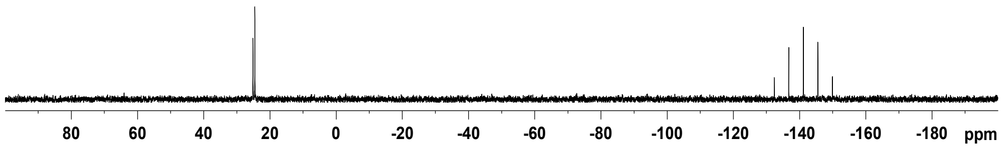
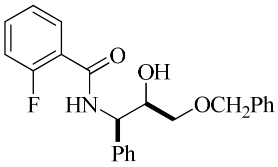


N-((1R,2R)-3-(benzyloxy)-2-hydroxy-1-phenylpropyl)-2-fluorobenzamide, 53b



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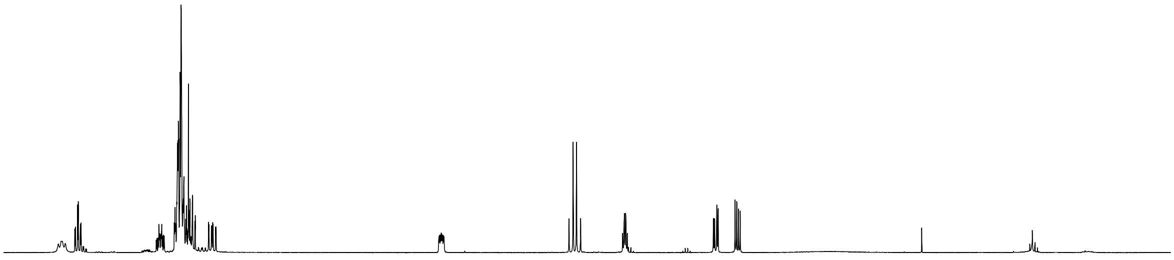

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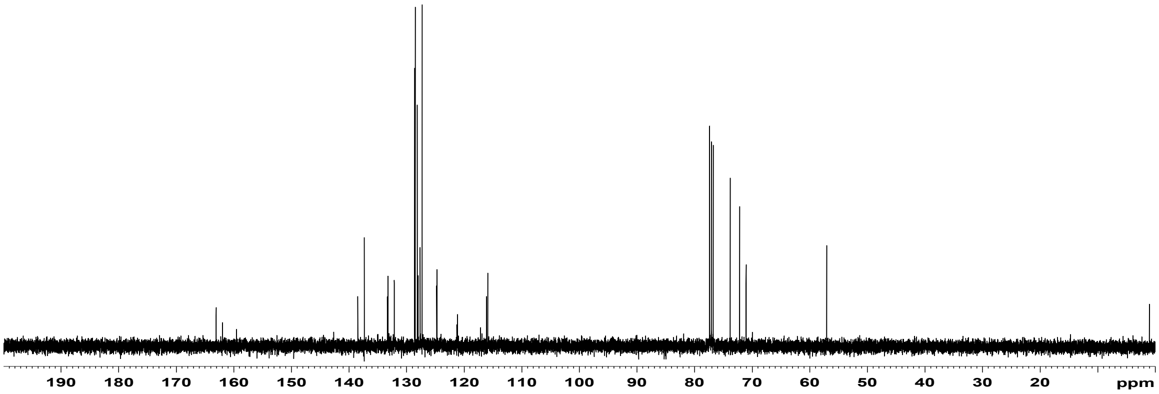
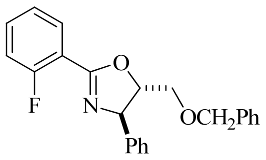


(4R,5S)-5-(benzyloxymethyl)-2-(2-fluorophenyl)-4-phenyl-4,5-dihydrooxazole, 48b



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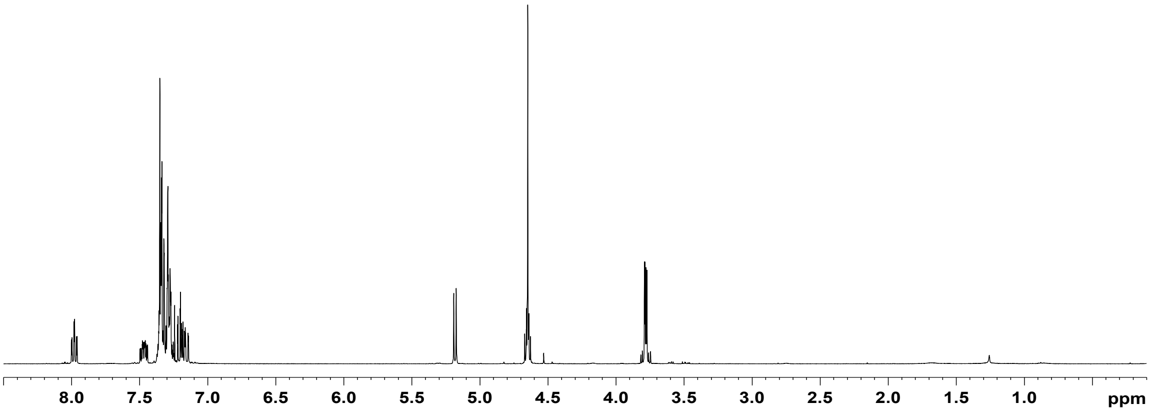

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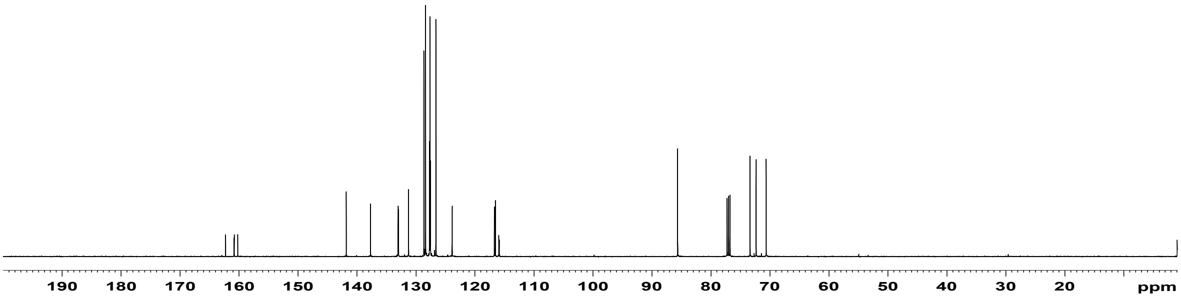
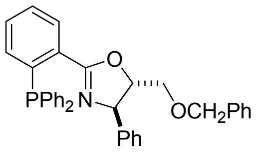


(4R,5S)-5-(benzyloxymethyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole, 55b



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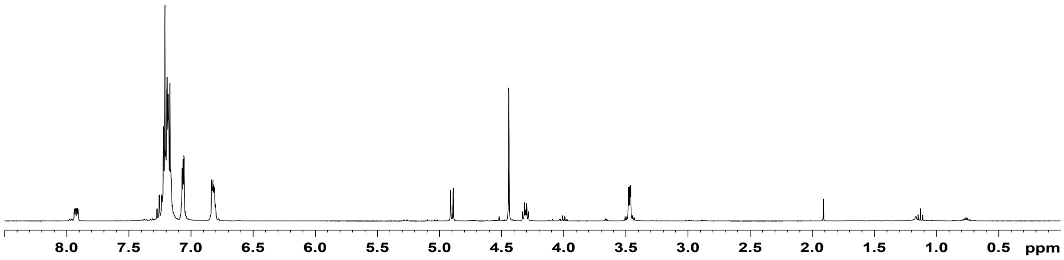

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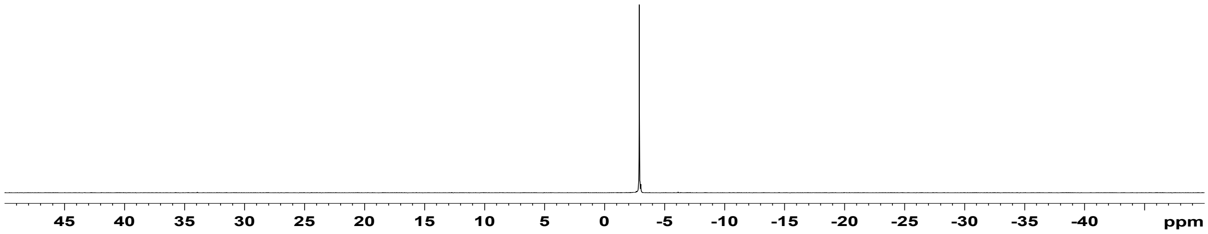
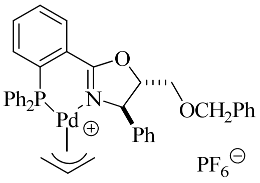


(η^3–allyl)-[(4R,5S)-5-(benzyloxymethyl)-2-(2-(diphenylphosphino)phenyl)-4-phenyl-4,5-dihydrooxazole] hexafluorophosphate palladium complex, 49b



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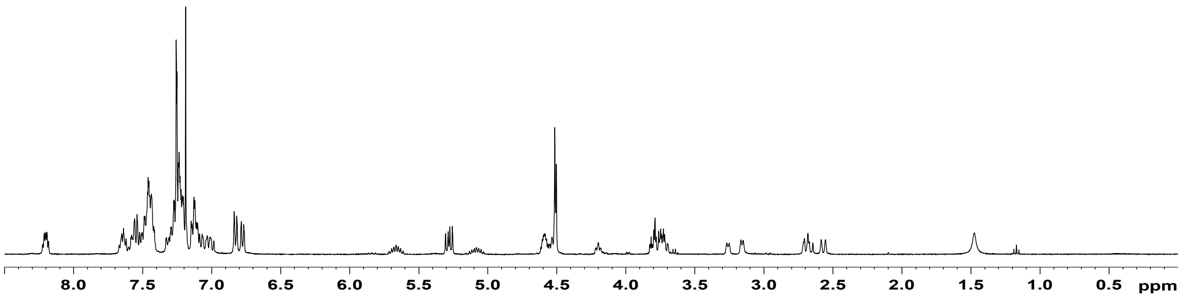

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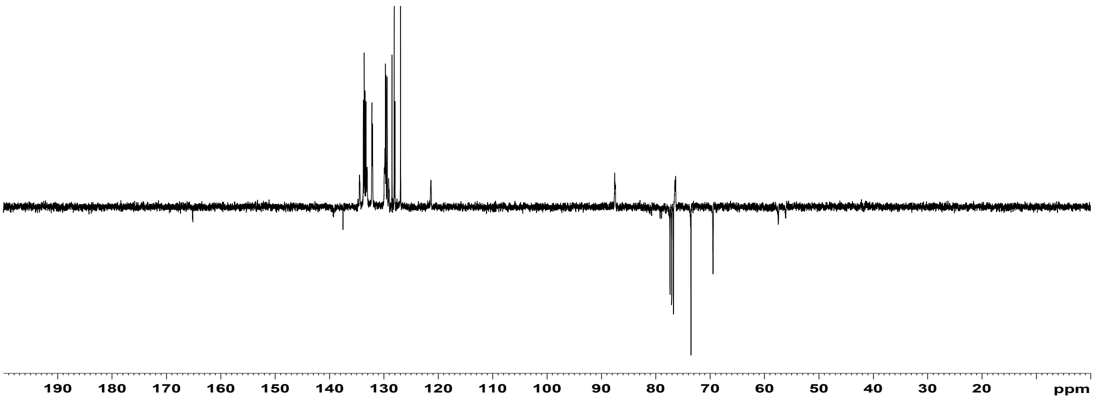

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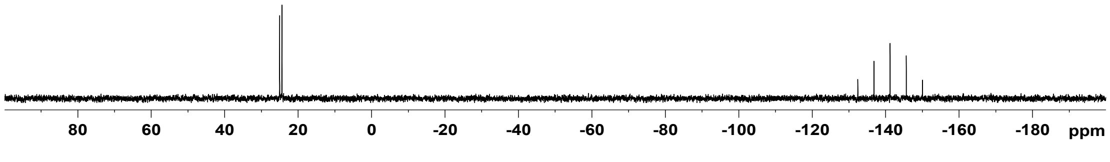
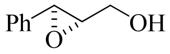


4. Structure Index



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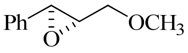

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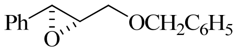

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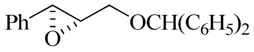

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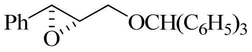

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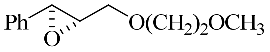

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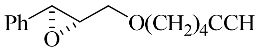

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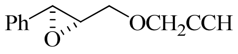

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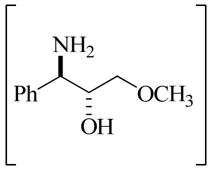

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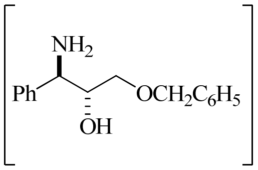

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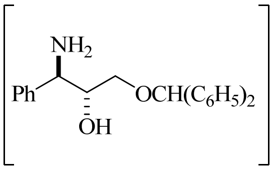

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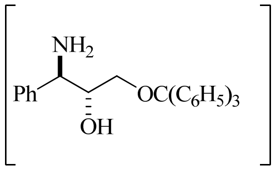

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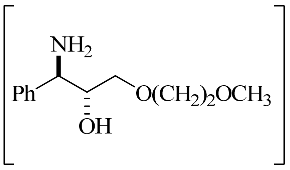

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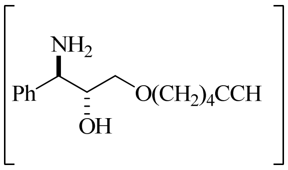

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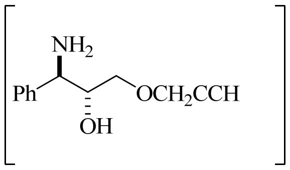
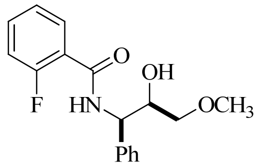


47g



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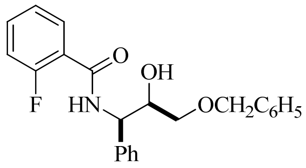

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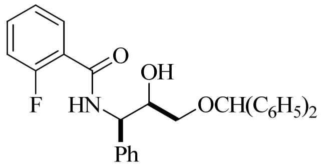

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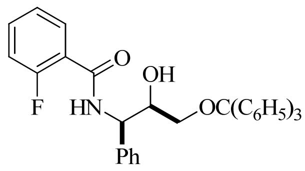

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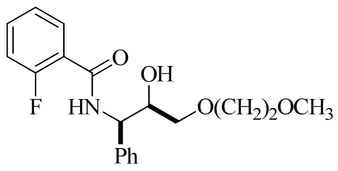

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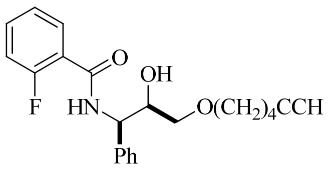

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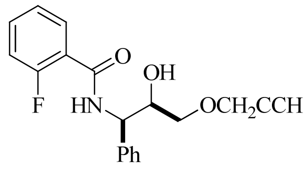

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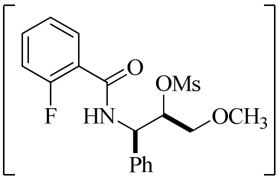

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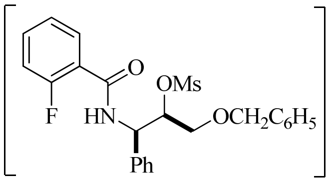

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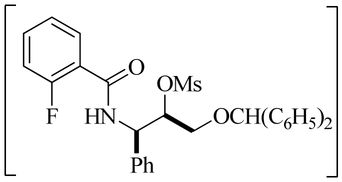

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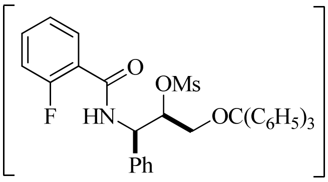

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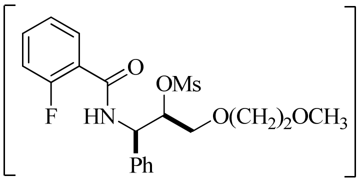

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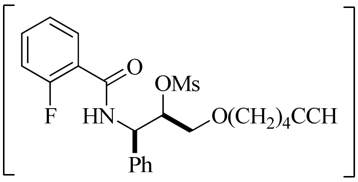

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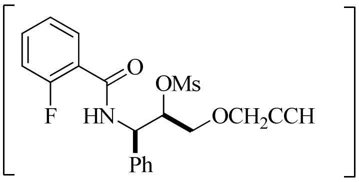

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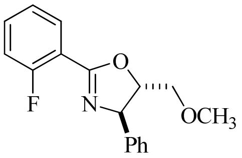

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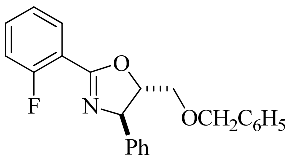

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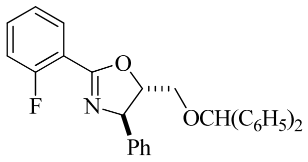

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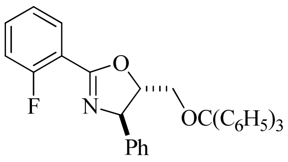

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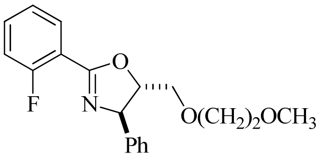

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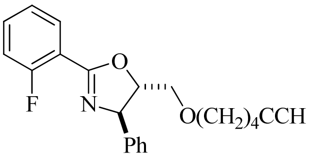

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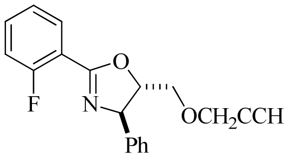

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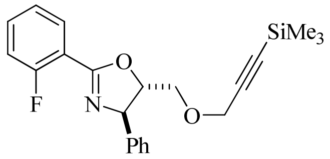

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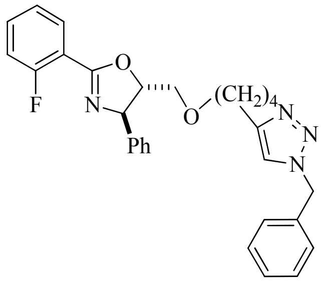

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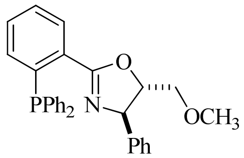

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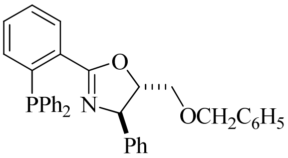

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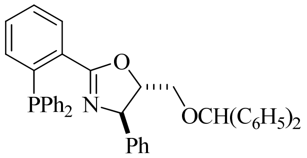

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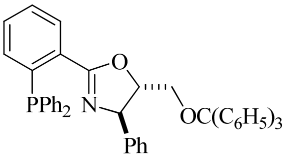

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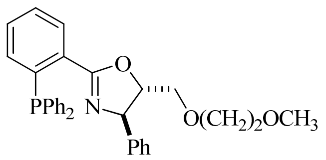

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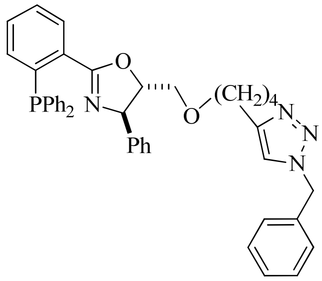

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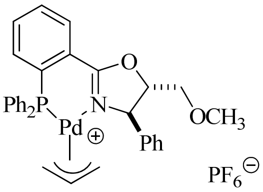

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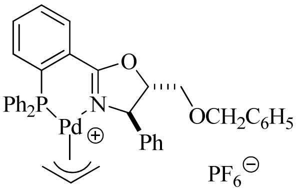

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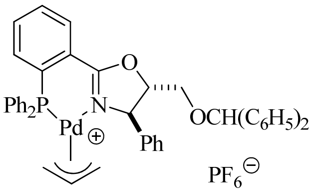

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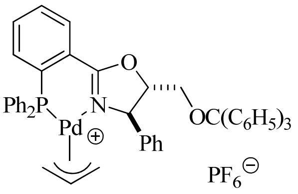

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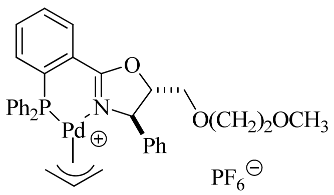

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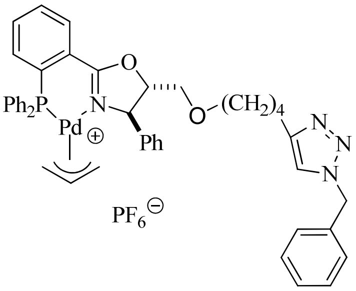

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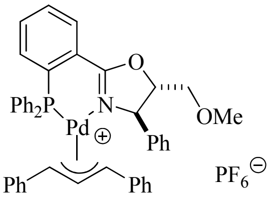

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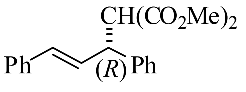

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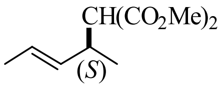

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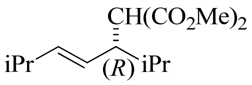

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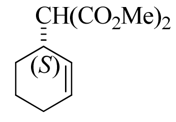

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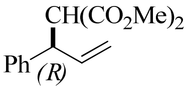

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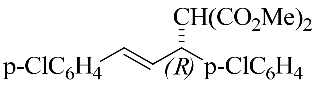

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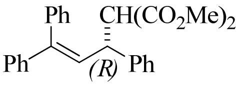

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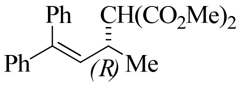

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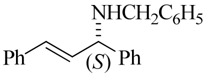

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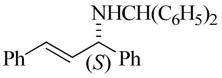

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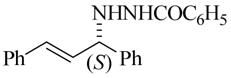

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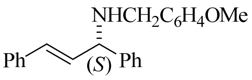

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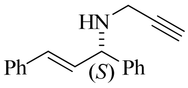

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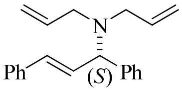

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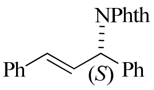

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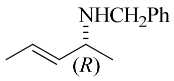

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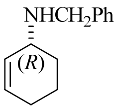

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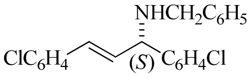

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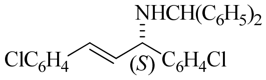

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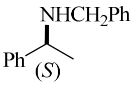

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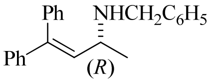

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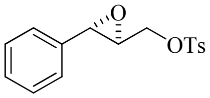

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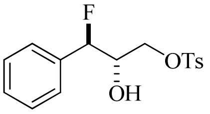

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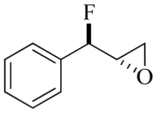

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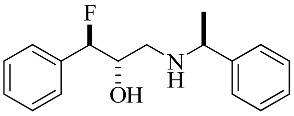

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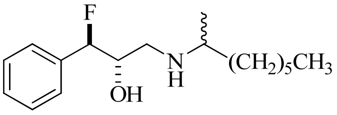

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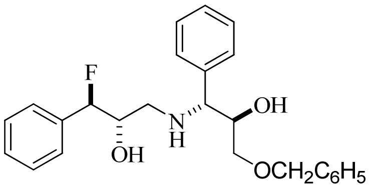

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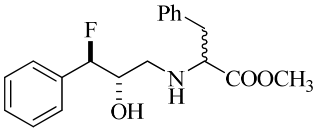

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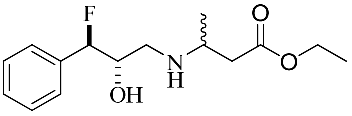

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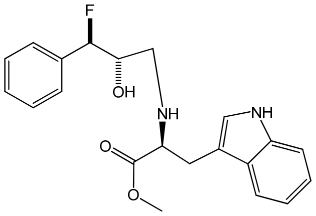

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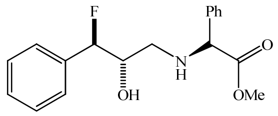

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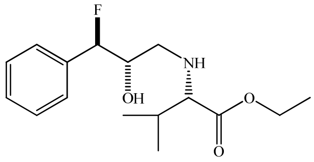

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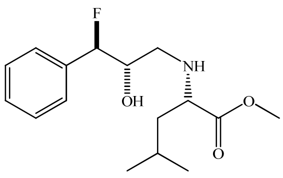

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