UNIVERSITA' DEGLI STUDI DELL'INSUBRIA

Dipartimento di Scienza e Alta Tecnologia

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DESIGN AND SYNTHESIS OF CHIRAL PROMOTERS FOR STEREOSELECTIVE CATALYSIS BASED ON THE 3,3'-BITHIOPHENE SCAFFOLD

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" The universe is dissymmetrical; for the whole of the bodies which compose the solar system were placed before a glass moving with their individual movements, the image in the glass could not be superimposed on reality... Life is dominated by dissymmetrical actions. I can foresee that all living species are primordially, in their structure, in their external forms, functions of cosmic dissymmetry."

Louis Pasteur

1.INTRODUCTION

These visionary words of Pasteur, written in the nineteenth century, have profoundly influenced the development of stereochemistry, since it has become increasingly clear that many fundamental phenomena and laws of Nature result from dissymmetry bases.

In chemistry, exactly as in our daily life, the most general term employed to describe dissymmetry is *chirality*, from Greek χείρ meaning hand.

Chirality is a fundamental property of many three-dimensional objects. An object is chiral if it cannot be superimposed on its mirror image. In such a case, there are two possible forms of the same object, which are called *enantiomers*, again from Greek: ἐναντίος meaning "opposite" and μέρος meaning "part".

Stereochemistry, again from Greek στερεός, meaning "rigid" is the field of chemistry which deals with properties-shape of the molecules relationships.

Figure 1.1: chiral and achiral objects

The development of stereochemistry can be traced as far back as the nineteenth century; in 1801, mineralogist Haüy noticed that some apparently identical quartz crystals exhibited a few facets arranged in such a way as not to allow the superimposition of the crystals which showed the typical relationship between on object and its mirror image. Hemihedrism and hemiedric are terms equivalent to chirality and chiral specifically used for crystals.

In 1809 physicist Malus observed that quartz crystals could induce light polarization and in 1812 physicist Biot found that a quartz plate, cut at right angles with respect to a particular crystal axis, rotated the plane of the polarized light of an angle proportional to the thickness of the plate; right and left forms of quartz crystals rotated the plane of the polarized light in opposite directions. Biot, in 1815, extended these observations to pure organic liquids and solutions; he demonstrated that there were some differences between the rotation caused by quartz crystals and that caused by the solutions of organic compounds he was studying. For example, he noted that optical rotation caused by quartz was due to the whole crystal, whereas optical rotation caused by the solutions of organic compounds was due to individual molecules.

In 1822 the astronomer Herschel observed that there was a correlation between hemihedrism and optical rotation. He found that all quartz crystals having the odd faces inclined in one direction rotated the plane of polarized light in one direction, while the enantiomorphous crystals rotate the polarized light plane in

opposite direction.

In 1846 Pasteur observed that all the crystals of dextrorotatory tartaric acid had hemihedral faces with the same orientation and thus assumed that the hemihedral structure of the crystals of tartaric acid salt was related to its optical rotatory power. In 1848 Pasteur manually separated enantiomorphus crystals; he found that a solution of enantiomorphous crystals could rotate the plane of polarized light: one solution rotated the polarization plane to right, while the other one rotated the polarized light plane to left. The manual separation of the antipodes was possible since racemic sodium ammonium tartrate crystallizes from water below 28 °C as a conglomerate.

Dextro — Levo

COOH COOH
H—OH HO—H
HO—H H—OH
COOH COOH
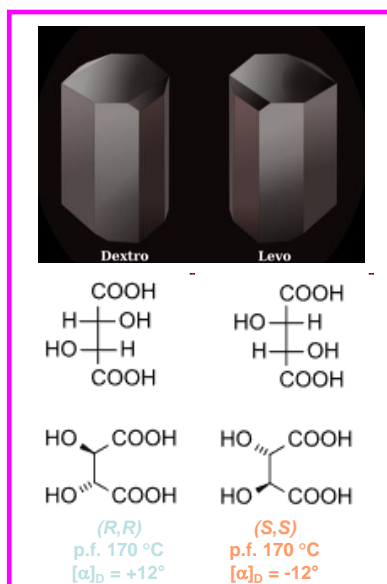
HO,,COOH HO,,,COOH
HO''''COOH HO''''COOH

(R,R) (S,S)
p.f. 170 °C p.f. 170 °C
$[\alpha]_D = +12°$ $[\alpha]_D = -12°$

Pasteur thus made the important deduction that the rotation of the polarized light plane caused by different tartaric acid salt crystals was the property of chiral molecules. The (+)- and (−)-tartaric acids were thought to be related as an object to its mirror image in 3-D. These tartaric acid salts were dissymmetric and enantiomorphous at the molecular level. Dissymmetry provided the power to the molecules to rotate the plane of the polarized light.

The work of these scientists in the nineteenth century led to basic understanding of chirality in chemistry. It became clear that the enantiomers of a chiral molecule were able to rotate the plane of the polarized light to a degree that is equal in magnitude, but opposite in direction; this fact was demonstrated, for the first time, by Emil Fischer through a Walden interconversion of the enantiomers of the 2-isobutyl malonic acid mono amide.

Within this historical frame, the actual birth of stereochemistry can be dated in 1874, when van't Hoff and Le Bel independently published two fundamental papers: both scientists suggested a three-dimensional disposition of atoms, basing their considerations on two central assumptions: that the four bonds of a saturated carbon atom were oriented along tetrahedron vertices, and that there was a correlation between the spatial arrangement of the four bonds and the properties of the molecules.

Van't Hoff and Le Bel proposed that the tetrahedral model for the carbon atom was the cause for molecular dissymmetry and optical rotation. By arguing that optical activity in a substance was an indication of molecular chirality, they laid the foundation of organic stereochemistry.[1]

1.1 Conditions for chirality

Chirality of a molecule or, more in general of an object, is dependent upon the symmetry of the molecule, or of the object.

Condition for chirality is the following: the molecule (the object) must display neither symmetry planes (σ), nor the inversion center (i), nor roto-reflection axes (S_n).

Axes (C_n) are, instead, compatible with chirality.

Molecules devoid of any symmetry element are obviously chiral and are properly called **asymmetric**.

Molecules displaying one or more C_n as the only symmetry element(s) are chiral and are defined as **dissymmetric**.

It is also evident that chirality is a property of the whole molecule, not of a molecular portion of it.

Stereogenic elements

In order to facilitate the description of how the atoms of stereoisomers are distributed in 2-D or 3-D space, chemists have selected some molecular elemental structures which are responsible, when present, for the production of stereoisomers: they are named stereogenic elements.

Stereogenic elements are structures, constituted either by a single atom or by a group of atoms, characterized by two or more directional ligands such as the permutation of two ligands produces a stereoisomer of the original molecule.

Sufficient, but not necessary, condition for the production of stereoisomers is the presence in the molecule of at least one stereogenic element.

In fact, some organic molecules are chiral even though devoid of rigid classical stereogenic elements, like topological stereoisomers, and the so called "residual" stereoisomers.

Topological stereoisomers, like three-foil knots and Moebius strips are characterized by "mechanical" bonds, while residual stereoisomers, like some three-bladed propellers, undergo low energy stereomerization mechanisms which do not allow enantiomerization, which is a process requiring a much higher activation energy.
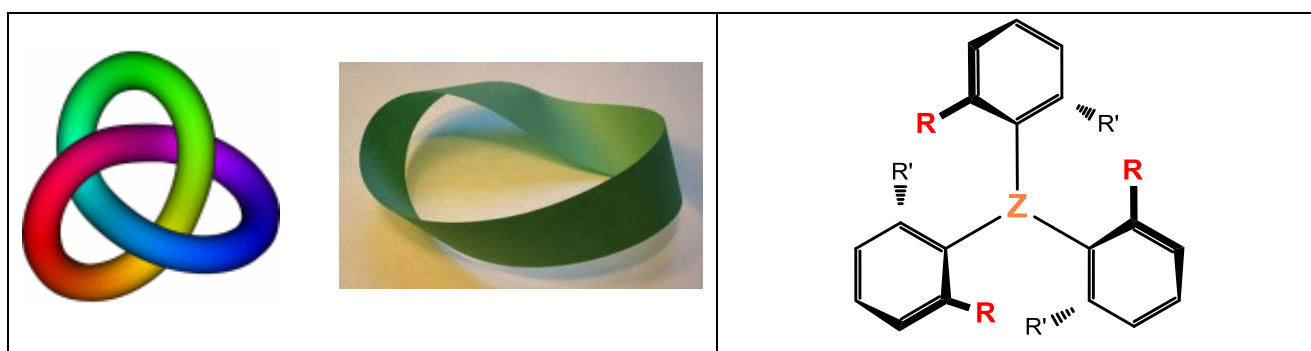
Figure 1.2

As for 2-D stereogenic elements, double bonds (C=C, C=N, N=N) carrying different substituents on each atom are stereogenic. Taking into account that double bonds are planar, this kind of stereogenic element does not originate chirality in the molecule which it belongs to. The stereogenicity descriptors of double bonds are E and Z, or *sequtrans* and *sequcis* respectively.
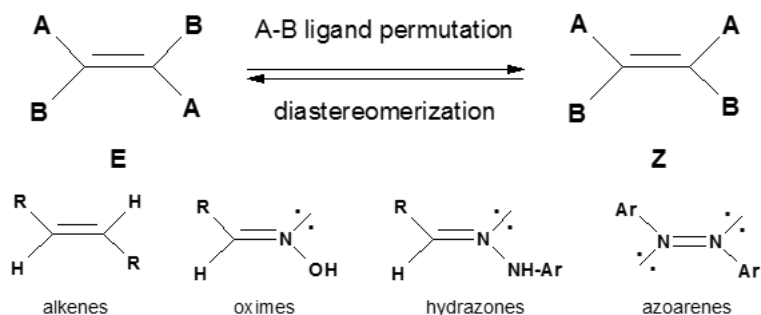
Figure 1.3

The most popular tridimensional stereogenic elements, then capable of generating chirality, are:

1-   The stereogenic center, or stereocenter

2-   The stereogenic axis

3-   The sterogenic plane

4-   The helix

1.1.1 Stereocenters

There are different kind of stereocenters: the most popular ones are the tetrahedral and the octahedral ones. Both of them are tridimensional and, by consequence able to produce chirality in the model.

Tetrahedral stereocenter

The tetrahedral stereocenter is a tetrahedral atom carrying four different ligands (a lone pair can behave as one of the ligands).
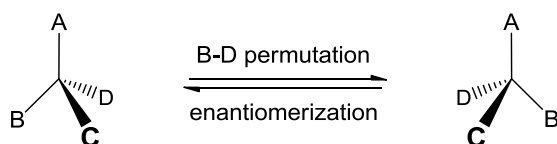
Figure 1.4

If only ONE tetrahedral stereocenter is present in the molecule, the molecule is chiral and asymmetric (C_1). In this case, any ligand permutation corresponds to an enantiomerization process.

The stereogenicity descriptors are *R* and *S*.

The most common stereogenic atom is C, but also Si, N, P, As, S are known to be stereogenic in several popular functions, like asymmetric phosphanes and arsines, sulfoxydes, quaternary ammonium or phosphonium salts, etc..

In the case of amines and tris-arylphosphanes (not in aryl-dialkyl and diaryl-alkylphosphanes) the lone pair inversion barrier is too low to allow the isolation of enantiopure enantiomers since the racemization of a single enantiomer is fast at room temperature.
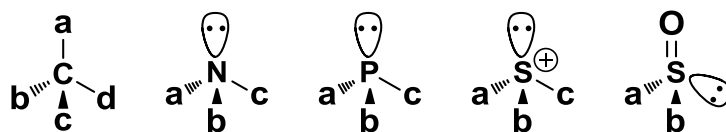
Figure 1.5

A situation analogous to that shown by the atoms cited above is provided by metals, like Mn, Cu, Bi, Zn etc. when in a tetrahedral coordination.

Stereocenters are often erroneously named "chiral centers", due to the fact that if a single stereocenter is present in the molecule, the latter is certainly chiral. It is, however, not correct to confine chirality, a property of the whole object, to a single atom. Furthermore, if more than one stereocenter is present in the molecule the latter, in some specific cases, could be achiral and it could be an evident nonsense to say that an achiral molecule contains several "chiral centers". Classical examples are the meso-tartaric acid (2 stereocenters) and the meso meso-2,3,4-trihydroxyglutaric acids (3 stereocenters)

Octahedral stereocenter

This kind of stereogenic element is rather common in organometallic compounds where the stereocenter is the metal atom
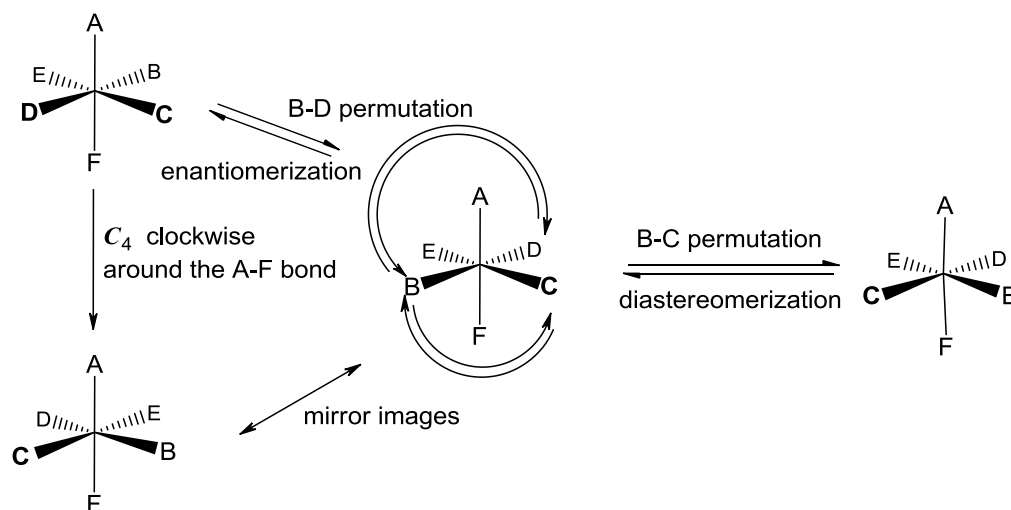
Figure 1.6

A ligand permutation can correspond either to enantiomerization or diastereomerization processes depending on which couple of ligand is involved in the exchange.

1.1.2 Stereogenic axis

The simplest version of the stereogenic axis is constituted by a system in which two identical pairs of different groups identify two orthogonal planes, the intersection of which is the stereogenic axis. In this case, the system display a C_2 axis and is dissymmetric. It is asymmetric (C_1) when the two group pairs on each side of the axis are different.
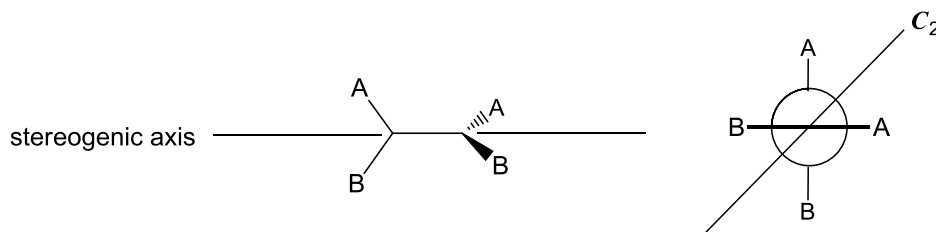
Figure 1.7

Some chiral molecules characterized by a stereogenic axis are spiranes, allenes, cyclohexanes and biaryls. Such systems are referred to as axially chiral systems, implying that the chirality of these molecules takes origin from the presence of a stereogenic axis (Figure 1.8). Instead, to call as "chiral axis" the stereogenic axis a wrong rather common habit, since makes confusion between chirality and stereogenicity.
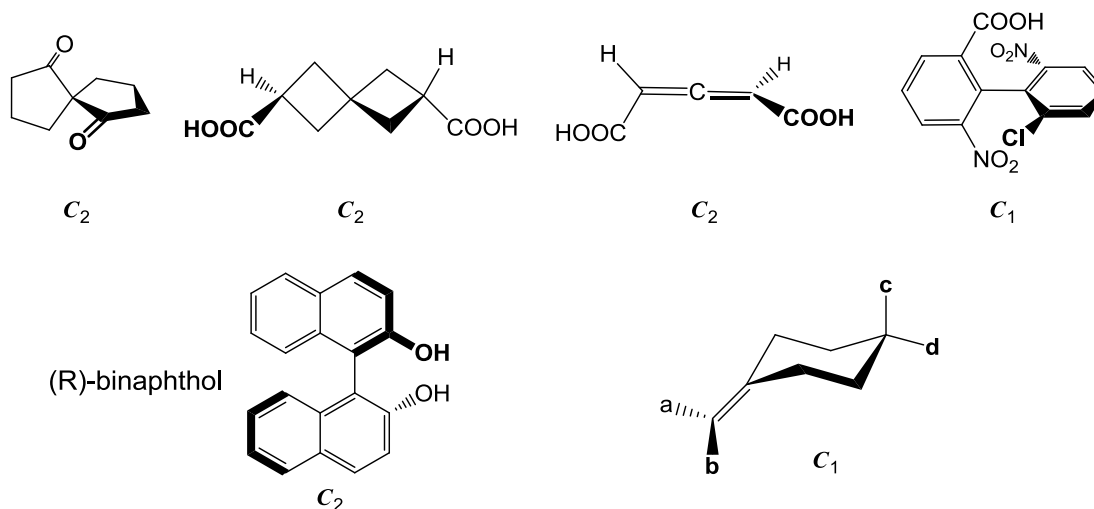
Figure 1.8: Some chiral compounds with stereogenic axis

This kind of stereoisomerism will be discussed in detail in Section 1.2.

1.1.3 Stereogenic Plane

The stereogenic plane is constituted by a sequence of three different atoms individuating a plane with a fourth group outside the plane, capable of distinguishing its enantiotopic faces (Figure 1.9).
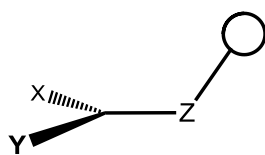
Figure 1.9

Stereogenicity descriptors are *R* and *S*, selected according to the clockwise or anticlockwise priority sequence of the atoms in the plane as seen from the so called "pilot" atom, which is the first atom outside the plane. If the priority sequence in the plane moves from Z to X, the stereogenic plane configuration is *R*, while is *S* if the priority sequence moves towards Y.

Typical molecules endowed with a stereogenic plane are ansa compounds and cyclophanes. They can be both dissymmetric and asymmetric.
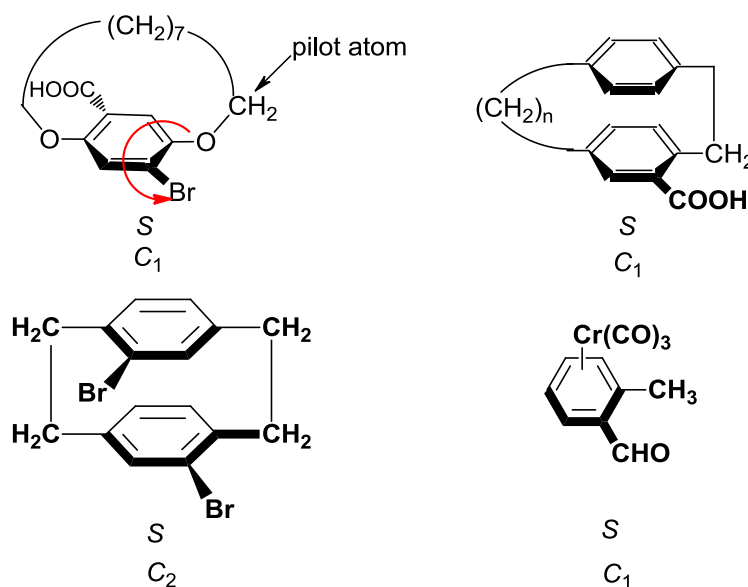
Figure 1.10: Some chiral compounds with stereogenic plane

For the same reasons previously discussed, to call as "chiral plane" the stereogenic plane is a wrong, even though rather common, habit.

1.1.4 Helicity

Helicity is a stereogenic element characterizing the chirality of two main molecular architectures: the helix and the propeller shaped molecules.

The helices are shaped as right- or left-handed screw thread or a spiral stair (Figure 1.11).

The propellers are characterized by blades which display the same bent with respect to the propeller hub.

The common characteristic property of these molecules is their theoretical ability to move back and forth along the axis by rotation. Molecular descriptors *P* and *M* are related to this property: if the molecule moves

away from the observer by clockwise rotation around the axis, helicity is *P*, while it is M if it moves towards the observer.
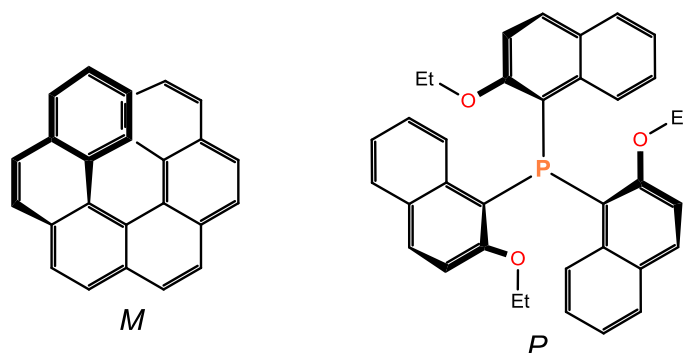
Figure 1.11: example of helical chiral compound

Chirality is of prime significance, as most of the biological macromolecules of living system occur in nature only as a single enantiomeric form. A biologically active chiral compound interacts with its receptor site in a diastereomeric manner, and enantiomers may be discriminated by the receptor in very different ways; thus, it is mandatory to keep in mind the bases of chiral discrimination when designing biologically active molecules: it's quite clear that chirality plays the most important role in life sciences[1].

The pharmaceutical industry has shown a deep interest in chiral drugs, since our body is a highly selective discriminator of chiral structures (see Figure 1.12); nowadays two thirds of the prescribed drugs contain active chiral compounds and most of new medicinal specialities are single enantiomers.
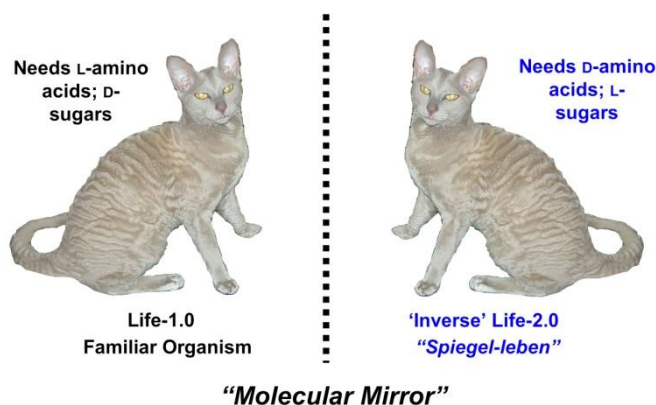
Figure 1.12: example of body discrimination

An often cited example that emphasizes the importance of stereochemistry in the pharmacological properties of bioactive compounds is related to the thalidomide disaster during the 1950s[2] (Figure 1.13): this is a powerful sedative and antinausea agent prescribed for pregnant women; unfortunately the drug was discovered to be a very potent teratogen, causing serious harmful effects on the fetus. Studies showed that

this teratogenicity was caused by the (*S*)-enantiomer (the distomer), but the drug was sold as racemate; the (*R*)-enantiomer (eutomer) was found to not cause deformities at all in animals even at high dosage levels.
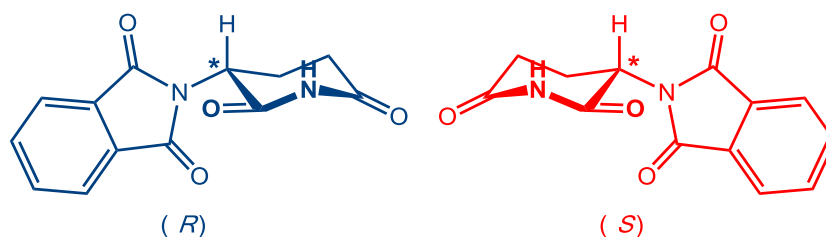
Figure 1.13: The enantiomers of Thalidomide

The attention on chirality has grown dramatically since 1992, when the Food and Drug Administration in the USA, the main regulatory organism in this field, published a directive imposing the development of new chiral drugs as single enantiomers in cases whenever this could improve safety and/or efficacy.[3] The necessity to synthesize pharmacologically active substances (API, Active Pharmaceutical Ingredients) as single enantiomers, rather than as racemates, prompted the chemical community to develop a wide range of methods aimed at achieving this goal.[4]

The main discriminating parameters to evaluate the different synthetic strategies are production costs, expectedly the fundamental voice in the world of industrial activity, and environmental protection, which is imposed as a prerequisite to the primary sector in the past twenty years.

Not only the pharmaceutical industry, but also other areas where chemistry is protagonist, such as agriculture, fragrance and the world of materials, are active in the development of new chiral molecules. Just consider, for example, insecticides and herbicides, which for years have been leading products of big multinationals like Monsanto, or LCD, which have now replaced the old systems of image display.

The discovery of highly efficient and reliable methods for obtaining enantiopure chiral substances at reasonable costs is a great challenge for the synthetic organic chemist.

The syntheses of enantiopure chiral compounds from achiral starting materials, in which one enantiomer is produced preferentially to its antipode through the mediation of a chiral catalyst, undoubtedly are those that, amongst the many methodologies available for this purpose, like the classical and the kinetic resolution of racemates and the asymmetric induction, combine operational simplicity with high efficiency in terms of stereoselectivity, kinetics and substrate/catalyst ratio.

The phenomenon of the so-called "chiral multiplication" by which a molecule of a chiral catalyst transforms thousands of molecules of an achiral substrate into a single enantiomer is a fascinating process that is now common for specific types of reactions, even at an industrial level.

It is evident that the key for success of an asymmetric catalytic process is related to the efficiency of the catalyst and it is well documented that each reaction, requires a specific mediator to attain high enantioselection levels and fast reaction rates.

The variety of chiral catalysts appeared in recent literature is incredible, ranging from those which are soluble in the reaction medium (homogeneous asymmetric catalysis) to those who are working in heterogeneous phases (asymmetric heterogeneous catalysis).

The catalytic enantioselective methodologies that chemists have available are essentially two: the organometallic catalysis, in which the chiral catalysts are organometallic complexes of a transition metal, which becomes the reaction center. The metal is complexed with a chiral ligand which enables it to perform the enantiofacial recognition process on the prochiral substrate, and organic catalysis, where organic molecules perform the same role of organometallic complex without requiring metal complexation.

Thousands of chiral ligands have been prepared so far, although a relatively small number of structural classes emerge for their wide applicability and synthetic accessibility. Examination of their structures indicates that an incredibly large number of them possesses C_2 symmetry, such as DIOP, the first C_2-symmetric ligand introduced by Dang and Kagan in 1971,[5] BINAP,[6] DIPAMP[7] and many others could be cited. In most of the scenarios for absolute stereochemical control, the presence of a C_2 symmetry axis within the chiral mediator can significantly reduce the number of possible diastereomeric transition states.[8]

1.2 Chiral catalysts with a stereogenic axis (Axial chirality)

Stereogenic axis is a very popular stereogenic element: it is a key feature of many important organic molecules, such as biologically active compounds, new functional materials and, in particular, it is widely applied in the design of chiral ligands (axial chirality). It is generally related to the presence of an atropisomeric scaffold.

Chirality due to the presence of stereogenic axes is well documented since the 20th century: in particular, Christie and Kenner reported the first experimentally proven case of optical activity in the case of the 6,6'-dinitro-2,2'-diphenic acid in 1922.[9]

In 1933 Kuhn[10] introduced the definition of atropoisomerism (from Greek: privative α and τρέπω = turn) and at was first referred to biaryl compounds only.

Biaryl systems isomerism has been exensively investigated. Oki arbitrarily defined the condition for the existence of atropisomers: one can say that atropisomerism occurs when the enantiomers can be isolated and, at a given temperature, they have a half-life of at least 1000 seconds.[11]

The configurational stability of chiral biaryl compounds is determined by three major factors:

a) the combined steric demand of the substituents in proximity of the stereogenic axis

b) the existence, length and rigidity of bridges interconnecting the two arene moieties

c) the involvement of isomerization mechanisms different from a merely physical rotation around the axis, for example, photochemically or chemically induced processes.

The most known biologically active compound equipped with a rotationally hindered biaryl systems is the antiobiotic vancomycin (Figure 1.14): this molecule contains three types of stereogenic elements (numerous

stereogenic centers, two stereogenic planes, and a stereogenic biaryl axis), which together impose the rigid 3D structure necessary for an efficient binding to peptides of bacteria cell walls.[12]
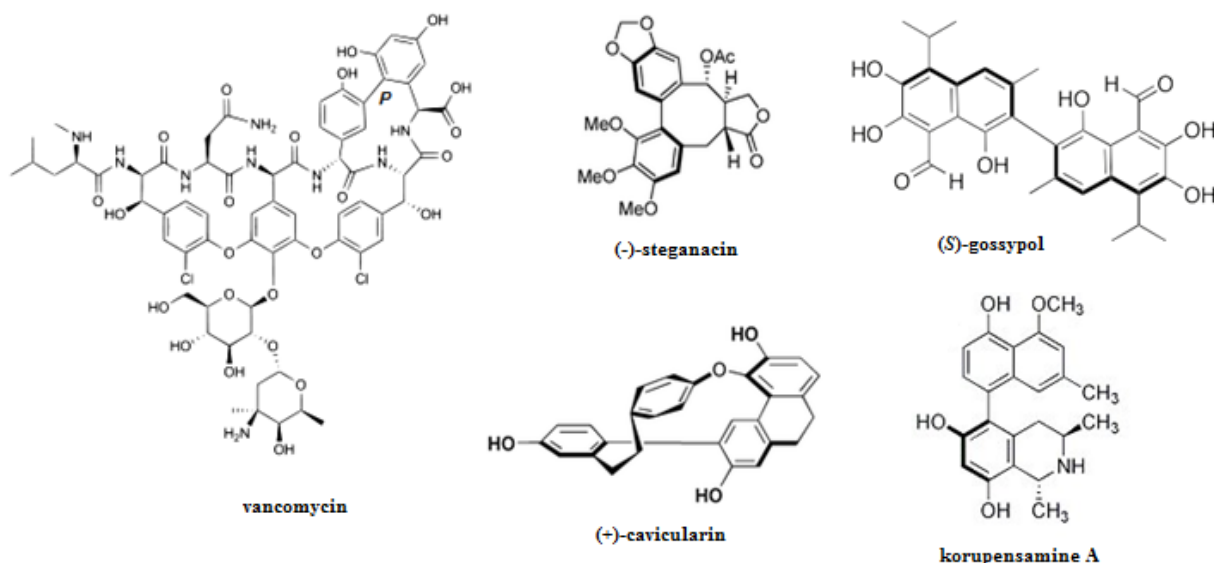
Figure 1.14: examples of natural compounds with stereogenic axis

Other selected examples of biologically active compounds exhibiting a stereogenic axis are korupensamine A, steganacin, gossypol and cavicularin (Figure 1.14); the class of chiral compounds characterized by a stereogenic axis is, however, not restricted to C-C coupled biaryl compounds: for example, (*M*)-murrastifoline-F is a bis-carbazole with the two "parts" interconnected through a biheteroaryl C-N bond (Figure 1.15).[13]
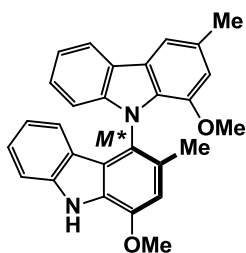
Figure 1.15: structure of (*M*)-murrastifoline-F

Also some modern materials, like liquid crystals, are characterized by atropoisomeric architectures; for example Diederich described the synthesis and the properties of *N*-arylated 3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepines and investigated both experimentally and computationally their ability to induce cholesteric supramolecolar assemblies in nematic liquid crystals (Figure 1.16).[14]
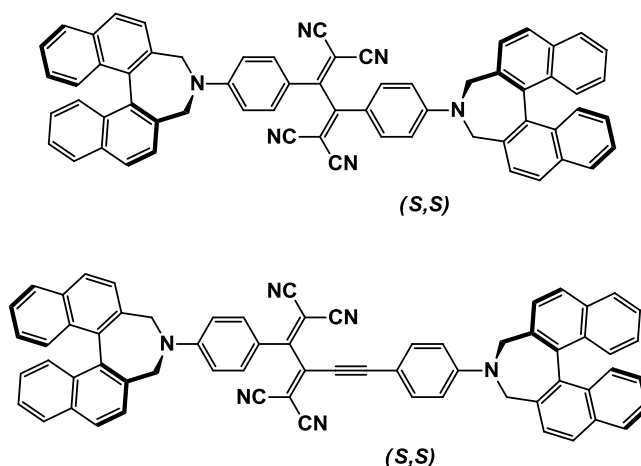
Figure 1.16

In the field of asymmetric synthesis, the atropoisomerism of biaryl molecules has been studied extensively; a particularly interesting class of biaryl compounds is that of 2,2'-disubstituted derivatives of 1,1'-binaphthyls. The stability of the enantiomers, with barriers of rotation ranging from 23.8 kcal/mol for 1,1'-binaphtyl to more than 46 kcal/mol for 2,2'-diiodo-1,1'-binaphthyl, enables their use as chirality inducers in stereoselective reactions.

The most important and popular compounds of this type are the 1,1'-binaphthyl-2,2'-diol (BINOL) and the 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl (BINAP).

1.2.1 The case of BINOL, BINAP and BINAPO

In the field of organometallic catalysis, BINOL was employed as ligand of various transition metals, displaying high enantioselection in a widespread series of reactions, such as enone epoxidations, ene-reactions, Diels-Alder and hetero Diels-Alder cycloadditions, aldol condensations and allylations of carbonyl compounds.

Enantiopure BINOL has been extensively used to develop catalytic or stoichiometric methods for enantioselective epoxidation; Shibasaki reported the use of lanthanum- or ytterbium modified BINOL derivatives as catalysts in the asymmetric epoxidation of enones, using hydroperoxides as oxidants such as *tert*-butyl hydroperoxide (TBHP).[15]

The best results were obtained employing La-BINOL-triphenyl arsine oxide complex, that exhibited higher activity and selectivity compared to the analogous ytterbium complexes and afforded a broad generality of optically active epoxy ketones in up to 99% yields and 99% ee (Scheme 1.1).[16]
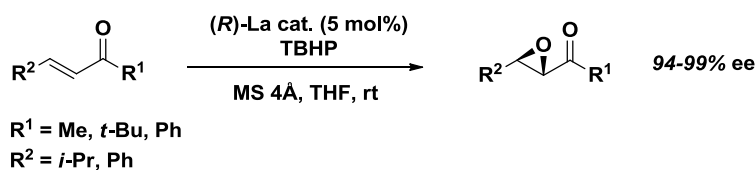
Scheme 1.1

Also the catalytic asymmetric synthesis of α,β-epoxy esters, aldehydes, amides, and γ,δ-epoxy-ketoesters has been investigated and high enantioselectivity levels were obtained (Scheme 1.2).[17]
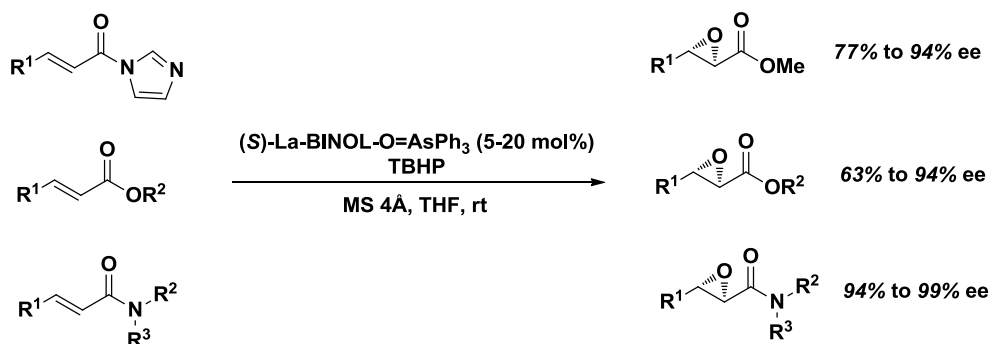
Scheme 1.2

In the field of the ene reaction, the first successful example of asymmetric induction with BINOL-Al catalyst was reported by Yamamoto, who dealt with the formation of limonene and bisabolenes.[18]

The greatest contribution to this field was given by Nakai and Mikami, who studied the glyoxylate-ene reaction in great detail.[19] Extensive screening of various chiral catalysts derived from optically active diols indicated that BINOL-Ti catalysts, employed in 1:1 ratio, provided the best levels of enantioselection (Scheme 1.3).
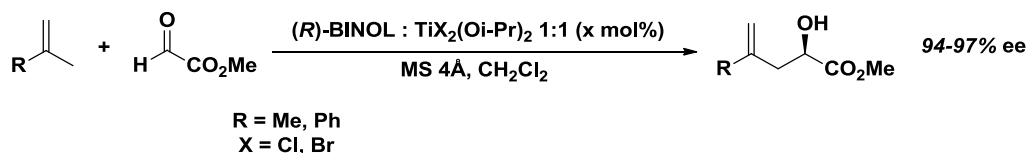
Scheme 1.3

This protocol was employed also for the synthesis of the precursors of natural products; the synthesis of an intermediate for the preparation of (R)-ipsdienol, an aggregation pheromone of bark beetles, is reported as example (Scheme 1.4).
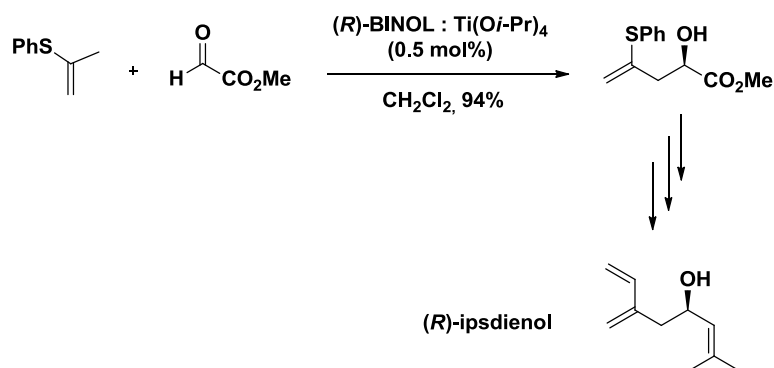
Scheme 1.4

Diels-Alder reactions were also extensively studied, employing BINOL with different metals as titanium,[20] boron,[21] zinc[22] and ytterbium.[23] Mikami reported the reaction of juglone with butadienyl acetate using BINOL-Ti catalyst; the achievement of the cycloadduct provided an efficient approach to the asymmetric synthesis of anthracycline and tetracycline antibiotics (Scheme 1.5).[24]
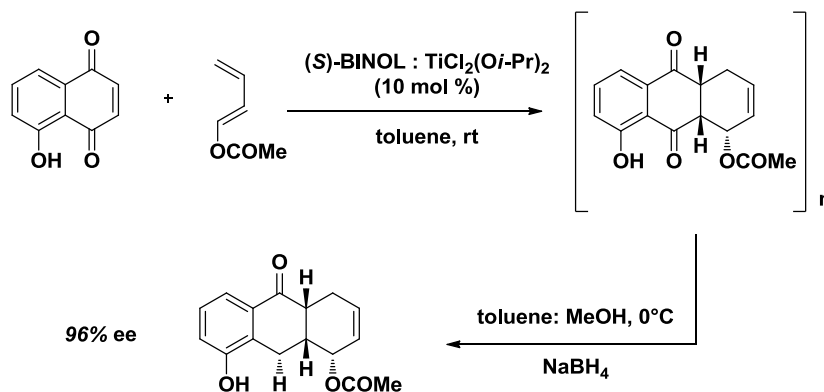
Scheme 1.5

In the field of aldol reaction, Mukaiyama reported the first encouraging results with a closely related BINOL-Ti complex;[25] up to 85% ee were reported with a complex formed from (*R*)-BINOL and (*i*-PrO)$_2$-Ti(O) (Scheme 1.6).
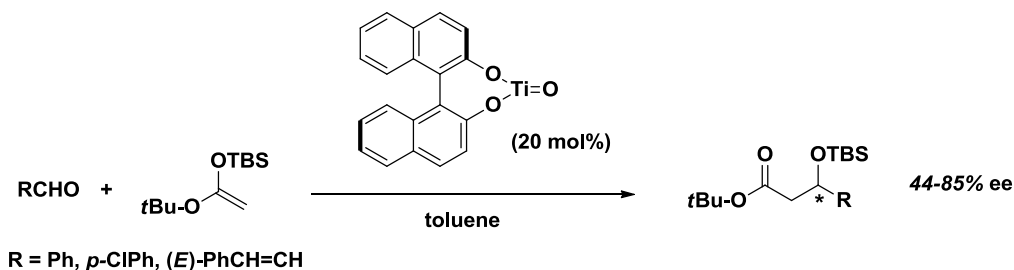
Scheme 1.6

Mikami studied the addition of ketene sylilacetals of ester or thioesters to various aldehydes catalyzed by mol 5% of a complex prepared from (R)-BINOL and TiCl$_2$(O*i*-Pr)$_2$; the reaction led to the sylilether of the expected aldol product in good yields and satisfactory enantiomeric excesses (Scheme 1.7).[26]
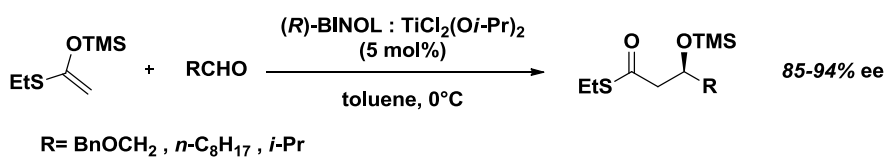
Scheme 1.7

Mikami also showed that the reaction involving ketene sylilacetal of thioesters could be applied to floural aldehyde allowing an enantioselective synthesis of a CF$_3$-substituted aldol of high biological importance (Scheme 1.8).[27]
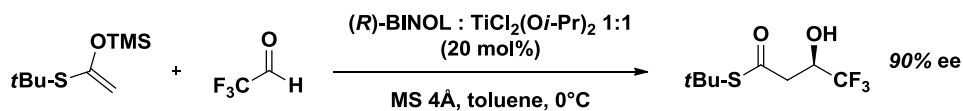
Scheme 1.8

Furthermore, the same research group made a tandem and two directional enantioselective aldolization: the pseudo-C_2 symmetric product of the condensation between the silyl enolether and two molecules of the methyl glyoxylate led, through a five step sequence, to a potential powerful analogue of HIV protease inhibitor (Scheme 1.9).[28]
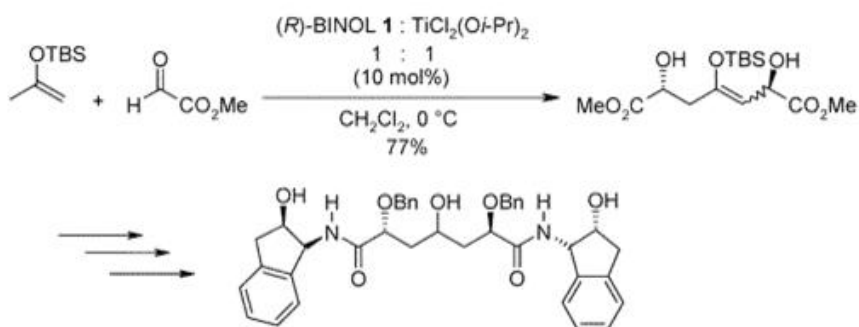
Scheme 1.9

For the allylation reaction of carbonyl compounds, in 1993 Mikami and Nakai used a complex prepared in situ from (S)-BINOL and TiCl$_2$(Oi-Pr)$_2$, in the presence of 4Å molecular sieves, in the enantioselective reaction of tri-n-butyl-allyltin with a wide variety of aldehydes; the condensation of tri-n-butyl-allyltin on glyoxylates develops with both good diastereoselectivity and high enantioselectivity (Scheme 1.10).[29]
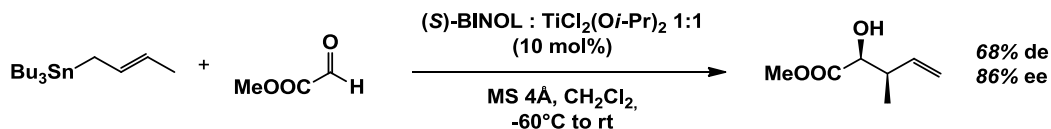
Scheme 1.10

The same catalyst, used by Tagliavini and Umani-Ronchi in mol 10 %, promotes the allylation of simple achiral aldehydes with good chemical yields and excellent enantiomeric excesses (Scheme 1.11).[30]
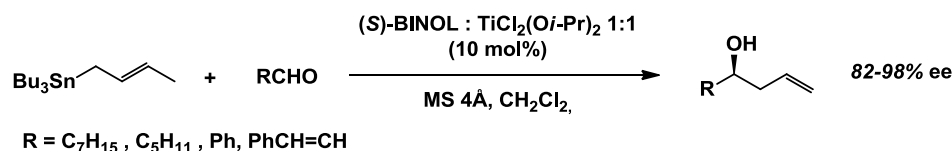
Scheme 1.11

In 1996 Kocienski reported a synthesis of the C_1-C_{21} fragment of the immunosuppressant rapamycin, who involved an asymmetric allylation to introduce the first stereogenic center of the target molecule; the reaction was run on a 350 mmol scale, and (R)-BINOL could be recycled (Scheme 1.12).[31]
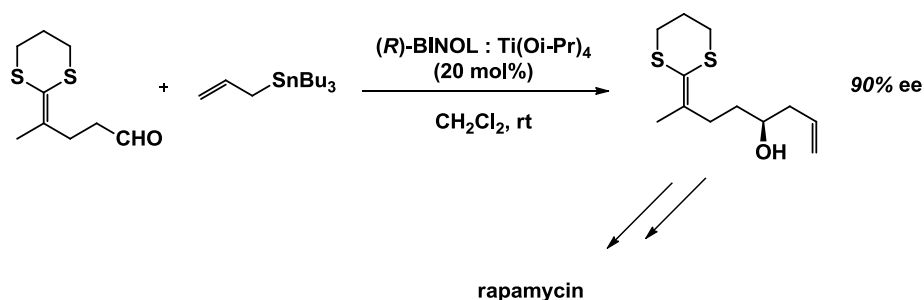
Scheme 1.12

More recently, new applications of BINOL in the organic catalysis were investigated, even though not always with satisfactory enantioselection levels; to improve these results, new BINOL derivatives were synthesized, characterized by more steric hindrance close to hydroxyl groups, or with a bulkier phenanthrene scaffold (Figure 1.17).

X=H, Br, Ph, 3,5-$(CH_3)_2$-C_6H_3 , SO_2CF_3
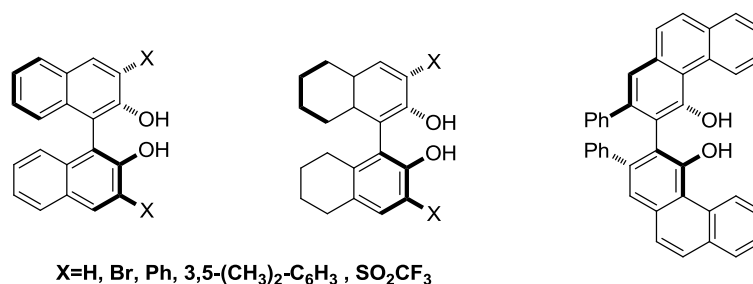
Figure 1.17

These new diols were successfully employed as organic catalysts in asymmetric allylboration of ketones[32] and acyl imines[33], and asymmetric in the three component Petasis condensation reaction involving secondary amines, glyoxylates and alkenyl boronates.[34] An important mechanistic aspect, in each reaction is the replacement of one of the boronate alkoxy group with the chiral diol in order to obtain a more reactive boronate species.

The reaction of acetophenone with allyl-diisopropyl borane led to the expected allylalcohol in 44% ee with the employment of BINOL, while the use of diol with X = Br allowed to obtain a 95% ee. The reaction was

extendend to a wide range of both electron-rich and electron-poor arylketones, heteroaromatic ketones and enones, maintaining high enantiomeric excesses (Scheme 1.13).
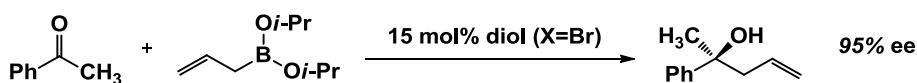
Scheme 1.13

Schaus applied a chiral diol catalyst screening protocol for the rapid identification of the best conditions for enantioselective catalytic reactions; the approach successfully identified a single catalyst for each of the boronates investigated able to efficiently promote the reaction with satisfactory enantioselectively. Furthermore the optimal catalyst identified proved to be general for each class of boronate nucleophiles.

The versatility of BINOL is due not only to its use in organometallic, or organic catalysis, but it can also be used as starting material to obtain different kind of derivatives, which in turn can be used in numerous asymmetric transformations; in particular phosphoric acids[35] were employed in organic catalysis, while phosphoroamides,[36] phosphoroamidites,[37] and phosphites[38] were employed as ligand of many transition metals in organometallic stereoselective catalysis (Scheme 1.14).
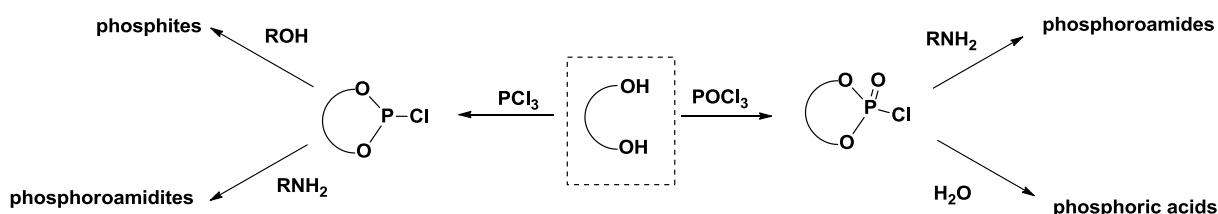
Scheme 1.14

Furthermore, commercially available enantiopure BINOL is now employed as starting material for the synthesis of enantiopure BINAP (Scheme 1.15).[39]
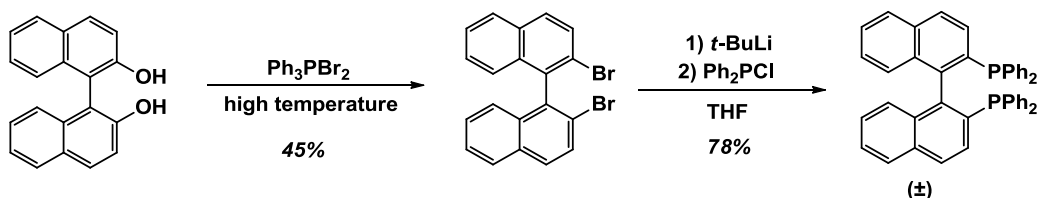
Scheme 1.15

The synthesis and the first application of BINAP were reported by Noyori and Takaya in 1980.[39] This ligand very effectively induces stereoselection by intra-complex steric interactions between the bulky

triarylphosphine system and the reactants bound to the metal; its application in asymmetric catalysis has been widely studied and well documented in numerous articles and textbooks.[40]

Ruthenium complexes of BINAP had proved to be successful in inducing high to excellent enantioselectivities in the hydrogenation of olefinic substrates, such as a range of α,β-unsatured carboxylic acids (Scheme 1.16).[41]

$$R^3 \diagup CO_2H \quad \xrightarrow[\substack{MeOH \\ 15\text{-}30°C, 12\text{-}24h}]{\substack{Ru(II)\text{-}BINAP \\ 4\text{-}135 \text{ atm } H_2}} \quad R^3 \diagdown{}_*CO_2H \qquad 85\text{-}99\% \text{ ee}$$

R^1 = alkyl, aryl, hydroxycarbonylalkyl
R^2 = H, hydroxyalkyl
R^3 = H, alkyl
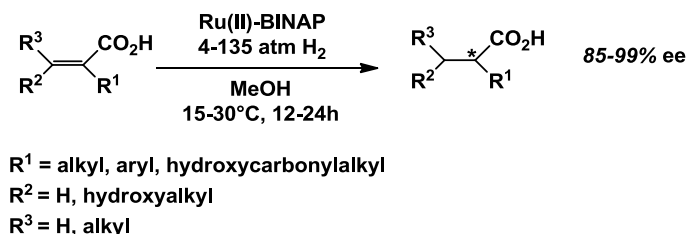
Scheme 1.16

N-acylaminoacrylic acids were successfully reduced using Ru(II)-BINAP and Rh(I)-BINAP complexes in high to excellent enantioselectivities[39,42] (Scheme 1.17). The use of Rh(I)-BINAP catalysis is however limited to a small range of suitably functionalized olefinic substrates, whereas Ru(II)-BINAP shown a much broader versatility.

$$R^3 \diagup CO_2H \quad \xrightarrow[\substack{MeOH \\ 25°C, \text{ up to } 24h}]{\substack{Ru(II)\text{-}BINAP \text{ or } Rh(I)\text{-}BINAP \\ H_2}} \quad R^3 \diagdown{}_{*}{}_{*}CO_2H \qquad \text{up to } 100\% \text{ ee}$$

R^1 = alkyl, aryl
R^2 = H
R^3 = H, alkyl, aryl
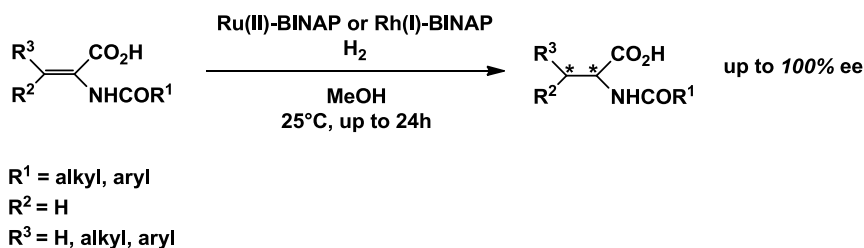
Scheme 1.17

Highly enantioselective reduction of substituted allylic alcohols has also been investigated (Scheme 1.18). With these substrates, the sense and the extent of asymmetric induction are highly dependent on the substitution pattern and on the reaction conditions, in particular hydrogen pressure.[43]

Racemic allylic secondary alcohols, as 4-hydroxy-2-cyclopentenone were successfully resolved by a kinetic resolution process using a Ru-BINAP catalyzed hydrogenation (Scheme 1.18).[44]
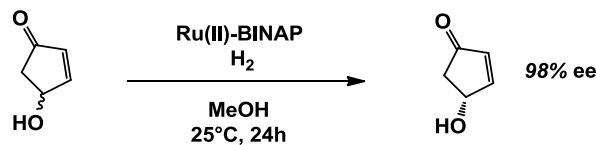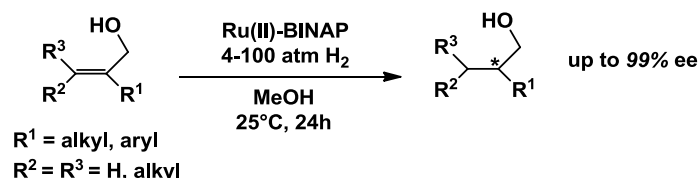
Scheme 1.18

Analogously to the C=C double bonds hydrogenation, the enantioselective reduction of carbonyl groups reached a high level of success by 1992. α-Keto acid derivatives were reduced in quantitative yields, with enantioselectivities up to 89%;[45] similarly, excellent activities and enantioselectivities were obtained with β-keto esters (Scheme 1.19).[46] However, as reporting in the following examples, high pressures are required in order to achieve good results.
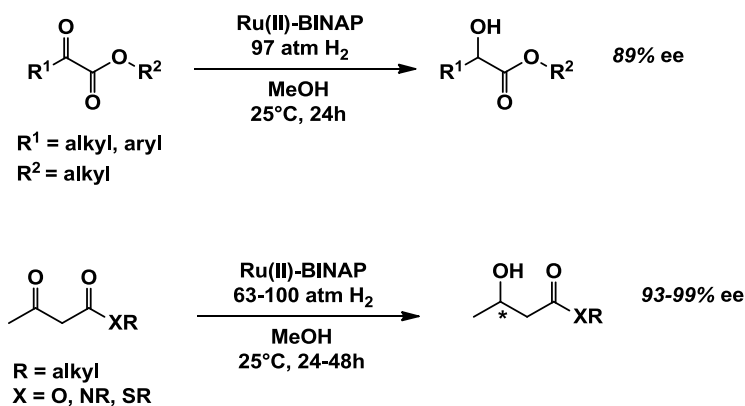
Scheme 1.19

Excellent enantioselectivities have been also obtained in the hydrogenation of γ-keto esters and *o*-acylbenzoic esters that allowed acceding to the corresponding γ-lactones and *o*-phthalides (Scheme 1.20).[47]
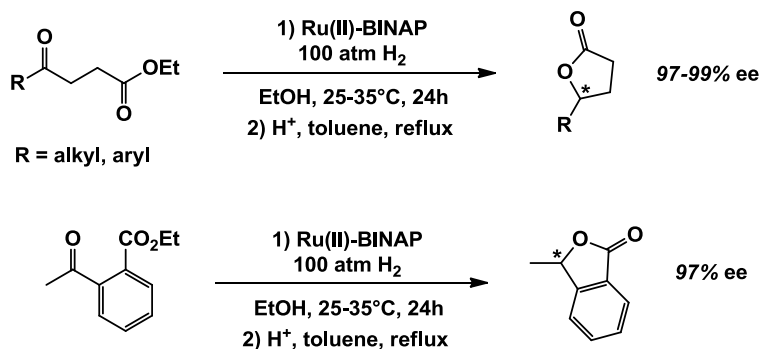
Scheme 1.20

The BINAP-Rh catalysed enantioselective isomerisation of allylamines to optically active enamines proceeds with high chemoselectivity and excellent enantioselectivity (96-99% ee); in this isomerisation process there is an excellent correlation between the substrate geometries, product (E)-enamine and BINAP configuration (Scheme 1.21).[48]
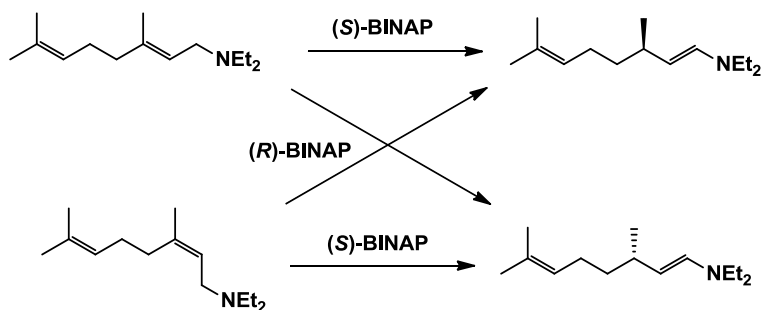
Scheme 1.21

The enantioselective substitution of allylic acetates is the most studied stereoselective carbon-carbon bond forming process catalyzed by transition metal complexes of palladium; it is an important transformation which has proved to be a useful testing ground for the design and the experimentations of novel ligands and for gaining mechanistic insight into organo-palladium chemistry.

Pd complexes of BINAP were applied with some success to the standard reaction of malonates and 1,3-diphenylpropenyl acetate; reaction times were relatively long and enantioselectivities and chemical yields were from moderate to good.[49]
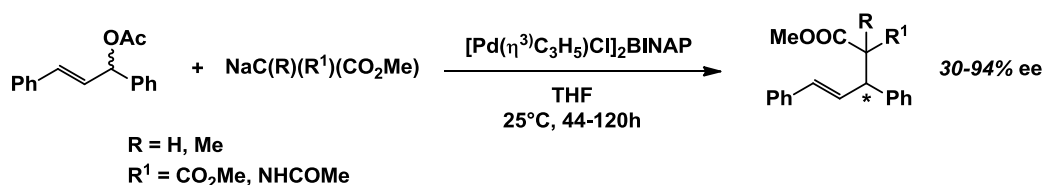
Scheme 1.22

A second carbon-carbon bond forming reaction in which palladium complexes of BINAP have been utilized is the Heck reaction. In the intermolecular variant, the reaction is between 2,3-dihydrofuran and the aryl triflates was chosen as test reaction; it proceeds in the presence of a base and a palladium catalyst generated in situ from Pd(OAc)$_2$ and (R)-BINAP. Hayashi reported that it affords the (R)-2-aryl-2,3-dihydrofuran and moderate amounts of the (S)-2-aryl-2,5-dihydrofuran (Scheme 1.23).[50] The base affected the enantiomeric purity of the (R) enantiomer and the sterically demanding 1,8-bis(dimethylamino)naphthalene afforded the best results for a wide range of aryl triflates.

Ar = *p*-ClC$_6$H$_4$, *o*-ClC$_6$H$_4$, *m*-ClC$_6$H$_4$,
   p-AcC$_6$H$_4$, *p*-NCC$_6$H$_4$, *p*-MeC$_6$H$_4$,
   2-naphthyl
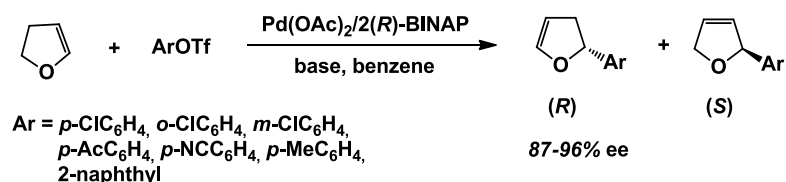
Scheme 1.23

The first successful intramolecular asymmetric Heck reaction using BINAP-Pd complexes was reported in 1989 by Shibasaki who focused on the preparation of the *cis*-decalin derivatives from prochiral alkenyl iodides or triflates, attaining enantioselectivities up to 92% even though in moderate yields.[51]

R = CO$_2$Me, CH$_2$OAc, CH$_2$OPiv, CH$_2$OTBDMS
X = I, OTf
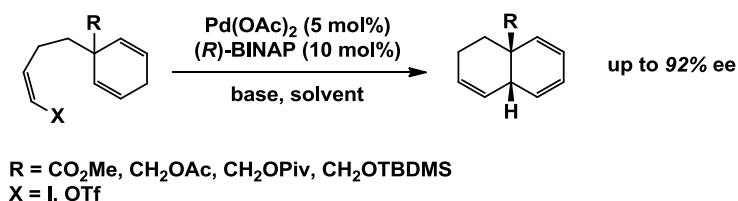
Scheme 1.24

Overman showed that, using a single enantiomer of BINAP, the enantioselection outcome could be opposite in the Heck cyclisation of aryl iodides depending on the reaction conditions:[52] for example, the aryl iodides afforded either the (R)-spirooxoindole or the (S)-spirooxoindole, with reasonable enantioselectivities, in a palladium catalysed cyclisation carried out either in the presence or in the absence of silver salts (Scheme 1.25).
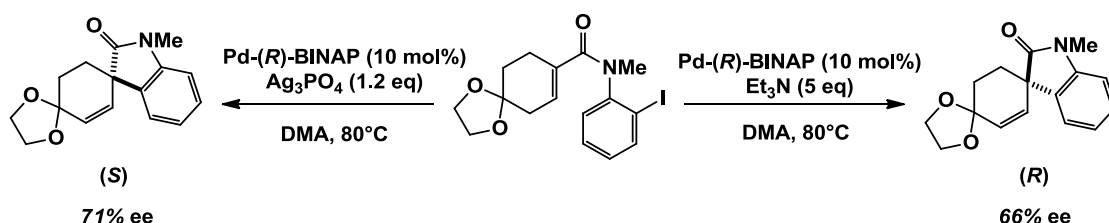
Scheme 1.25

Given the great efficiency and the high levels of enantioselectivity affordable with the metal complexes of BINAP in a very wide range of reactions, the design and the synthesis of new atropoisomeric diphosphines is a field in continuous research development.

Due to the success of the 2,2'-binaphthyl backbone as chiral promoter, both in BINOL and BINAP, Kobayashi in 2004[53] investigated the potentiality of BINAPO, the product of oxidation of the latter, as organic catalyst in the addition of allyl-trichlorosilane to *N*-benzoylhydrazones; the catalyst was used in stoichiometric amounts to obtain high yields and high enantioselectivity levels (Scheme 1.26). This represents one of the few examples of enantioselective allylation of the C=N double bond mediated by a non-

metallic promoter.

(S)-BINAPO

R = Et, *i*-Pr, *c*-Hex, Bn
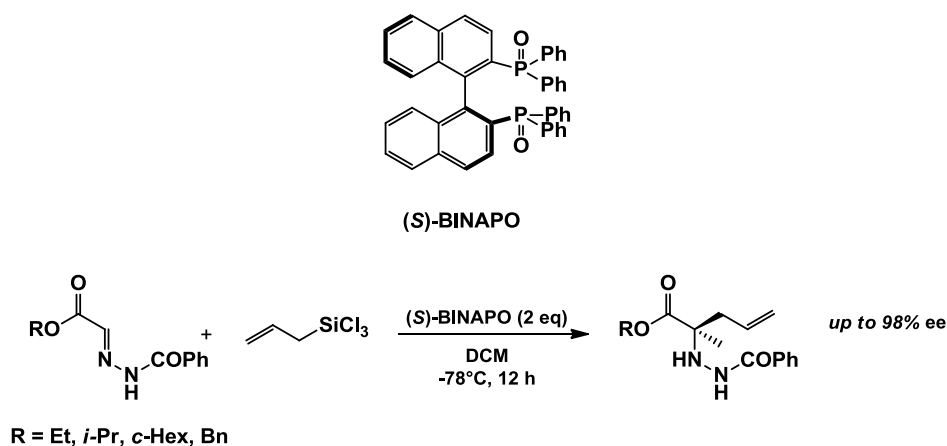
Scheme 1.26

In 2009, Nakajima showed that Lewis base-catalyzed allylations with allyltrichlorosilanes proceed via chair-like transition states that involve hypervalent silicates, in which the addition of (*E*)- and (*Z*)-silane provide the *anti*- and *syn*-product, respectively, with high diastereoselectivity (Scheme 1.27).[54]
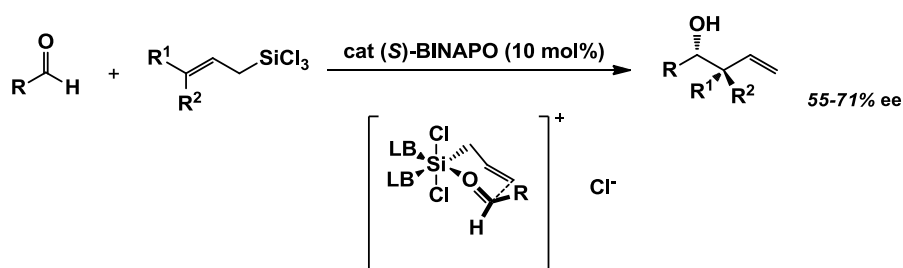
Scheme 1.27

Further applications of BINAPO as organic catalysts have been found in the epoxide ring opening, that led to the products in high yields and surprising enantiomeric excess, and in the aldol condensation between benzaldehyde and cyclohexanone, activated as silyl enol ether.[55] In the latter reaction, the addition of DIPEA was found to increase the yields and to raise diastereoselectivity to the 86% in favor of the *anti* diastereoisomer, that was obtained in a 87% ee (Scheme 1.28). The base develops the function both to neutralize the hydrochloric acid and to increase the reaction rate, encouraging the diphosphine oxide dissociation from the silicon atom.
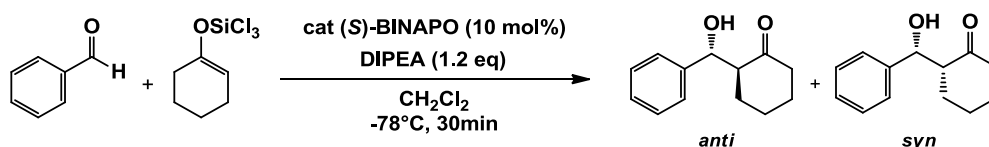
Scheme 1.28

1.2.2 Bisoxazoline ligands

Not only ligands bearing phosphorous atoms or hydroxy groups were employed in asymmetric catalysis, but also nitrogen ligands played important role in this field. Among the most common nitrogen ligands (e.g. amines, Schiff bases, etc.), compounds containing a chiral oxazoline represent one of the most successful classes of ligands, due to their ready accessibility and applicability in a wide range of metal-catalyzed transformations.

In particular bisoxazolines have received a great deal of attention as ligands: after communications appeared in 1991, one by Evans group dealing with asymmetric cyclopropanation of alkenes and one by Corey group about the enantioselective Diels-Alder reactions, applying chiral Cu(I)- and Fe(III)-box complexes as catalysts respectively, bisoxazolines quickly became widely adopted as bidentate ligands for their easy and flexible synthesis and for the excellent enantioselectivities induced, not only in the two reactions already cited, but also in a large variety of other reactions, as aziridination, allylic substitution, Mukaiyama, Michael, and many others.[56]

Modification both on nature, size and flexibility of the spacer that connects the two heterocycle rings and the substituents on the two oxazoline rings led to the development of a wide range of chiral ligands: some representative examples are reported below (Figure 1.18).

R = *i*-Pr, *t*-Bu
R¹ = H, Me, Bn

R = *i*-Pr, Bn
X = H, NO₂, Me, OMe
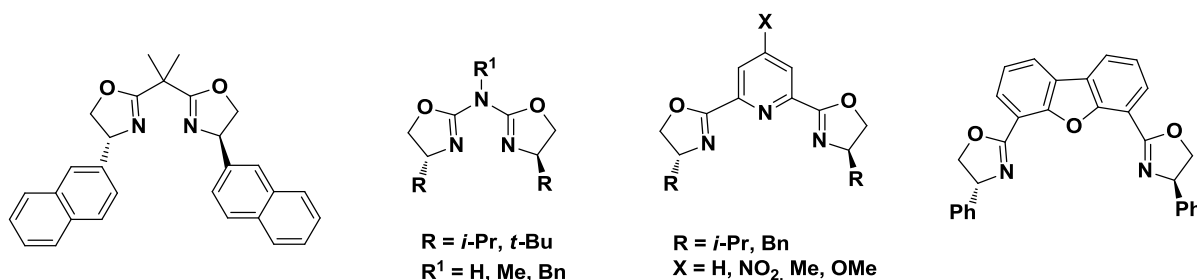
Figure 1.18

The bidentate bisoxazoline ligands endowed with a C_2-symmetry are constructed by two homochiral oxazoline rings connected to a central structure, defined spacer; in these ligands the coordination to the metal occurs through both the nitrogen atoms. The degree of substitution of the two oxazoline rings and the metal employed in the catalyst are crucial factors governing the efficiency and the applicability of these ligands in asymmetric catalysis.

Bisoxazolines with a single carbon spacer between the two oxazoline rings are the most frequently used, affording high selectivity in a wide range of metal-catalyzed reactions.

Ligands with biphenyl and binaphthyl backbons were the first stereoaxis-containing bisoxazolines to be employed in asymmetric reactions.[57] A wide range of biphenyl analogs **A** (Scheme 1.29) were prepared by Rippert and their characteristics were investigated in the copper(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate. Enantioselectivity was found dependent on the steric hindrance of thesubstituent in the 5-position of the oxazoline ring.[58]

Ligands **B** based on the binaphthyl backbone were used by Hayashi in palladium(II)-catalyzed Waker-type cyclizations[59] (Scheme 1.29). Fine-tuning of the chiral catalyst was attained by a proper combination of the substituents in position 4 of the oxazoline ring and in position 3 of binaphthyl moiety. Bisoxazoline ligands functionalized with ester groups (Scheme 1.29) turned out to be the most effective ligand.

R^1 = Me, OMe, Br
R^2 = H, OMe
R^3 = H, OMe, Br
R^4 = Et, *i*-Pr, Ph, Me, *t*-Bu
R^5, R^6 = H, Ph

R = CO_2Me, $SiMe_3$, $CONMe_2$, CHO, I

ligands A   **ligands B**
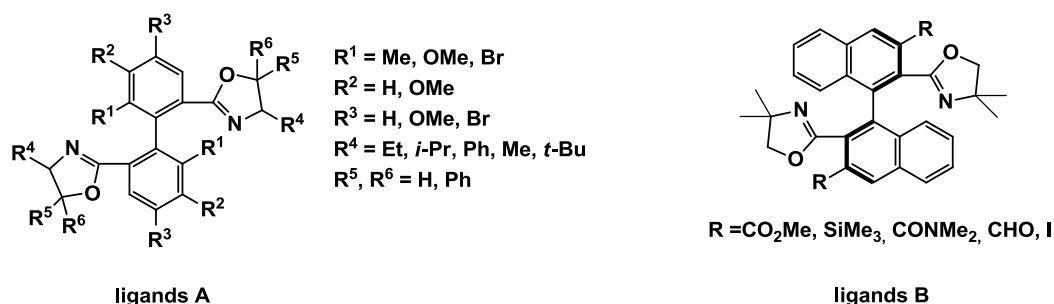
Scheme 1.29

An interesting class of bisoxazolines, the chiral spiro ligand **C** (Scheme 1.30) was introduced by Sasai in 2004 and employed in a wide range of asymmetric reactions,[60] that were refined by Zhou.

In this context, Zhou reported also the synthesis of ligands **D** and their applications to the catalytic asymmetric N-H insertion of amines with diazoesters,[61] and to the enantioselective insertion of carbenoids into the O-H bonds of phenols.[62] The same authors recently described the intramolecular phenolic O-H bond insertion (Scheme 1.30).[63]

R = H, Me, *i*-Pr, *t*-Bu, Ph, Bn

ligand C   **ligands D**

R^1NHR^2 + (diazoester) $\xrightarrow{\text{CuCl (5 mol%)} \atop \text{ligand D (6 mol%)} \atop \text{NaBARF (6 mol%)} \atop \text{CH}_2\text{Cl}_2\text{, rt}}$ (product) up to **98% ee**

(phenol) + (diazoester) $\xrightarrow{\text{CuCl (5 mol%)} \atop \text{ligand D (6 mol%)} \atop \text{NaBARF (6 mol%)} \atop \text{MS 4Å, CH}_2\text{Cl}_2\text{, rt}}$ (product) up to **99% ee**

(substrate) $\xrightarrow{\text{Cu(MeCN)}_4\text{PF}_6 \text{ (5 mol%)} \atop \text{ligand D (6 mol%)} \atop \text{NaBARF (6 mol%)} \atop \text{CH}_2\text{Cl}_2\text{, rt}}$ (product) up to **99% ee**
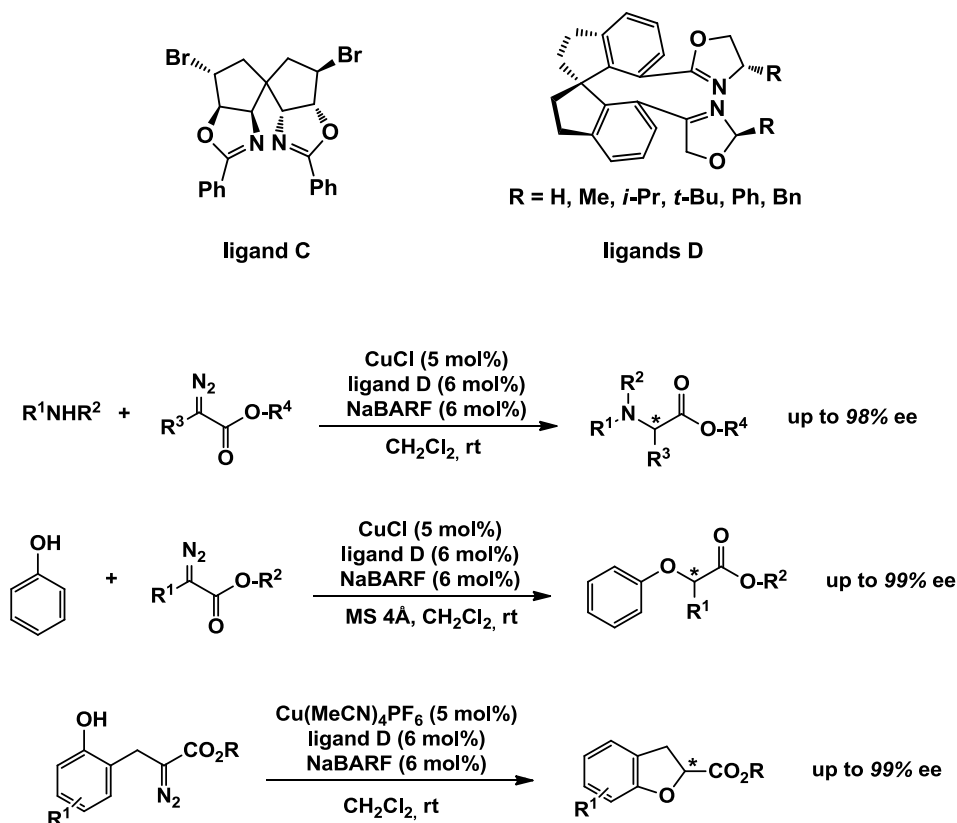
Scheme 1.30

1.3 Heteroaromatic derivatives

The research group, where the present PhD Thesis has been developed, has devoted great efforts in the field of asymmetric homogeneous catalysis in the past by developing chiral ligands with donor phosphorous introducing the structural substitution of the classical aromatic carbocyclic backbone with a five-membered heteroaromatic system (Figure 1.19).
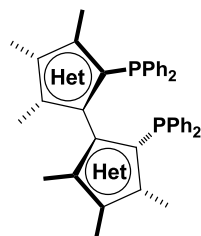
Figure 1.19

Compared with classical carbocyclic biaryls, the design of biheteroaromatic systems leads to the following structural and synthetic advantages:

• The electron-donor properties of the phosphorus atoms, a crucial parameter for catalytic activity, can be tuned by changing the supporting heterocyclic system. In fact, it is well known that aromatic five-membered heterocycles range from very electron-rich systems, like pyrrole, furan and thiophene, to very electron poor rings, like thiazole and triazole. Alternatively, the electronic properties of the phosphane groups can be modulated by changing their position and/or that of the interanular bond of a given heterocycle.

• A properly substituted biheteroaryl system can easily satisfy both symmetry and configurational stability requirements, since C_2 symmetric atropisomeric biaryls are recognized among the most efficient ligands for many transition metal-catalyzed stereoselective reactions.

• The geometry of the chelated ring in the complexes should depend on the nature of the heterocycle, since it is well documented that each heteroaromatic system shows typical internal angles and characteristic bond directions.

• The synthetic approaches to substituted pentatomic heteroaromatic rings are much more flexible than those generally followed to prepare carbocyclic aromatic systems. The easy and regioselective metalation of heteroaromatic five-membered rings can be a very helpful tool to introducing the phosphane functions, as well as in forming the interanular bond.

Phosphane ligands synthesized so far (Figure 1.20) cover a rather wide field, ranging from systems based on electron-rich heterocycles such as *N*-Me-BINP to systems based on electron-poor heterocycles, such as BIMIP.

As for the evaluation of the electronic properties of the ligands, from the various parameters available, the electrochemical oxidative potential, determined by cyclic voltammetry, was used. This parameter is related to the energy required to remove an electron from the system, and, in the case of the biheteroaromatic

diphosphanes, the electron is usually removed from the phosphorus atom. The higher its value, the electron-poorer the diphosphane; the lower its value, the electron-richer the diphosphane and easier the abstraction of the electron.

It is evident that both the electronic availability of the heterocyclic backbone and the electronic density of the position where the diphenylphosphino group is located are crucial; electronic demand progressively increases from indole to thiophene, to thianaphthene and then to benzofuran, with parallel increase in the oxidative potential.

The influence of the position of the phosphorus atom on the same heterocycle is also clearly demonstrated in the series of thiophene-based diphosphanes: phosphane groups located in α position are definitely more electron-poor than those bonded to β carbons; the electron releasing effect of methyl groups also works along the expected lines. In fact, the most electron-rich diphosphane is N-Me-2-BINP, where the phosphorus resides in the position having the highest electron density of the electron-excessive indole ring; BISCAP, which is a constitutional isomer of N-Me-2-BINP, differing only in the exchanged positions of the methyl and phosphine groups on the same backbone, is a rather electron-poor ligand.[64]
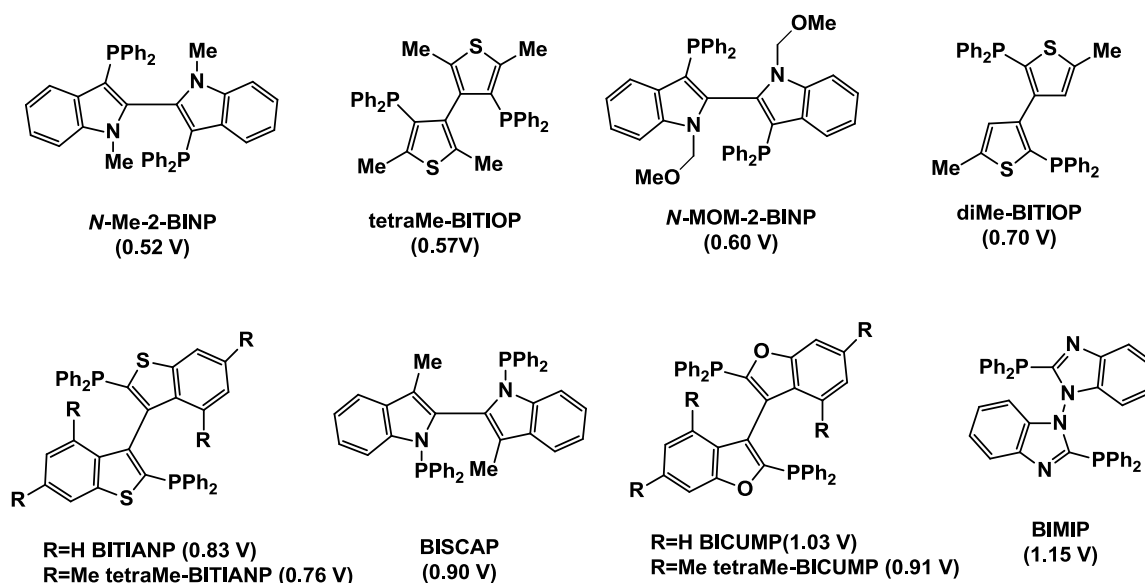
Figure 1.20

The possibility of modulating the electronic properties at phosphorus is very useful to tailor the structure of the ligand according to the requirements imposed by the reaction typology and by the substrate. Moreover, a strong relationship exists between the electronic availability at the phosphorus of the free ligand and the kinetic behavior of their metal complexes, when employed as homogeneous chiral catalysts.

The data obtained for the asymmetric hydrogenation of α- and β-ketoesters, employing ruthenium (II) complexes of the heterocyclic diphosphanes, demonstrated that electron-rich diphosphanes facilitate the reaction, and the reaction rate in nearly tripled respect the same reaction employing BINAP.

Furthermore, when using electron-poor ligands, the rate was reduced to about one twentieth. The results of the hydrogenation of ethyl 3-oxobutanoate employing different ligands (Table 1.1) clearly demonstrate the correlation between electronically availability and reaction rate.[65]
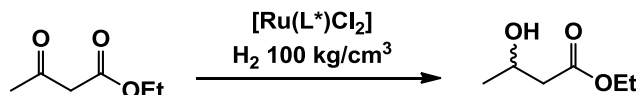
Table 1.1:

Ligand	$E°$ (V)	k_{obs} (s^{-1})	$k_{obs}^i/k_{obs}^{BINAP}$	ee%
(+)-*N*-Me-2-BINP	0.52	3.47×10^{-5}	2.67	95
(+)-tetraMe-BITIOP	0.57	3.76×10^{-5}	2.89	98
(+)-*N*-MOM-2-BINP	0.60	3.33×10^{-5}	2.56	91
(+)-BINAP	0.63	1.3×10^{-5}	1	99
(+)-tetraMe-BITIANP	0.76	1.08×10^{-5}	0.83	99
(±)-BISCAP	0.90	2.17×10^{-6}	1.7×10^{-1}	-
(±)-BICUMP	1.03	2.17×10^{-7}	1.7×10^{-2}	-

The same trend can be observed in the stereoselective Diels-Alder cycloaddition reactions promoted by palladium (II) complexes: electron-rich biheteroaromatic diphosphanes give catalyst with a high stereoselection ability, while meager diastereomeric and enantiomeric excesses follow the use of electron-poor ligands.

The bench reaction employed to test the diastereo- and the enantioselection was the cycloaddition of *N*-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene in the presence of the Pd (II) complexes of different biheteroaromatic diphosphines and BINAP (Table 1.2).[66]
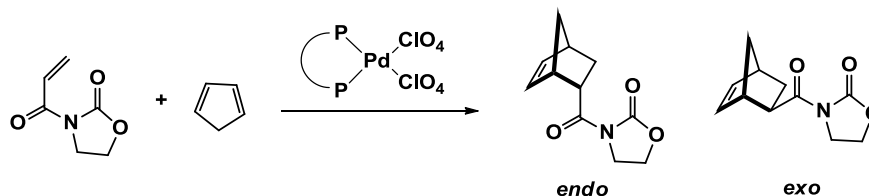
Table 1.2:

Ligand	$E°$ (V)	Conv. (%)	de(%)	ee(%)	Abs. conf.
(+)-*N*-Me-2-BINP	0.52	100	87	91	*R*
(+)-tetraMe-BITIOP	0.57	100	81	90	*R*

(+)-BINAP	0.63	100	86	89	*S*
(-)-BITIANP	0.76	100	82	72	*R*
(-)-BIMIP	1.15	60	59	48	*S*

An opposite situation was found in the inter- and intramolecolar Heck reaction, where the Pd(0) complexes produced by medium electron-rich diphosphanes were found to produce faster kinetics than those obtained when electron-rich ligands were used.

Tietze reported the intramolecular Heck reactions of iodoarenes with an allyl silane function in the presence of the chiral ligands (+)-tetraMe-BITIOP, one of the most electron-rich biheteroaromatic diphosphines, or (*R*)-BITIANP, a medium electron-rich ligand (Scheme 1.31).[67]
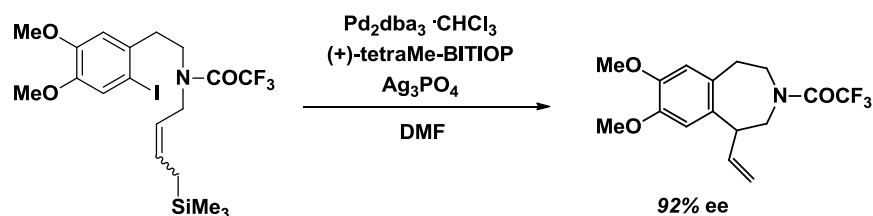
Scheme 1.31

Furthermore, palladium complexes of (*R*)-BITIANP were applied in the asymmetric Heck reactions of aryl and alkenyl triflates with 2,3-dihydrofuran.[68] In contrast to the behavior of BINAP, which affords a mixture of regioisomers, the use of (*R*)-BITIANP gave the 2-substituted 2,3-dihydrofurans with almost complete regioselectivity, remarkable enantioselectivity (80-91%) and verygood yields.

Even better results were obtained in the Pd catalyzed reaction of cyclohex-1-enyl triflate with dihydrofuran, with enantioselectivities ranging between 86 and 96% and yields of 76-93%.
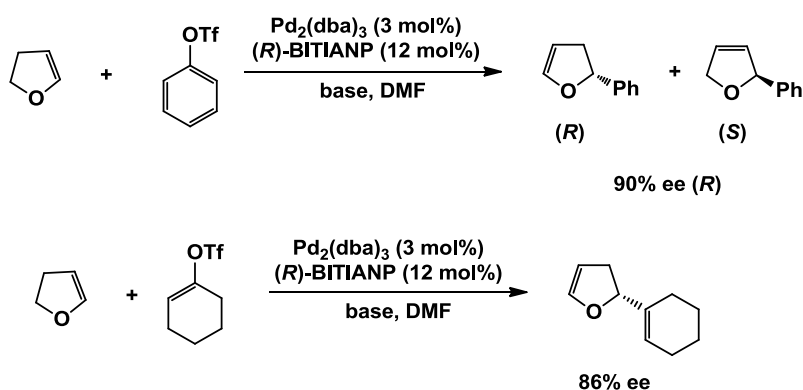
Scheme 1.32

Furthermore, tetraMe-BITIOPO, which the synthetic precursor of tetraMe-BITIOP, was successfully used as organic catalyst, in a research developed in collaboration with Professor M. Benaglia of the Università degli Studi di Milano, in many stereoselcetive reactions.

In the stereoselective direct aldol condensation of ketones with aromatic aldehydes, the trichlorosilyl enolether was generated in situ in the presence of tetrachlorosilane and activated by the phosphane oxide to react with an aldehyde, which was also coordinated to a chiral cationic hypervalent silicon species.[69] Direct condensation of cyclohexanone with benzaldehyde using (S)-tetraMe-BITIOPO, in the presence of tetrachlorsilane and DIPEA, led to the corresponding β-hydroxyketones in 53% yields, in an *anti*/*syn* ratio of 92/8, and 60% of enantiomeric excess for the *anti* isomer.

Comparison between (S)-tol-BINAPO and (S)-tetraMe-BITIOPO showed that BINAPO was less enantioselective than tetraMe-BITIOPO, being the enantiomeric excess produced with the carbocyclic ligand of 40% only.

On the contrary, catalytic activity and *anti*/*syn* ratio were almost the same.

Furthermore, performing the reaction at lower temperature, BITIOPO afforded the aldol adduct in 93/7 *anti*/*syn* ratio and 80% ee, while BINAPO gave the products in a 60% ee and 79/21 *anti*/*syn* ratio.

TetraMe-BITIOPO-catalyzed aldol condensation of cyclohexanone was carried out using different aromatic and heteroaromatic aldehydes, producing from moderate to outstanding enantiomeric excesses (Table 1.3).
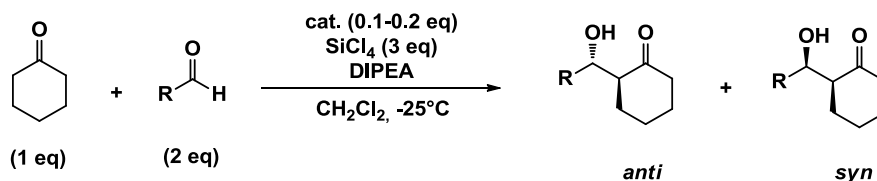
Table 1.3:

R	Yield (%)	*anti/syn*	ee *anti* (%)
Ph	70	93/7	81
4-NO$_2$C$_6$H$_4$	71	87/13	93
4-ClC$_6$H$_4$	56	98/2	71
2-ClC$_6$H$_4$	55	90/10	87
3,5CF$_3$C$_6$H$_4$	65	94/6	83
2-MeC$_6$H$_4$	56	94/6	73
4-MeC$_6$H$_4$	55	98/2	77
1-naph	40	93/7	77
2-thioph	55	98/2	53
2-furyl	36	98/2	51

In addition, high enantiomeric excesses were obtained in the addition of allyltrichlorosilane to aromatic aldehydes, functionalized with electron-withdrawing as well as electron-donating groups (Scheme 1.33).[71]

R = Ph, 4-NO$_2$C$_6$H$_4$, 4-ClC$_6$H$_4$, 4-OMeC$_6$H$_4$, 2-OMeC$_6$H$_4$, 3-OMeC$_6$H$_4$, 1-naphthyl, Ph-CH=CH
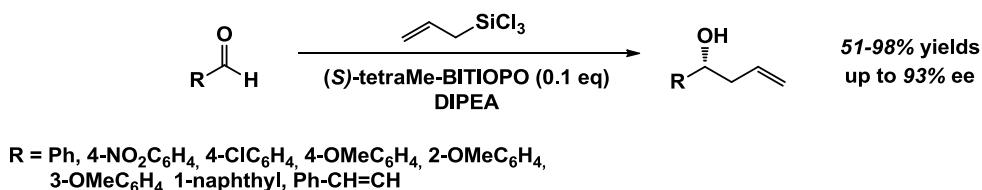
Scheme 1.33

Moreover, (S)-tetraMe-BITIOPO promoted the ring opening of *cis*-stilbene oxide by addition of tetrachlorosilane, in the presence of DIPEA; the corresponding chlorohydrins were isolated in quantitative yield and 81% ee (Scheme 1.34).[71]
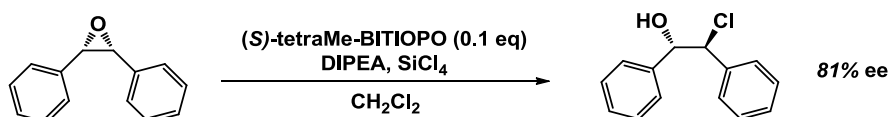
Scheme 1.34

Our research group, in collaboration with Professor Maurizio Benaglia also developed a new class of bisoxazoline ligands characterized by an atropoisomeric 3,3'-bithiophene backbone and applied them in the Cu(I)-catalyzed stereoselective cyclopropanation of styrene effected with ethyl diazoacetate (Scheme 1.35).[70]
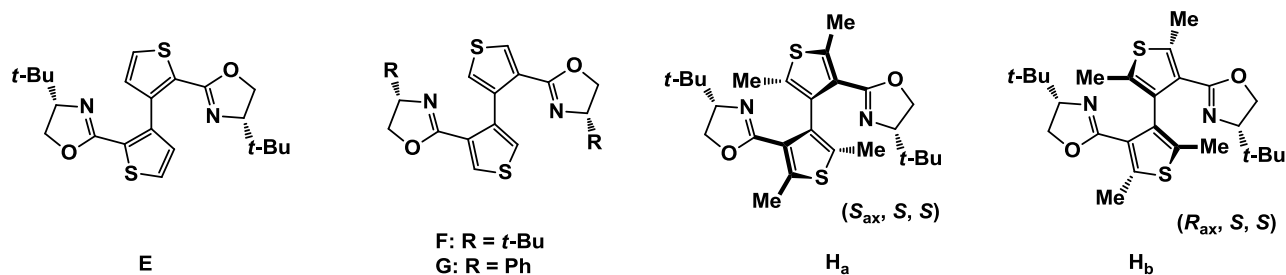
Scheme 1.35

The results obtained (Table 1.4), compared with those exhibited by ligand **A,** characterized by a carbocyclic biphenyl backbone, suggested that the steric properties of the ligand play a crucial role in controlling both the stereoselection levels and the reaction rate. The scaffold bearing the chelating functions would be rigid and capable of orienting the oxazoline moieties in such a way as to direct the substituents in 4-position around the metal core of the complex. In this type of reaction, electronic properties are scarcely relevant; in fact, the results obtained with the bisoxazolines based on a carbocyclic or on heterocyclic backbone are very similar, being the substitution on the oxazolinic ring identical.
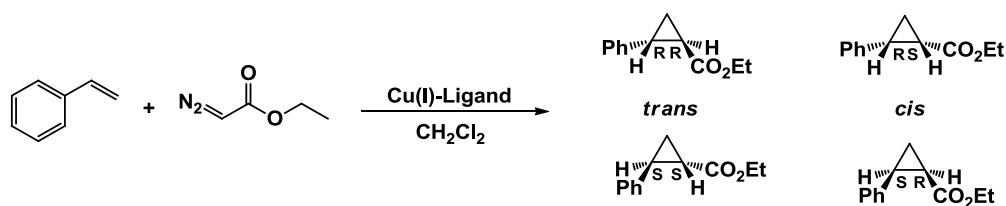
Table 1.4:

ligand	substrate/catalyst	yield (%)	trans/cis	trans ee(%)	abs. conf.
A	100	29	77/23	65	1*R*,2*R*
E	100	30	57/43	2	1*S*,2*S*
F	100	29	75/25	6	1*R*,2*R*
G	100	32	70/30	11	1*R*,2*R*
H_b	100	12	73/27	16	1*R*,2*R*
H_a	100	30	74/26	67	1*R*,2*R*
H_a	20	55	67/33	66	1*R*,2*R*
H_a	10	81	67/33	67	1*R*,2*R*

1.4 Aim of the Thesis research

The aim of the project of the present Ph.D. Thesis was to synthesize and investigate new families of chiral promoters, characterized by the 3,3'-bithiophene scaffold and differing for the nature of the substituents in the positions *ortho* to the interanular bond.

In particular, we decided to investigate diphosphanes and diphosphane-oxides, functionalized with aryl and isopropyl groups in order to evaluate the structural and the electronic differences in comparison with tetraMe-BITIOP[65] and its oxide tetraMe-BITIOPO,[71] previously successfully applied in the field of asymmetric homogeneous catalysis and organic catalysis.

Furthermore, we focused our attention on the class of bisoxazolines, either by enlarging the families of bisoxazolines based on the backbone of the tetramethyl-3,3'-bithiophene and by investigating new atropisomeric scaffolds.

A further aim of the research on atropisomeric biheteroaromatic chiral promoters was directed to the synthesis of a biheteroaromatic diol which would be the first example of this kind of compounds, since it is well known that heteroaromatic alcohols are always in equilibrium with the corresponding carbonyl derivatives, which are the prevalent species insolution.

The general formulas of the chiral promoters designed for the project are reported below (Figure 1.21).

R= Me, *i*-Pr, Ph

X = —P(R¹)(R¹)

16

X = —P(=O)(R¹)(R¹)

15

R = Ph, R¹ = *p*-Tol

X = -OH

18: R = Me
17: R = Ph

X =

42a,b: R = Me, R² = Ph
44a,b: R = Ph, R² = Ph
47a,b: R = Me, R² = *i*-Pr
48a,b: R = Ph, R² = *i*-Pr
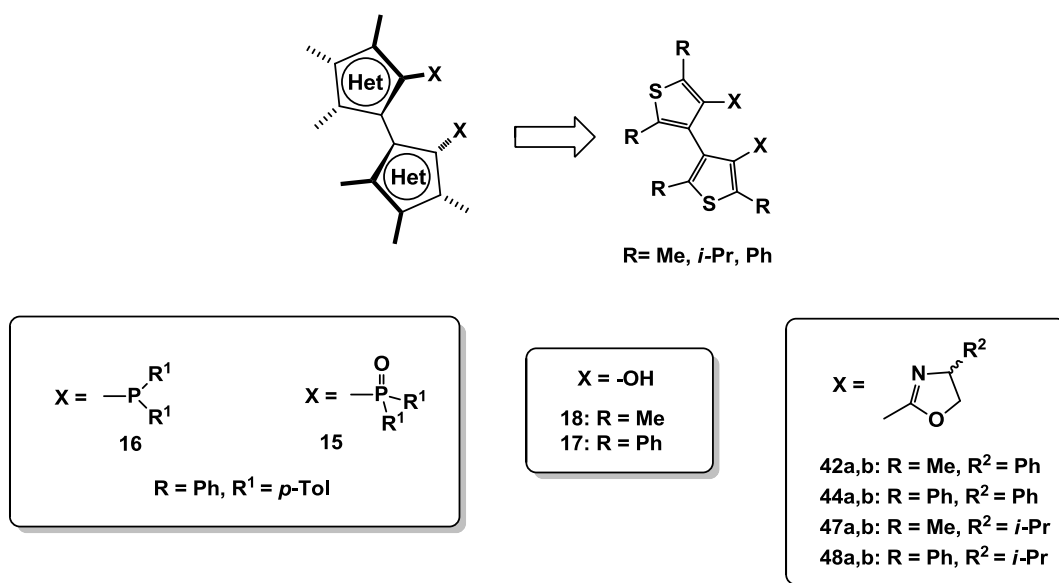
Figure 1.21

An advantage of this design is the fact that the synthesis of all these classes of compounds, characterized by the same 3,3'-bithiophene backbone, is based on a common intermediate, namely the 2,2',5,5'-tetrasubstituted-4,4'-dibromo-3,3'-bithiophene.

The synthesis of the different key intermediates are described in Chapter 2.

R= Me, *i*-Pr, Ph
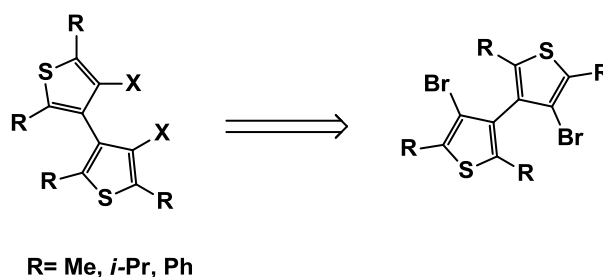
Scheme 1.36

In fact the bromine atoms can be, in principle, exploited to introduce several different functions:

a) the phosphane groups, through the formation of a dianion;

b) the methoxy groups, which is the precursor of the hydroxy functionality, taking advantage of a substitution reaction mediated by Cu(I);

c) the carboxy groups, again through a lithiation-carbonation reaction, necessary to build the oxazoline rings.

2. SYNTHESIS OF THE KEY INTERMEDIATES

The experience acquired by our research group on compounds characterized by the atropoisomeric scaffold of 2,2',5,5'-tetramethyl-3,3'bithiophene, prompted us to envisage the 4,4'-dibromo-2,2',5,5'-tetrasubstituted-3,3'bithiophene as key intermediate for the synthesis of the new atropoisomeric systems.

In this section the synthetic route to obtain the dibromoderivatives characterized by the presence of tetraphenyl-, tetramethyl- and tetraisopropyl- groups are discussed.

2.1 *Synthesis of 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene (3)*

The synthetic strategy already developed in the research group, has been optimized and it is reported in Scheme 2.1.
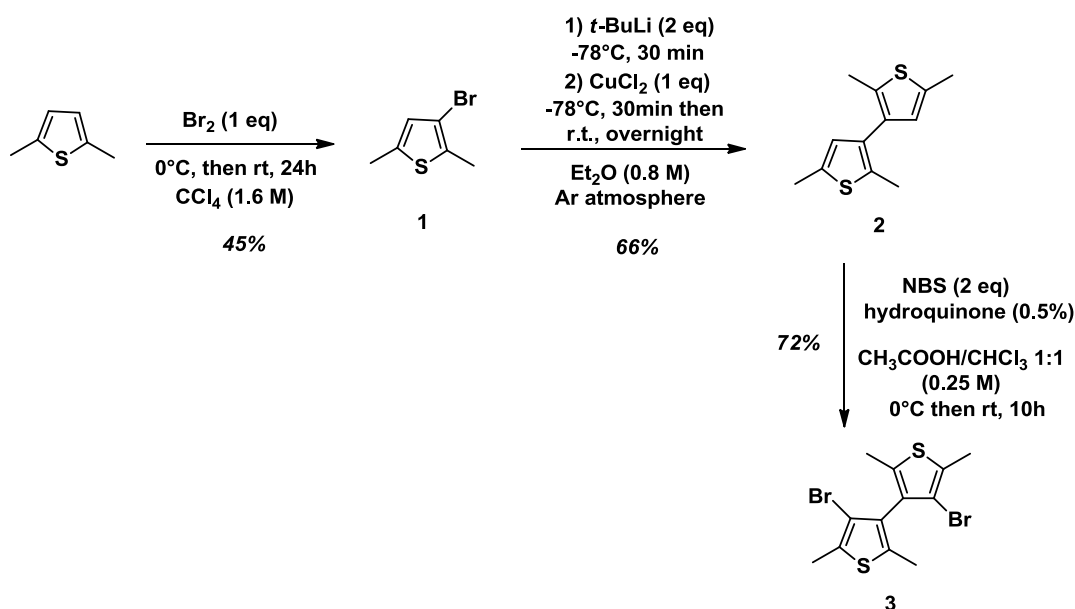
Scheme 2.1

The first step was the bromination of the commercial available 2,5-dimethylthiophene, that was achieved with bromine in carbon tetrachloride solution.

The interanular C-C bond was formed through oxidative coupling with anhydrous $CuCl_2$ of the dianion of **1**, obtained in turn by transmetalation with *t*-BuLi. Treatment of dimer **2** with NBS, in the presence of hydroquinone as radicals scavenger, gave the dibromoderivative **3** in good yields.

2.2 *Synthesis of 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene (7)*

Three different synthetic strategies have been developed to accede to the intermediate **7**, with the aim to reduce the overall number of steps and increase the yield of the whole process.

The first synthetic strategy involves four steps, as reported in Scheme 2.2.
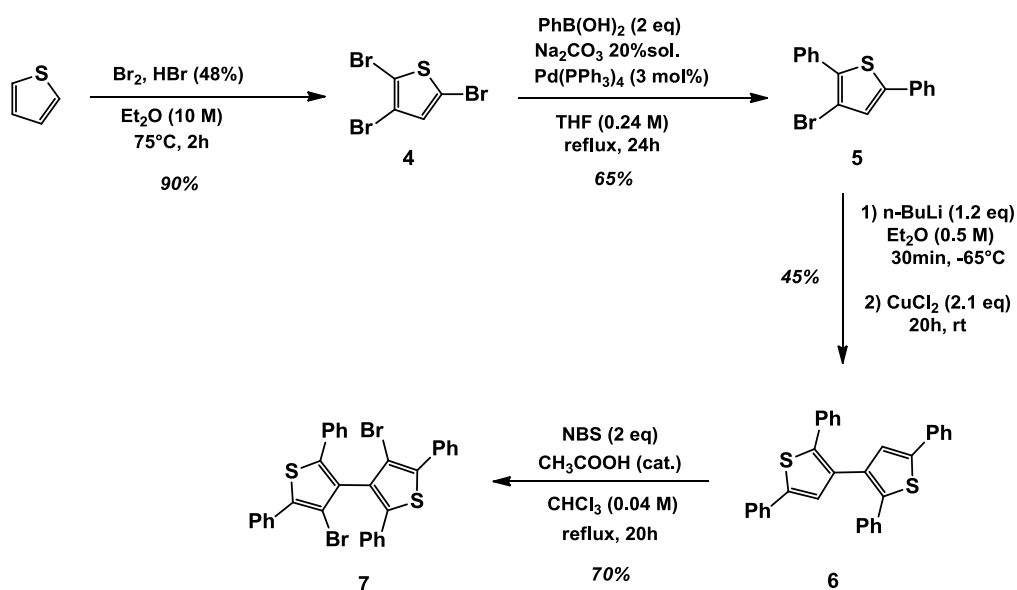
Scheme 2.2

The first step was the bromination of the position 2,3,5 of the thiophene ring, employing a 48% bromine solution in bromidric acid, as reported in literature,[72,81] and the resulting 2,3,5-tribromothiophene (**4**) was obtained by careful distillation of the reaction crude; yields are satisfactory, even if the distillation is tedious due to the presence of different bromoderivatives.

The 2,5-diphenyl-3-bromothiophene (**5**) was obtained in good yields, taking advantage of the regioselectivity of Suzuki reaction on the thiophene ring.[73]

The dimer **6** was obtained through oxidative coupling mediated by copper chloride of two units of 2,5-diphenyl-3-lithiumthiophene, generated *in situ* by transmetallation of the 2,5-diphenyl-3-bromothiophene.

The formation of the interanular bond was the most critical step: in particular, the lithiation reaction required optimization both of the experimental conditions and of the metallating agent.

The occurred lithiation is checked by ^{1}H NMR. Best results were obtained by employing diethyl ether as solvent and *n*-buthyllithium as transmetallating agent.

Despite having optimized the formation of the anion, we couldn't obtain higher yield in the coupling process, probably due to the steric hindrance exerted by phenyl groups.

The final step is the bromination with *N*-bromosuccinimide in the presence of catalytic amount of acetic acid; in this condition the dibromoderivative **7** was obtained in 70% yield. The presence of acetic acid is essential in order to obtain the dibromoderivative; in fact only the product of monobromination was isolated carrying out the reaction in pure chloroform.

In the second synthetic strategy, the tetrabromothiophene was used as starting material, since it could be obtained in quantitative yields by exhaustive bromination of thiophene (Scheme 2.3). Furthermore, its use could have allowed to reduce the synthetic steps being the product obtained from the omocoupling reaction

already brominated.

However, the regioselectivity of the Suzuki reaction and the possibility of carrying out the coupling in the presence of bulky substituents, such as bromine atoms, had to be checked.

The thiophene was exhaustive brominated by Br_2 and the tetrabromothiophene was obtained as a white solid in quantitative yield without any purification.

This was the first advantage of this strategy in comparison with the previous one, in which the starting material required a tedious purification process.

The Suzuki reaction demonstrated the same regioselectivity in the α position of the tetrabromothiophene and it allowed to obtain the 3,4-dibromo-2,5-diphenylthiophene in 70% yields.
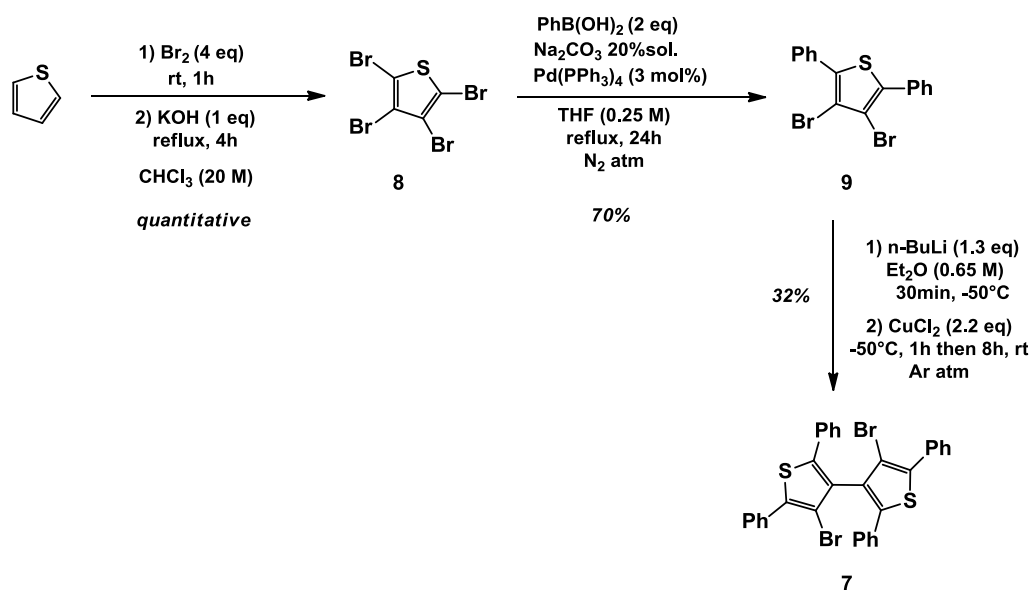
Scheme 2.3

The oxidative coupling of compound **9** is the bottleneck of the whole synthetic procedure since the steric hindrance plays a decisive role for the success of this kind of reaction. The compound **7** was obtained in 32% yields and even if reaction optimizations were carried out, any enhancement in the yield was observed.

However this strategy represented an improvement compared to the previous one: in fact the overall yields increased from 18% to 23% and there was a reduction in the number of synthetic step from four to three.

Furthermore, from this experience, we realized that steric hindrance is detrimental for the formation of the interanular bond and we planned a new strategy, in which the formation of the interanular bond was anticipated in order to minimize the problems connected to steric hindrance.

The new strategy is reported in Scheme 2.4 and the formation of the interanular bond takes place at the first step.
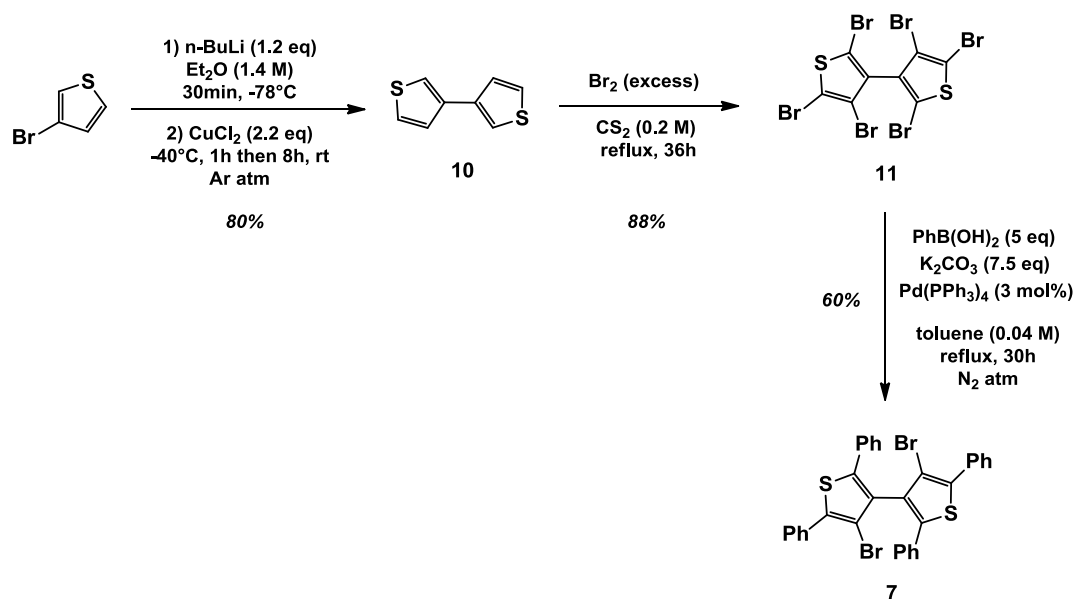
Scheme 2.4

3,3'-Bithiophene,which is also commercially available, was obtained in 80% yields by oxidative coupling of the lithiumderivative of the 3-bromothiophene.

The exhaustive bromination of the 3,3'-bithiophene was performed by employing carbon disulfide as solvent, that it was found to be essential for the success of the reaction. In fact the 2,2',5,5'-tetrabromothiophene wasn't obtained carrying out the reaction with other solvents, such as carbon tetrachloride, chloroform or acetic acid, or performing the bromination in the absence of solvent. In this condition the hexabromoderivative **11** was obtained with high yield without further purification.

The Suzuki reaction conditions employed in the previous synthetic strategies didn't lead to the formation of the desired product, but rather to a complex mixture of compounds in which the main product was characterized by the presence of three phenyl groups.

To force the entry of the substituents, the reaction was conducted in toluene at reflux, using a large excess of base and 5 equivalents of phenylboronic acid: the reaction took place in a clean way and the 2,2',5,5'-tetraphenyl-4,4'-dibromo-3,3'-bithiophene was obtained as the main product by carrying out the reaction at the reflux temperature for 36 hours.

Xylene was also used as solvent with the purpose of performing the reaction at higher temperature in order to reduce reaction time. The reaction was completed in three hours, but with a dramatic decrease of the regioselectivity. In fact different dibromoderivatives were formed, characterized on the basis of mass spectrum spectroscopy, and we couldn't isolated them neither by column chromatography or fractional crystallization.

Following these strategies, we achieved a satisfactory approach to the synthesis of the key intermediate **7**; in fact the desired compound was obtained in 42% overall yields.

2.3 _Synthesis of 4,4'-dibromo-2,2',5,5'-tetraisopropyl-3,3'-bithiophene_

In order to functionalized the thiophene with isopropylic groups, we tried to take advantage of the regioselectivity previously observed in the Suzuki reaction with phenylboronic acid and we started to investigate the functionalization of the 2,3,5-tribromothiophene. In the case of alkyl boronic acid, it is well known that bulky phosphine ligands are essential to inhibit isomerization and reduce side reactions; thus we planned to use as ligands Cy_3P, Xantphos, RuPhos and a Pd"cycle" that was available in our laboratory, reported in the Scheme 2.5.

Different experimental conditions were investigated and the results are shown in the Table 2.1.
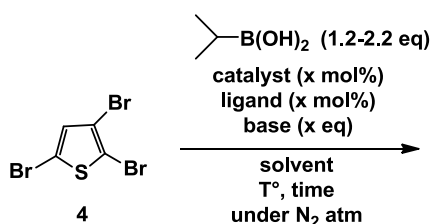
Table 2.1:

Entry	Catalyst (x mol%)	Ligand (x mol%)	Base (eq)	Solvent	T°(°C)/ time(h)	Result
1[74]	Pd(OAc)$_2$ (5)	Cy$_3$P (10)	K$_2$CO$_3$ (3.3)	Toluene/H$_2$O (10:1)	80/14	s.m.
2[75]	Pd"cycle" (4)		K$_2$CO$_3$ (4)	25% DMA in H$_2$O	100/72	s.m.
3	Pd"cycle" (4)		K$_2$CO$_3$ (4)	25% H$_2$O in DMA	100/72	s.m.
4	Pd"cycle" (4)		K$_2$CO$_3$ (4)	Toluene	100/48	s.m.
5	Pd(OAc)$_2$ (5)	Xantphos (5)	K$_2$CO$_3$ (4)	Toluene	100/72	Isomer+sm
6[76]	Pd(PPh$_3$)$_4$ (5)	RuPhos (5)	K$_2$CO$_3$ (4)	DMF/H$_2$O (9:1)	80/24	sm+ traces of product
7	Pd(OAc)$_2$ (2)	RuPhos (4)	K$_2$CO$_3$ (4)	Toluene	100/48	s.m.
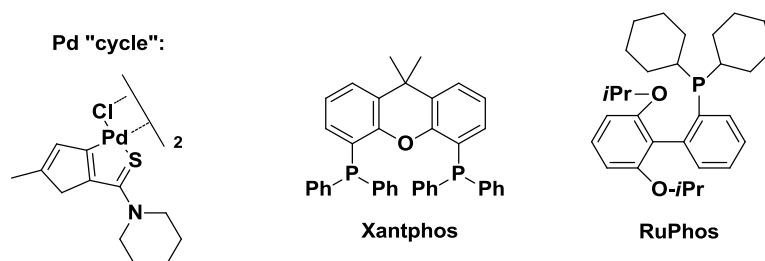
Scheme 2.5

Unfortunately, almost all the reactions didn't take place and the starting material was recovered unreactive; only Xantphos led to the formation of a mixure of 2,3,5-tribromothiophene and another product, that, on the basis of ^{1}H NMR spectroscopy, was identified as the 3,5-dibromo-2-propylthiophene.

The ^{1}H NMR spectrum of the crude of the reaction catalyzed by RuPhos showed the presence of the ligand, the starting material and traces of the desired product.

The failure of the cross-coupling reactions led us to change synthetic strategy and prompted us to follow the synthetic route employed for the preparation of tetraMe-BITIOP starting from the 2,5 dialkylthiophene.

2,5-Diisopropylthiophene isn't commercially available and we decided to build the thiophene ring starting from 2,7-dimethyl-octa-3,6-dione (**12**), that was synthesized starting from 3-methylbutan-2-one using literature methods[77] (Scheme **2.6**).

We couldn't obtain the desired product employing P_4S_{10} as sulphonating agent: in fact the reaction led to the formation of (*Z*)-2,7-dimethyl-6-thioxo-oct-4-en-3-one, that can't evolve to give the heterocyclic ring.
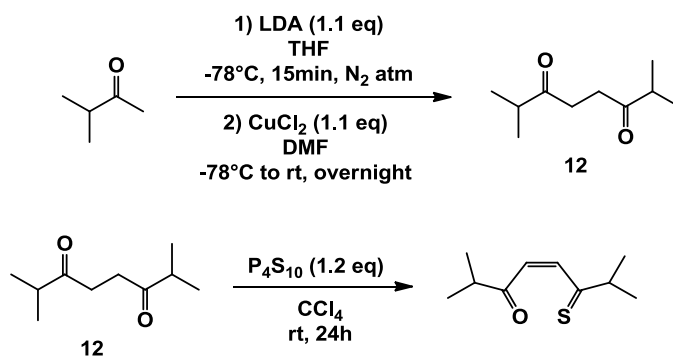
Scheme 2.6

We could acceded to the 2,5-diisopropylthiophene in 54% yields employing Lawesson reagent as sulphonating agent (Scheme **2.7**).
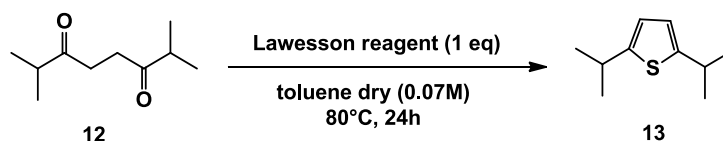
Scheme 2.7

The following step was the bromination of the position 3 of the thiophene ring: firstly, we carried out the reaction using Br_2 as brominating agent; ^{1}H NMR spectrum of the crude showed the presence of brominated product, both on thiophenic ring and on alkyl groups.

Finally, we achieved the bromination of position 3 employing *N*-bromosuccinimide in the presence of catalytic amount of hydroquinone; in this condition the bromoderivative **14** was obtained in 55% yield (Scheme **2.8**).
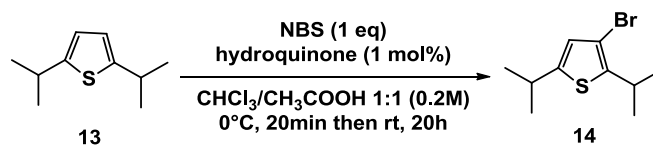
Scheme 2.8

2.4 *Conclusions*

In this chapter, we described the synthesis of 4,4'-dibromo-2,2',5,5'-tetrasubtituted-3,3'-bithiophene derivatives, which represent the key intermediates for the construction of the atropoisomeric biheteroaromatic scaffolds reported in this Thesis.

The synthesis of 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene, already developed, was optimized, obtaining the desired product in three steps.

For the synthesis of 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene, three synthetic strategies were developed: the best one consists of three steps, in which the formation of the interanular bond is anticipated at the first step, to avoid the problems connected with the steric hindrance.

Furthermore, we identified the synthetic scheme to accede to the 2,5-diisopropyl-3-bromothiophene, which is the key intermediate for the construction of the 4,4'-dibromo-2,2',5,5'-tetraisopropyl-3,3'-bithiophene.

2.5 <u>*EXPERIMENTAL SECTION*</u>

2.5.1 General information

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen or argon. Dry solvents were used as received and stored under inert gas. All reagents, if not otherwise specified, were used as received and, if necessary, stored under inert gas.

For thin layer chromatography analysis, pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV254were used. Visualization was accomplished by irradiation with a UV lamp and/or staining with potassium permanganate alkaline solution. Column chromatography was performed on 230-400 mesh Sigma-Aldrich silica gel.

Melting point determinations were performed by using a Buchi B-540 instrument.

^{1}H NMR, ^{13}C NMR were measured on a Brucker FT 300 or a Brucker AMX 300 instrument. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling costants are reported in Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, m = multiplet, br s = broad singlet.

Mass analysis were performed using a VG 7070 EQ-HF instrument.

2.5.2 Synthetic procedures

Synthesis of 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene (3)

- **Synthesis of 3-bromo-2,5-dimethylthiophene (1)**
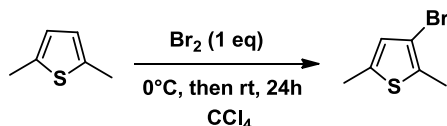
A solution of Br_2 (14.6g, 89mmol, 1 eq) in CCl_4 (30mL) was added dropwise to a stirred solution of 2,5-dimethylthiophene (10g, 89mmol, 1 eq) in CCl_4 (25mL) at 0°C,over a period of 1 hour, then the reaction mixture was left under stirring until no gaseous HBr was formed.

Dichlorometane (40mL) and water (40mL) were added to the solution, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 30mL). The combined organic layer were washed with a saturated $NaHCO_3$ solution (40mL), water (40mL), then dried and the solvent was removed under reduced pressure. The residue was distilled (78°C, 6.5mbar) to give 3-bromo-2,5-dimethylthiophene as a colourless oil, isolated in 45% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.63 (s, 1H), 2.48 (s, 3H), 2.42 (s, 3H).[78]

- **Synthesis of 2,2',5,5'-tetramethyl-3,3'-bithiophene (2)**
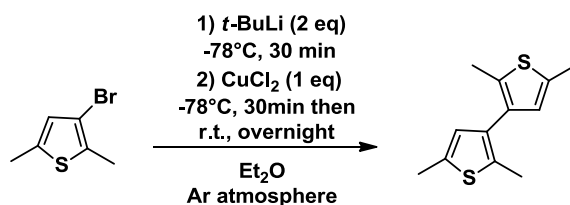
A solution of **1** (6.9g, 36mmol, 1 eq) in dry diethyl ether (37mL) was slowly added to *t*-Buli (1.6M solution in hexane, 25mL, 1.1 eq) in dry ethyl ether (37mL) at -78°C, under Ar atmosphere; the reaction mixture was stirred for 30 minutes at -78°C, then anhydrous $CuCl_2$ (5.30g, 40mmol, 1.1 eq) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. Water (40mL) was added to the solution; the aqueous phase was extracted with CH_2Cl_2 (3 x 40mL); the combined organic layers were washed with water, then dried and concentrated in vacuo. Flash chromatography (hexane) led to 2,2',5,5'-tetramethyl-3,3'-bithiophene as a colourless oil, isolated in 66% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.52 (s, 2H), 2.42 (s, 6H), 2.27 (s, 6H).[79]

- **Synthesis of 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene (3)**
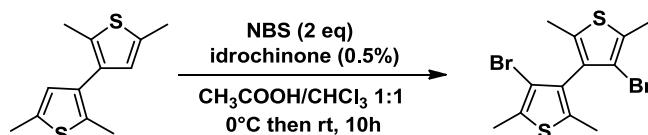
NBS (1.3g, 5.8mmol, 2 eq) was added to a stirred solution of dimer **2** (0.646g, 2.9mmol, 1 eq) and hydroquinone (1.6mg, 0.0145mmol, 0.5 mol%) in a mixture of $CHCl_3/CH_3COOH$ 1:1 (16mL), at 0°C. The reaction mixture was stirred at room temperature for 10 hours, then dichlorometane (10mL) and water (10mL) were added to the solution, the organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude was filtered over a short pad of silica gel (hexane) to afford pure 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene as a white solid, isolated in 72% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.39 (s, 6H), 2.19 (s, 6H).[80]

**Synthesis of 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene (7)**

- **Synthesis of 2,3,5-tribromothiophene (4)**

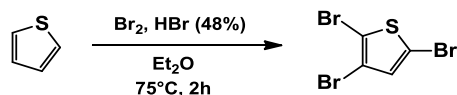A mixture of thiophene (10g, 120mmol, 1 eq) and 48% HBr solution (31mL) in diethyl ether (12mL) was added dropwise to a solution of Br_2 (20mL, 3.2 eq) in 48% HBr solution (20mL), at room temperature, then the mixture was stirred for 2h at 75°C; excess of bromine was reduced by a saturated solution of sodium metabisulphite. The mixture was extracted with CH_2Cl_2 (40mL); the organic phase was washed with a saturated solution of $NaHCO_3$ (40mL). Then the organic layer was dried over Na_2SO_4 and concentrated at reduced pressure. Distillation (90°C, 5mmHg) led to the 2,3,5-tribromothiophene as a pale yellow oil, isolated in 90% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.93 (s, 1H).[81]

- **Synthesis of 3-bromo-2,5-diphenylthiophene (5):**
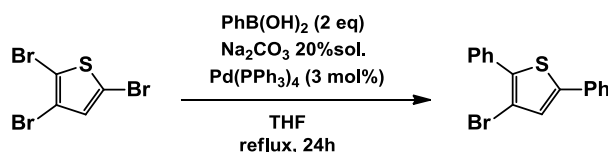
Phenylboronic acid (3.8g, 31.2mmol, 2 eq) was added to the biphasic system made of deoxygenated tetrahydrofuran (66mL) and a 20% solution of Na_2CO_3 (66mL), under N_2 atmosphere; after 2,3,5 tribromothiophene (5g, 15.6mmol, 1 eq) and palladium tetrakis (0.540g, 0.47mmol, 3 mol%) were added and the mixture was stirred for 24 hours at reflux. The solvent was removed at reduced pressure, and the mixture was extracted with dichlorometane (40mL); the organic layer was washed with brine (40mL), then with water (40mL), dried over Na_2SO_4 and concentrated at reduced pressure.

Gravimetric column chromatography (hexane) led to 3-bromo-2,5-diphenylthiophene as a white solid, isolated in 65% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.32 (s, 1H), 7.52-7.34 (m, 6H), 7.63 (d, 2H, J = 7.5 Hz), 7.76 (d, 2H, J = 6.9 Hz).[82]

- **Synthesis of 2,2',5,5'-tetraphenyl-3,3'-bithiophene (6**):
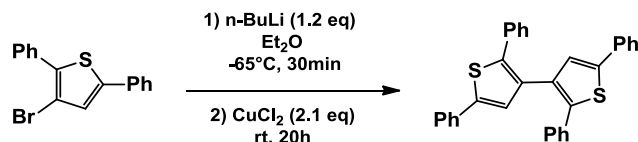
n-BuLi (1.6M solution in hexane, 3.4mL, 1.2 eq) was added dropwise to a solution of 3-bromo-2,5-diphenylthiophene (1.55g, 4.94mmol, 1eq) in dry diethyl ether (10mL), under N$_2$ atmosphere and at -65°C,; after 30 minutes, anhydrous CuCl$_2$ (1.35g, 9.85mmol, 2.1 eq) was added rapidly. The reaction mixture was stirred for 20 hours at room temperature, then diethyl ether was removed at reduced pressure and the crude was washed with dichlorometane (15mL) and a 5% HCl solution (15mL); the organic layer was washed with a saturated solution of NaHCO$_3$ (15mL) and then with water (15mL), dried and concentrated in vacuo.

Gravimetric column chromatography (hexane/CH$_2$Cl$_2$ 9.5:0.5) led to 2,2',5,5'-tetraphenyl-3,3'-bithiophene as a white solid, isolated in 45% yield.

^{1}H NMR (DMSO, 300 MHz) δ 7.65 (d, 4H, J = 6.0 Hz), 7.48 (s, 2H), 7.46 (t, 4H, J = 6.0 Hz), 7.31(d, 2H, J = 6 Hz), 7.18-7,11 (m, 10H).

MS (EI): 470 (M$^+$).

- **Synthesis of 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene (7):**
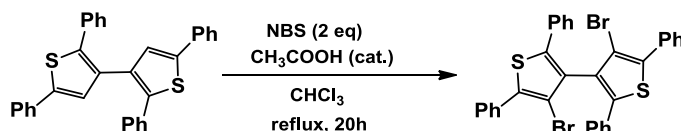
N-bromosuccinimide (0.36g, 1.82mmol, 2 eq) was added to a solution of 2,2',5,5'-tetraphenyl-3,3'-bithiophene (0.43g, 0.91mmol, 1 eq) in chloroform (20mL) and acetic acid glacial (2mL). The mixture was stirred for 20 hours at reflux; the crude mixure was treated with a saturated solution of Na$_2$S$_2$O$_5$, then with a saturated solution of NaHCO$_3$ (20mL) and with a 5% NaOH solution (20mL). The aqueous layer was extracted with dichlorometane (20mL), the organic phase was dried and concentrated in vacuo.

Gravimetric column chromatography (hexane/CH$_2$Cl$_2$ 9.5:0.5) led to 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene as a white solid, isolated in 75% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.79 (d, 4H, J = 6.0 Hz), 7.48 (t, 2H, J = 6.0 Hz), 7.41 (d, 4H, J = 6.0 Hz), 7.23-7.09 (m, 10H).

MS (EI): 629 (M$^+$).

- **Synthesis of tetrabromothiophene (8):**
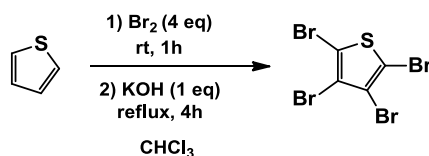
Bromine (30mL, 585mmol, 4.5 eq) was added dropwise to a solution of thiophene (10.5g, 125mmol,1 eq) in chloroform (6mL) and the reaction mixure was stirred for 1 hour at room temperature, then for 3 hours at reflux; after a 95% KOH solution in ethanol (7g, 125mmol, 1 eq) was slowly added and the mixure stirred at reflux for further 4 hours.

The crude was poured in an equivalent volume of ice, and the solid formed was recovered by filtration and washed with water to obtain the tetrabromothiophene without any further purification as a white solid, isolated in quantitative yield.

mp: 115-117°C.

^{1}H NMR (CDCl$_3$, 300 MHz) no proton signals.[83]

- **Synthesis of 3,4-dibromo-2,5-diphenylthiophene (9):**
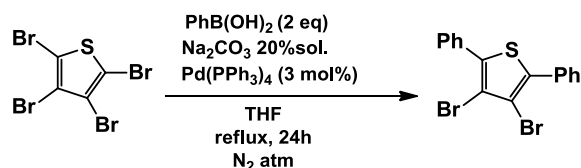
Phenil boronic acid (0.9g, 7.4mmol, 2 eq) was added to the biphasic system made of deoxygenated tetrahydrofuran (15mL) and a 20% solution of Na$_2$CO$_3$ (15mL), under N$_2$ atmosphere; after 2,3,5 tetrabromothiophene (1.5g, 3.7mmol, 1 eq) and palladium tetrakis (0.13g, 0.111mmol, 3 mol%) were added and the mixture was stirred for 24 hours at reflux. The solvent was removed at reduced pressure, and the mixture was extracted with dichlorometane (15mL); the organic layer was washed with brine (15mL), then with water (15mL), dried over Na$_2$SO$_4$ and concentrated at reduced pressure. Gravimetric column chromatography (hexane/CH$_2$Cl$_2$ 9:1) led to 3,4-dibromo-2,5-diphenylthiophene as a white solid, isolated in 70% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.55-7.47 (m, 6H), 7.73 (d, 4H, J = 6.0 Hz).

MS (EI): 394 (M$^+$).[84]

- **Synthesis of 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene (7):**
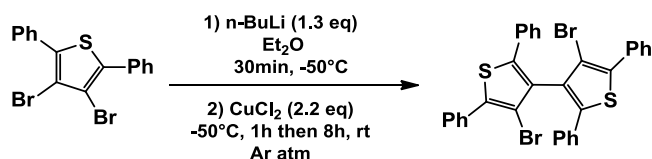

n-BuLi (1.6M solution in hexane, 5mL, 1.3 eq) was added dropwise to a solution of 3,4-dibromo-2,5-diphenylthiophene (2.5g, 6.4mmol, 1 eq) in dry diethyl ether (10mL), at -65°C, under N$_2$ atmosphere; after

30 minutes, anhydrous $CuCl_2$ (1.9g, 14mmol, 2.2 eq) was rapidly added. The reaction mixture was stirred for 20 hours at room temperature, then diethyl ether was removed at reduced pressure and the crude was washed with dichlorometane (15mL) and a 5 % HCl solution (15mL); the organic layer was washed with a saturated solution of $NaHCO_3$ (15mL) and then with water (15mL), dried and concentrated in vacuo.

Gravimetric column chromatography (hexane:CH_2Cl_2 8.5:1.5) led to 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene in 32% yield.

- **Synthesis of 3,3'-bithiophene (10):**
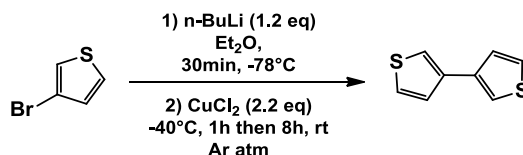
n-BuLi (1.6M solution in hexane, 46mL, 1.2 eq) was added dropwise to a solution of 3-bromo-thiophene (10g, 61.3 mmol, 1 eq) in dry diethyl ether (43mL) at -78°C, under N_2 atmosphere and the mixure stirred vigorously; after 30 minutes, anhydrous $CuCl_2$ (18.5g, 137mmol, 2.2 eq) was rapidly added at a temperature of -50°C. The reaction mixture was stirred at -50°C for 30 minutes, then for 20 hours at room temperature, then the crude was washed with 1N HCl solution (30mL); the aqueous phase extracted with dichlorometane (40mL) and the organic layer was washed with a saturated solution of $NaHCO_3$ (30mL) and then with water (30mL), dried and concentrated in vacuo.

Flash chromatography (hexane) led to 3,3'-bithiophene as a white solid, isolated in 80% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.38 (m, 2H), 7.35 (m, 4H).[85]

- **Synthesis of hexabromo-3,3'-bithiophene (11):**
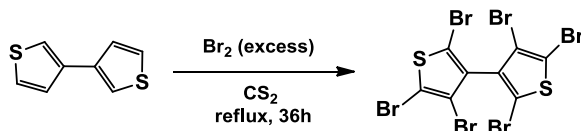
Bromine (40mL) was added dropwise to a stirred solution of 3,3'-bithiophene 3.8g, 23 mmol, 1 eq) in carbon disulphide (114mL); the reaction mixture was heated at reflux and stirred for 36 hours; then the excess of bromine was reduced by slowly adding of a saturated solution of sodium metabisulphite, at 10°C, until clarification of the mixture. After the mixture was extracted with toluene (100mL); the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Hexabromo-3,3'-bithiophene was obtained without any further purification as a white solid, isolated in 88% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) no proton signals. **mp:** 178-181°C.[86]

- **Synthesis of 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene (7):**
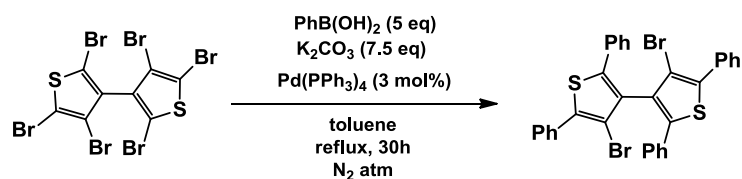
Hexabromo-3,3'-bithiophene (0.5g, 0.78mmol, 1 eq), phenyl boronic acid (0.62g, 5.1mmol, 6.5 eq) and K_2CO_3 (0.65g, 4.7 mmol,6 eq)were dissolved in dry toluene (20mL), under N_2 atmosphere; after 10 minutes of stirring, palladium tetrakis (0.027g, 0.023mmol, 3 mol%) was added and the mixture was heated at reflux for 24 hours. The solvent was removed at reduced pressure, and the crude dissolved in dichlorometane (20mL) and washed with water (20mL); the organic layer was dried and concentrated in vacuo.

Flash chromatography (hexane/CH_2Cl_2 9:1) led to compound **7** as yellow solid which is then titritated to obtain **7** as white solid in 60% yield.

Synthesis of 4,4'-dibromo-2,2',5,5'-tetraisopropyl-3,3'-bithiophene

- **Synthesis of 2,7-dimethyl-octa-3,6-dione (12)**
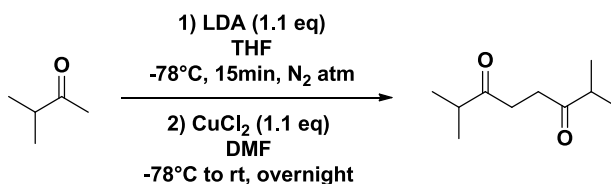
3-Methylbutan-2-one (3.7mL, 34.8 mmol, 1 eq) was slowly added at -78°C to a stirred solution of LDA (38.3mmol, 1.1 eq) in dry THF (38 mL); after 15 minutes, at the same temperature, $CuCl_2$ (5.15g, 38.3mmol, 1.1 eq) in DMF (38mL) was added. The reaction mixture was allowed to warm at rt and stirred overnight. The mixture was concentrated and extracted with 10% HCl solution (30mL) and Et_2O (40mL); the organic layer was washed with water (30mL), saturated aqueous $NaHCO_3$ solution (30mL) and again with water, then it was dried over Na_2SO_4 and concentrated in vacuo. The product **12** was obtained in 49% yields as a pale yellow oil, isolated in 49% yield.

^{1}H NMR (CDCl3, 300 MHz) δ 2.71 (s, 4H), 2.64 (qn, 2H, J = 6.9 Hz), 1.11 (d, 12H, J = 6.9 Hz).[87]

- **Synthesis of 2,5-diisopropylthiophene (13)**
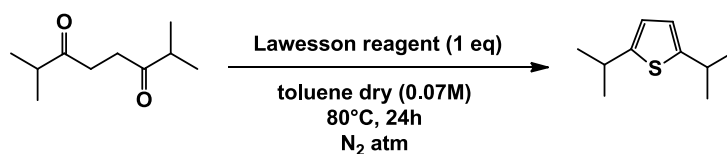
According to a literature procedure[88], Lawesson reagent (4g, 10.1mmol, 1 eq) was added to a stirred solution of 2,7-dimethyl-octa-3,6-dione (1.72g, 10.1 mmol, 1 eq) in toluene dry (145mL), under N_2

atmosphere; the mixture was stirred for 24 hours at 80°C.

The solid was filtered off and the mixture was concentrated in vacuo.

Gravimetric column chromatography (petroleum ether) led to 2,5-diisopropylthiophene as a colourless oil, isolated in 54% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.69 (s, 2H), 3.21 (qn, 2H, J = 6.9 Hz), 1.31 (d, 12H, J = 6.9 Hz).[89]

- **Synthesis of 3-bromo-2,5-diisopropylthiophene (14)**
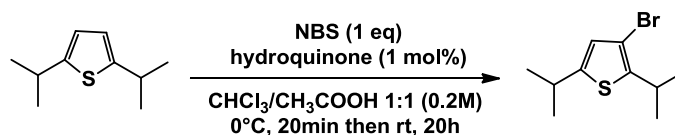
NBS (0.212g, 1.2mmol, 1 eq) and hydroquinone (1mg, 0.012mmol, 1 mol%) were added to a stirred solution of 2,5-diisopropylthiophene (0.2g, 1.2mmol, 1 eq) in CHCl$_3$/CH$_3$COOH 1:1 (6.6mL), at 0°C; the reaction mixture was stirred for 20 minutes at 0°C, then for 20 hours at room temperature. The mixture was extracted with CH$_2$Cl$_2$ (10mL) and H$_2$O (10mL); the organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo.

Flash column chromatography led to 3-bromo-2,5-diisopropylthiophene as a colourless oil, isolated in 55% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.62 (s, 1H), 3.32 (qn, 1H, J = 6.9 Hz), 3.09 (t, 1H, J = 6.9 Hz), 1.31 (d, 12H, J = 6.9 Hz).

3. PHOSPHINE AND PHOSPHINE OXIDE

3.1 *Synthesis of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphinyl)-3,3'-bithiophene (15)*

The general synthetic strategy to obtain diphosphine oxide from halogen-substituted substrate involves a transmetallation reaction, promoted by an alkyllitium as metallating agent, and subsequent electrophilic attack of chlorodiarylphosphine. The resulting diphosphine is then oxidized *in situ* to give the corresponding diphosphine oxide, which is the derivative necessary to perform the resolution process.

Normally, this procedure allows to obtain the final product in a range of yield between 40% and 65%.

In order to maximize the yields, the experimental conditions for the dianion formation and for the functionalization of the bithiophenic scaffold with the phosphinic groups were developed.

In the first experiment, lithiation was carried out at -65°C with *n*-BuLi, then the chlorodiarylphosphine was added and the mixture kept at same temperature for 30 minutes and allowed to reach room temperature in 20 hours. The subsequent addition of a 30% hydrogen peroxide solution led to tetraPhPO **15** in yields lower than 15%, associated with monophosphine oxide and products derived from chlorodiarylphosphine degradation.

The presence of the mono substituted derivative in the reaction crude highlighted two critical points: first, high steric hindrance of phenylic groups on bithiophene backbone inhibits the entry of second phosphinic group. Considering the high reactivity of the electrophile, the other critical point had to be the double lithiation of the dibromo derivative **7**. The dianion formation was performed by using both *n*-BuLi and *t*-BuLi which permits to operate at higher temperature without the formation of alkyl-substituted compound. Deuteration confirmed that both metallant agents led to the dilithium derivative, and *n*-BuLi was preferred for the lower risks related to its use.

Being experimental condition of the lithiation reaction optimized, we focused our attention on the reaction with the chlorodiarylphosphine. We performed this step at higher temperature, to promote the insertion of the second phosphinic group; after the addition of the electrophile to the dianion, the temperature was increased at 40°C and the reaction mixture was stirred overnight. Following this procedure, yield was improved from 15% to 46%, verifying the goodness of our hypothesis.

A further improvement of the yields was obtained carrying out the reaction at reflux for 8 hours; the diphosphine oxide was obtained in 55% yields. The best reaction conditions were reported in Scheme 3.1.
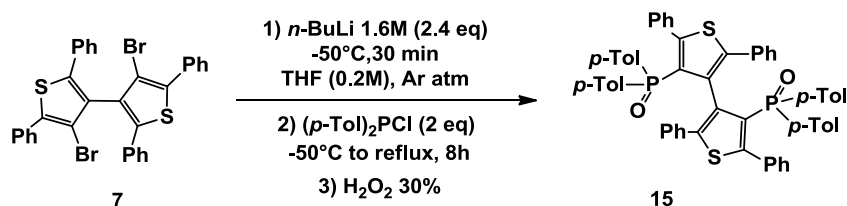
Scheme 3.1

3.2 _Synthesis of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphino)-3,3'-bithiophene (16)_

The diphosphine tetraPhP **16** was obtained following two procedures, as shown in Scheme 3.2:
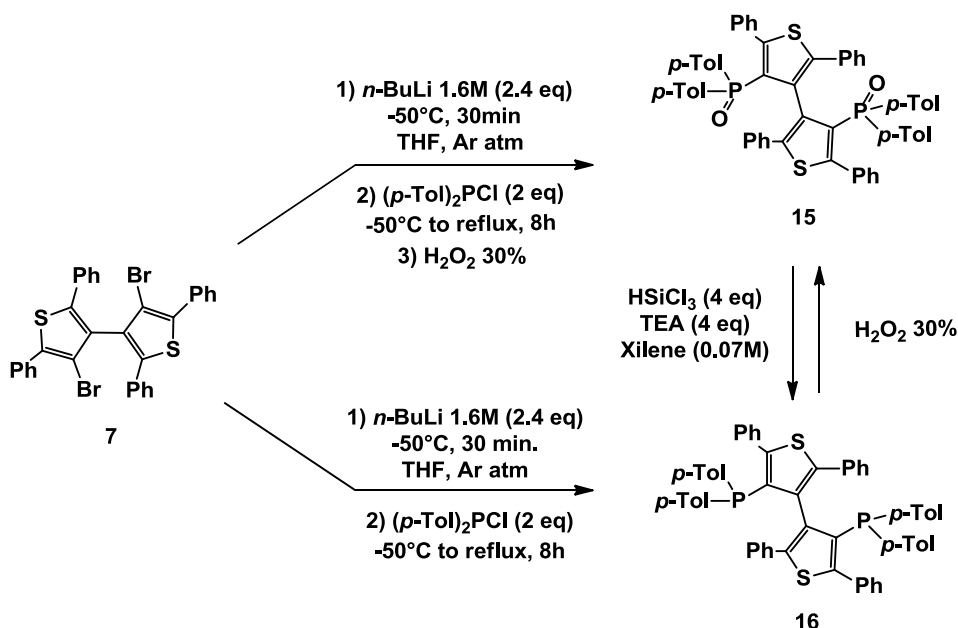
Scheme 3.2

The first synthetic strategy has already been discussed for the synthesis of the tetraPhPO **15**; in this case when the reaction with chlorodiarylphosphine was complete, the reaction was worked under a nitrogen atmosphere in order to avoid the oxidation. The purification was performed by column chromatography, under nitrogen pressure.

In the second strategy, the diphosphine oxide **15** was reduced with an excess of trichlorosilane and triethylamine, in quantitative yields, and the work-up was carried out under inert atmosphere.

3.3 _Resolution of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphinyl)-3,3'-bithiophene (15)_

The resolution of electron-rich diphosphines is usually carried by fractional crystallization of the diastereomeric adducts of the corresponding racemic diphosphine oxides with an optically pure chiral acid, generally the dibenzoyltartaric acid (Scheme 3.3), followed by alkaline decomposition of the diastereomerically pure adducts.
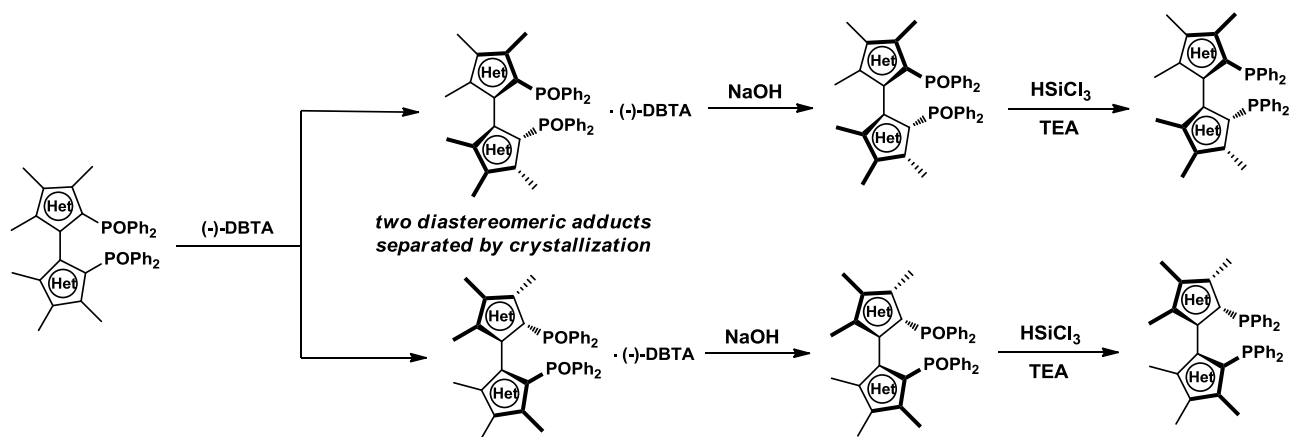
Scheme 3.3

Resolution of the diphosphine oxide with dibenzoyltartaric acid appeared to be difficult, due to the lack of a different solubility of the two diastereomeric salts.

A wide range of solvents were employed, but when the precipitation was observed, the precipitated was invariably composed of both of the enantiomers, as reported in Table 3.1.

In order to obtain the two enantiopure diphosphine oxides for the purpose of studying the solubility of the two diastereomeric salts, the resolution of the racemate was performed by a semipreparative HPLC analysis on a chiral stationary phase by Dr. Roberto Cirilli at the Istituto Superiore di Sanità di Roma. The chromatogram, reported in Figure 3.1, shows a perfect separation between the two enantiomers.
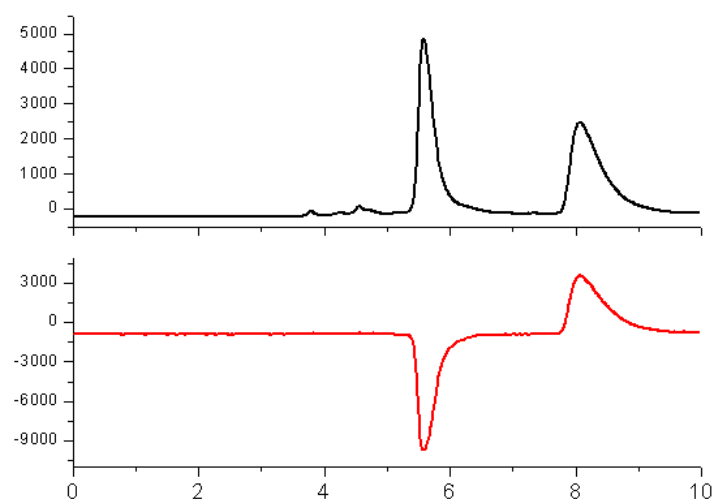
CSP: Chiralpak IB (250 x 4.6 mm i.d.); Eluent: n-hexane–2-propanol–ethanol 75:20:5 (v/v/v);
Temperature: 40°C; Flow-rate: 1 ml/min; Detector: UV (black) and CD (red) at 254 nm.

Figure 3.1

The chiroptical characterization of the two enantiomers was completed with the registration of the CD curves, which are perfectly specular, and the measurement of the specific rotations. Furthermore, the

absolute configuration was assigned to the enantiopure antipodes by comparison of the experimental CD curves with that calculated for the (*S*)-enantiomer, which corresponds, in this case, to the second eluted one, namely the dextrorotatory enantiomer.
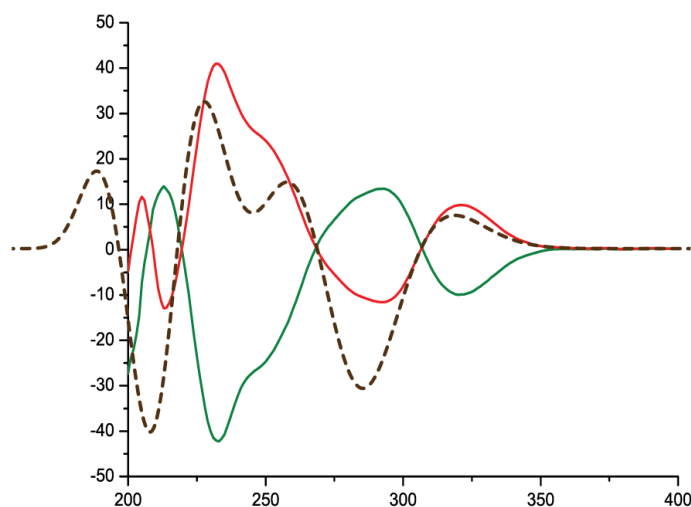
CD graphic: Ellipticity (mdeg) vs wavelength (nm);
(- - - - - : CAM-B3LYP/tzvp)
$[\alpha]_D^{20}$ *(green) = -174; c: 0,1 in ethanol;*
$[\alpha]_D^{20}$ *(red) = +177; c: 0,1 in ethanol.*

Figure 3.2

The availability of the two enantiopure antipodes allowed an investigation on the solubility of the diasteropure adducts with levorotatory dibenzoyltartaric acid. Different solvents were tested, but unfortunately any differences of solubility was observed between the two diastereoisomers: in all the experiments we observed the precipitation of the racemate.

Finally, a few tests were performed also with different resolving agents, as camphorsulfonic acid, naproxen, binaphthyl phosphoric acid, but, every time that a salt precipitated, HPLC chromatogram showed its racemic nature. All the experiments are reported in Table 3.1.

Table 3.1:

Solvent	Resolving agent	mol	Precipitation	e.e.%
AcOEt	(-)-DBTA	1	Yes	Rac.
CHCl$_3$	(-)-DBTA	1	Yes	Rac.
THF	(-)-DBTA	1	No	-
THF/Et$_2$O	(-)-DBTA	0,5	Yes	Rac.
THF/Et$_2$O	(-)-DBTA	1	Yes	Rac.

CHCl$_3$	(+)-Naproxen	0,5	No	-
CHCl$_3$	(+)-Naproxen	1	Yes	Rac.
AcOEt	(+)-Naproxen	1	Yes	Rac.
THF	(+)-Naproxen	1	Yes	Rac.
AcOEt	(+)-camphorsulfonic acid	1	Yes (4°C)	Rac.
THF	(R)-binaphthyl phosphoric acid	0,5	No	-
THF	(R)-binaphthyl phosphoric acid	1	Yes	Rac.

Given the disastrous results obtained, we decided to try to resolve the corresponding diphosphine **16**, from which it would be possible to obtain the diphosphine oxide by oxidation with H$_2$O$_2$.

3.4 *Resolution of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphino)-3,3'-bithiophene (16)*

As anticipated, electron-rich diphosphines are resolved at level of diphosphine oxides, as discussed in **Paragraph 3.3**, while electron-poor diphosphines, for which diphoshine oxides are not able to form salts with chiral acids, are resolved through an alternative methodology that requires the formation of diastereomeric complex of aminopalladium. We employed as chiral complex the di-μ-chloro-bis[(N,N')-dimethyl((R)-α-methylbenzyl)aminate-C$_2$N]palladium (II) which is prepared from (R)-phenylethylamine with PdCl$_2$, in the presence of LiCl.

The formation of diastereomeric complex was proven by ^{31}P NMR, as reported in Figure 3.3, in which are evident, as expected, the presence of four doublets.
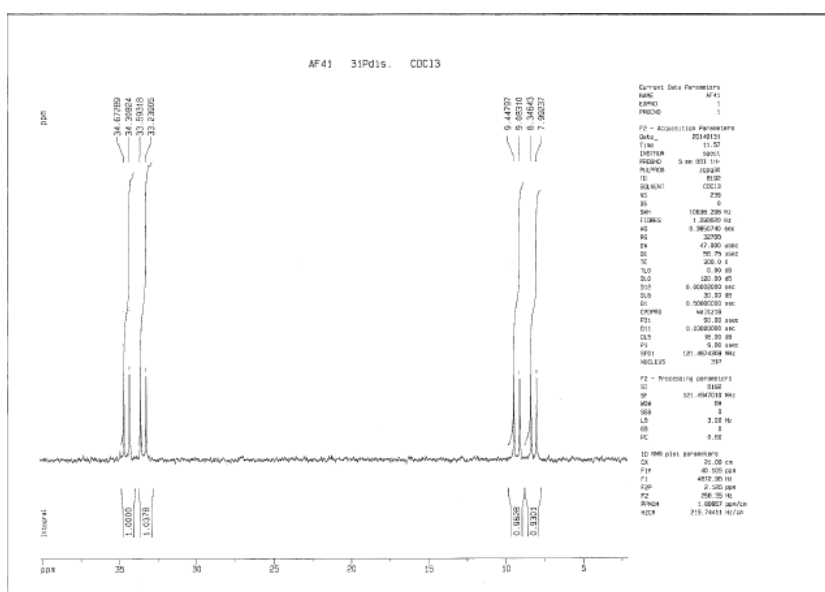
Figure 3.3

In fact each diastereomeric complex shows two doublets, respectively around 8 and 33 ppm, related to the two heterotopic phosphorus atoms.

This experiment is also useful for evaluating the configurational stability of diphosphine: if the integral relative to phosphorus signal of one diastereisomer is equal to that assignable to the other diastereoisomer, it means that the original ligand is configurationally stable; on the other hand, if the integrals of the two diastereoisomer are different, it's sure that the diphosphine isn't configurationally stable. It's necessary to assume that kinetic resolution of configurationally unstable enantiomers takes place; the enantiopure complexing agent selects and favors the association with one enantiomer of diphosphine. The penalize enantiomer amasses in the solution but, due to its instability, racemizes and it supplies to the enantiopure complexing agent the favorite antipode. This situation leads to disequilibrium between the diastereomeric complex, and this situation is recognized by NMR.

Being the integrals of the doublets relatives to the two diastereomeric complex identical, we can affirm that the diphosphine **16** is configurationally stable at room temperature. This result is rather obvious, since the corresponding diphosphine oxide was found to be configurationally stable.

Having checked the formation of chiral complexes, the following step was the kinetic resolution with half equivalent of palladium complexes: partial resolution took place, as resulted evident in the ^{31}P NMR spectrum reported in Figure 3.4. Flash chromatography had done under nitrogen, to separate the diphosphine-complex from free diphosphine and diphosphine oxide.

The complex diastereomerically enriched was treated with NaCN to obtain the enantiomerically enriched diphosphine. However, due to the scarce amount of the diphosphine, it wasn't possible to complete the resolution process so far.
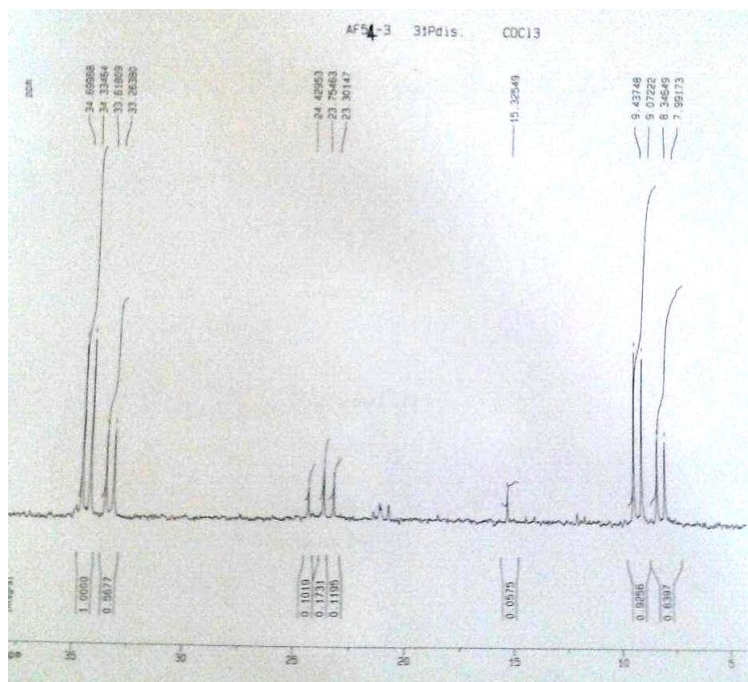
Figure 3.4

3.5 _Electronic availability of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphino)-3,3'-bithiophene (16)_

As already discussed in the introduction (see **Paragraph 1.3**), we are usual to use the electrochemical oxidative potential to determine the electronic availability of diphosphines. Measurements were carried out using 3 electrodes: glassy carbon as work electrode, platinum anode and SCE as reference electrode. (t-BuN)$_4^+$ ClO$_4^-$ is used as supporting electrolyte and the concentration of phosphine solution was kept at $2.23 \cdot 10^{-4}$M.

CV curves are reported in Figure 3.5, blue curve for tetraMe-BITIOP and red curve for tetraPh-BITIOP **16**; the graph shows that the first oxidation peak relative to diphosphine **16** is anticipated with respect to that of tetraMe-BITIOP, demonstrating that diphosphine **16** is electron-richer than tetraMe-BITIOP.
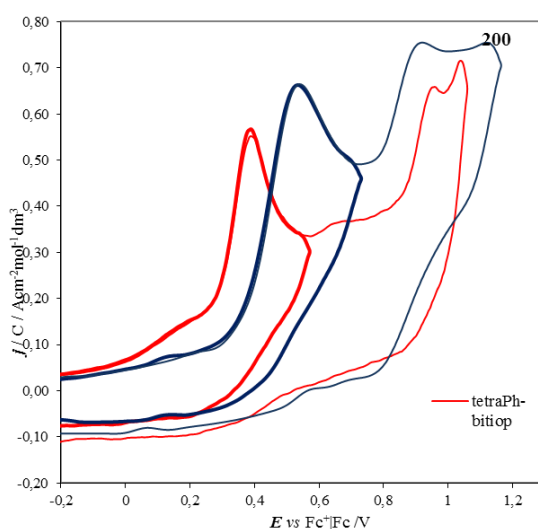
Figure 3.5

3.6 _Application of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphinyl)-3,3'-bithiophene in enantioselective reactions_

The enantioselective addition of allyl trichlorosilane to aldehydes represents a clear example of how metal-based enantioselective catalysts may be effectively replaced with simple organic molecules while maintaining high levels of chemical and stereochemical efficiency.[90]

Preliminary experiments were performed employing pure diphosphine oxide **15** (_S_ configuration) as catalyst in the stereoselective addition of allyl-trichlorosilane to _para_-nitrobenzaldehyde and cynnamil aldehyde. The results and comparison between tetraMe-BITIOPO and diphosphine oxide **15** as catalysts are reported in Table 3.2.
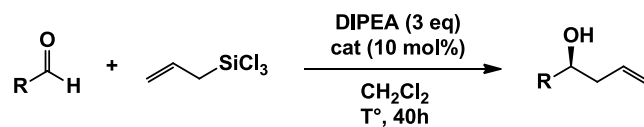
Table 3.2

Entry	R	Catalyst	T°(°C)	Yield (%)	ee (%)
1	4-NO$_2$-Ph	**15**	0	50	90
2	4-NO$_2$-Ph	tetraMe-BITIOPO	0	53	94
3	PhCH=CH-	**15**	0	98	70
4	PhCH=CH-	tetraMe-BITIOPO	0	74	82
5	PhCH=CH-	**15**	-20	96	69
6	PhCH=CH-	tetraMe-BITIOPO	-20	54	82

As for the reaction with *para*-nitrobenzaldehyde, the behaviour of the two ligands was almost the same, being tetraMeBITIOPO slightly superior, while with α,β-unsaturated benzaldehyde tetraPhPO exhibited an higher catalytic activity, but lower enantioselectivity. However, due its better catalytic activity, the reaction could be performed at lower temperature, hoping in an increase of the enantiodiscrimination level.

3.7 *Conclusions*

In this chapter the synthesis of new diphosphine and diphosphine oxide based on the 2,2',5,5'-tetraphenyl-3,3'-bithiophene scaffold were developed.

We tried to carried out the resolution of tetraPhPO **15** through fractional crystallization of their diastereomeric adduct, using different optically pure chiral acid, but without success. Enantiopure diphosphine oxides were obtained by semipreparative chiral HPLC and the (*S*)-antipode **15** was tested in the enantioselective addition of allyltrichlorosilane to aldehydes, exhibiting higher catalytic activity than tetraMeBITIOPO, but lower enantioselectivity.

First experiments concerning the resolution of diphosphine **16** were undertaken through formation of aminopalladium diastereomeric complex.

The electronic availability of diphosphine **16** was evaluated by cyclic voltammetry.

3.8 *EXPERIMENTAL SECTION*

3.8.1 General information

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen or argon. Dry solvents were used as received and stored under inert gas. All reagents, if not otherwise specified, were used as received and, if necessary, stored under inert gas.

For thin layer chromatography analysis, pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV254 were used. Visualization was accomplished by irradiation with a UV lamp and/or staining with potassium permanganate alkaline solution. Column chromatography was performed on 230-400 mesh Sigma-Aldrich silica gel.

Melting point determinations were performed by using a Buchi B-540 instrument.

^{1}H NMR, ^{13}C NMR and ^{31}P NMR were measured on a Brucker FT 300 or a Brucker AMX 300 instrument. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling costants are reported as Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet.

Mass analysis were performed using a VG 7070 EQ-HF instrument.

3.8.2 Synthetic procedures

- *Synthesis of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphinyl)-3,3'-bithiophene (15)*
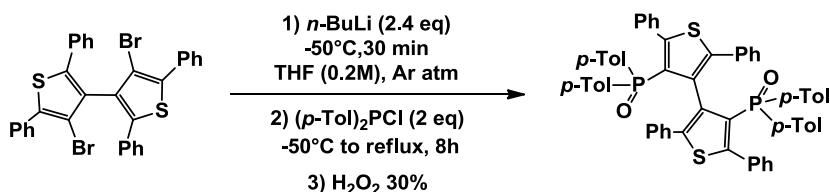
n-BuLi (1.6M solution in hexane, 6mL, 2.4 eq) was added dropwise to a stirred solution of **7** (2.5g, 4mmol, 1 eq) in dry THF (20mL), under Ar atmosphere at -50°C; after 45 minutes, the reaction was warmed up at -40°C and chlorophosphine (2g, 8mmol, 2 eq) was added, then the reaction was stirred at reflux for 8 hours. THF was removed under reduced pressure and the crude was dilute with CH_2Cl_2 (20mL); after a solution 30% of H_2O_2 was added and the mixture was stirred for 1 hour.

The mixture was extracted with 1N HCl solution (15mL); the organic layer was washed with saturated solution of $NaHCO_3$ (15mL), the aqueous phase extracted with CH_2Cl_2 (3 x 15mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo.

Flash chromatography (CH_2Cl_2/AcOEt/Et_3N 7:3:0.1) afford the compound **15** as a white solid, isolated in 55% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30-7.60 (m, 32H), 6.81 (m, 4H), 6.71 (m, 10H), 2.22 (s, 6H), 2.16 (s, 6H).

^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 21.5, 29.8, 127.1, 127.5, 127.6, 128.1, 128.4, 128.7 130.8, 132.1, 132.2, 140.5.

^{31}P NMR (CDCl$_3$, 121.4 MHz) δ 19.7 (s).

MS (EI): 926 (M$^+$).

- *Synthesis of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphino)-3,3'-bithiophene (16)*
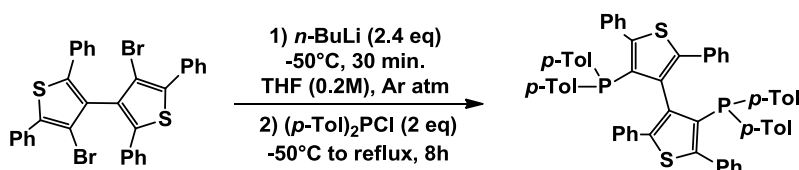
n-BuLi (1.6M solution in hexane, 0.5mL, 2.4 eq) was added dropwise to a stirred solution of **7** (0.2g, 0.32mmol, 1 eq) in dry THF (1.6mL), under Ar atmosphere, at -50°C; after 45 minutes, the reaction was warmed up at -40°C and chlorophosphine (0.2g, 0.64mmol, 2 eq) was added, then the reaction was stirred at reflux for 8 hours. THF was removed under reduced pressure. Flash chromatography under nitrogen atmosphere (hexane/CH_2Cl_2 8:2) afford the compound **16** mixed with the monophosphine.

- *Synthesis of 2,2',5,5'-tetraphenyl-4,4'-bis(ditolylphosphino)-3,3'-bithiophene (16) by reduction of diphosphine oxide 15*
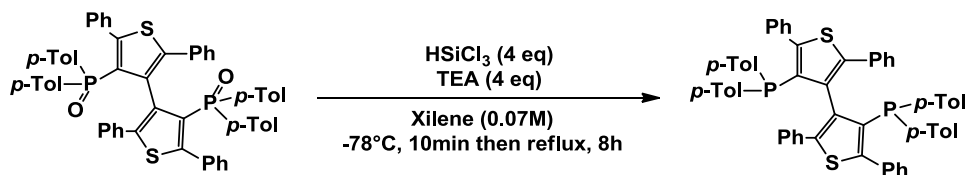
Diphosphine oxide **15** was dissolved in xylene and the mixture was cooled at -78°C, under Ar atmosphere; triethylamine and trichlorosilane were added and the mixture was stirred at reflux for 8 hours.

The mixture was washed with water, and precipitation of salts was observed; these salts were filtered off and the organic phase was dried and xilene was removed by distillation under vacuum, to afford the product , titritated with methanol, as a white solid, isolated in 60% yield.

^{31}P NMR (CDCl$_3$, 121.4 MHz) δ -18.02 (s).

- *Synthesis of di-μ-chloro-bis[(N,N')-dimethyl((R)-α-methylbenzyl)aminate-C$_2$N]palladium (II)*
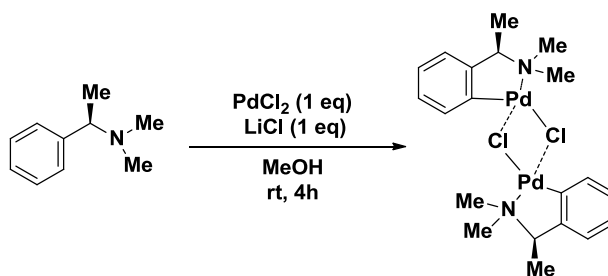
PdCl$_2$ and LiCl were dissolved in methanol; the mixture was stirred for 30 minutes and then filtered. Optically pure chiral amine was added dropwise to the filtered solution and the mixture stirred for 4 hours. The precipitate was filtered off and washed with cold methanol and diethyl ether and purified by crystallization with CH$_2$Cl$_2$/MeOH. The complex was obtained with 50% yield.

- *Synthesis of diastereomeric complex of 16*
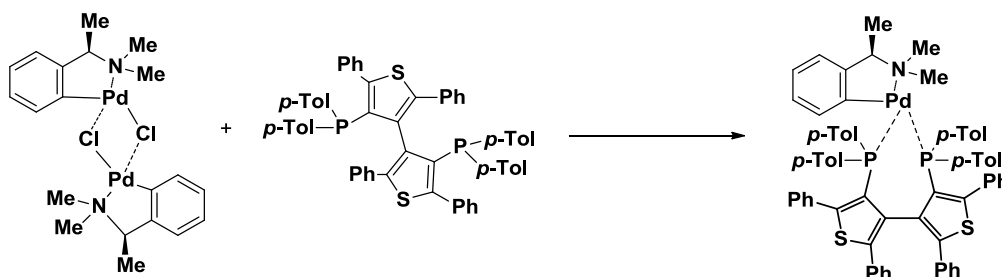
2,2',5,5'-tetraPh-P was dissolved in CHCl$_3$, under Ar atmosphere; the complex previously prepared was added and the mixture reaction was sirred for 30 minutes. The solvent was removed at reduced pressure.

- *Allylation reaction*
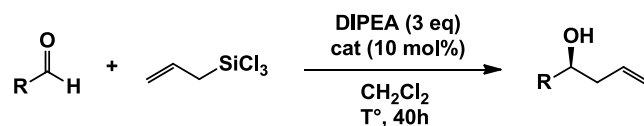
To a stirred solution of catalyst in dichloromethane kept under nitrogene, an aldehyde and DIPEA were added in this order. The mixure was kept to the desired temperature and allyl thriclorosilane was added dropwise. After 40 hours stirring the reaction was quenched by the addition of saturated aqueous solution of NaHCO$_3$, then water and AcOEt were added. The organic phase was separated and dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the crude products. These were purified by flash chromatography with different hexane:AcOEt mixture as eluent. Enantiomeric excess were determined by HPLC on a chiral stationary phase.

4. ATROPOISOMERIC BIHETEROAROMATIC DIOLS

To start the investigation on the new class of atropoisomeric diols based on the 3,3'-bithiophene skeleton, we though to synthesize and characterize **17** and **18**, reported in Figure 4.1, as forefather of 3,3'-bithiophen-4,4'-diol class.

17: R = Ph
18: R = Me
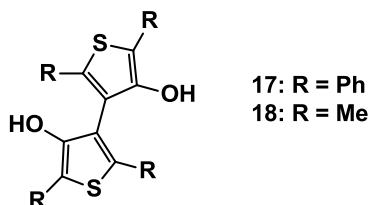
Figure 4.1

This class of compounds is particularly interesting, due not only to the possible applications in the field of catalysis, but also for synthetic and structural perspectives: in fact, based on our knowledge, in literature there are no examples of 3,3'-bithiophen-4,4'-diols and also 3-hydroxythiophenes are compounds scarcely investigated, due to the existence of a fast keto-enol tautomerism in which ketonic tautomer is the predominant one (Figure 4.2). However, equilibrium shift is strongly affected by solvents and it can be directed towards enol tautomer by the introduction of electron-withdrawing groups on the ring.[91]
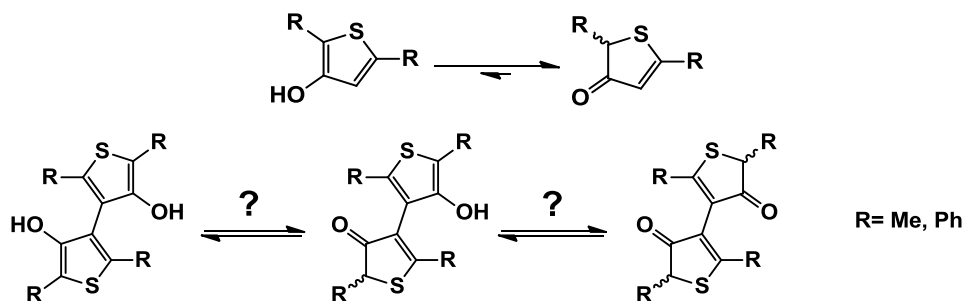
Figure 4.2

Another essential perspective to evaluate was the configurational stability that couldn't have been high enough due to the reduced size of hydroxylic groups and the geometry of pentatomic rings which spatially distances the hydroxy groups more than the hexatomic rings.

Functionalization of 3,3'-bithiophene skeleton with phenylic groups discloses dual advantages, that is to increase steric hindrance closed to the interanular bond and, by consequence, configurational stability, and to promote enol tautomer due to the extended conjugation.

Derivative **18**, although less promising in terms of structure, appeared easier to synthesize, since 2,5-dimethylthiophene is commercially available; moreover this derivative could contribute to define the essential structural requirement to promote enol tautomer to ketonic one, highlighting the role of the substituents on the atropoisomeric scaffold in extending molecule conjugation.

If the diols **17** (named "bithienol") had revealed configurational stability, they could have been resolved in their antipodes through HPLC on a chiral stationary phase and, potentially, on large scale through classical chemical methods.

On the contrary, if diols hadn't been configurationally stable, they could have been converted into derivatives that could ensure a higher conformational rigidity and employed in the asymmetric catalysis.

Retrosynthesis of the diols **17** and **18** could be approached by following two different strategies, in which the functionalization of the thiophene ring with the hydroxy groups could take place subsequently (strategy 1) or before (strategy 2) the formation of the interanular bond, which can be formed through oxidative coupling of the 3-lithiumthiophene with copper (II) salts.

Since the synthesis required the use of alkyl lithium compounds, hydroxy groups must be conveniently protected, and the easiest way to protect them is as methoxy groups, easily removable with boron tribromide.

Following both the strategies, the introduction of the methoxy groups on the thiophenic rings would have been achieved directly through the conversion of the bromine atoms.

Another pathway, the simplest one, was to carry out the "direct" conversion of bromine atoms in hydroxyl group (Figure 4.3).
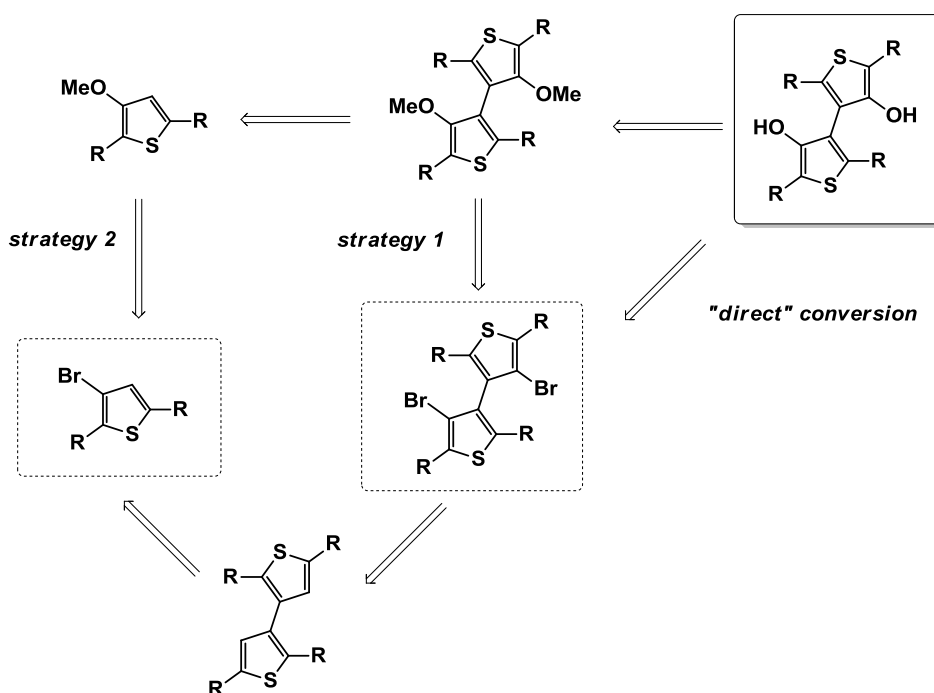
Figure 4.3

4.1 *2,2',5,5'-Tetraphenyl-4,4'-diol-3,3'-bithiophene (17)*

Due to the availability of the 4,4'-dibromo-2,2',5,5'tetraphenyl-3,3'-bithiophene, we started our investigation following an approach in which the introduction of the hydroxy group was direct since this scheme appeared the simplest one.

The dibromoderivative **7** was converted in the diboronate **19** by transmetallation with *n*-BuLi and

subsequent reaction of the bislithium derivative with triethylborate. Finally, the addition of 30% H_2O_2 solution in the reaction mixture converted the borate groups in the hydroxy ones (Scheme 4.1).

According to this procedure, bithienol **17** was obtained in 21% yields.
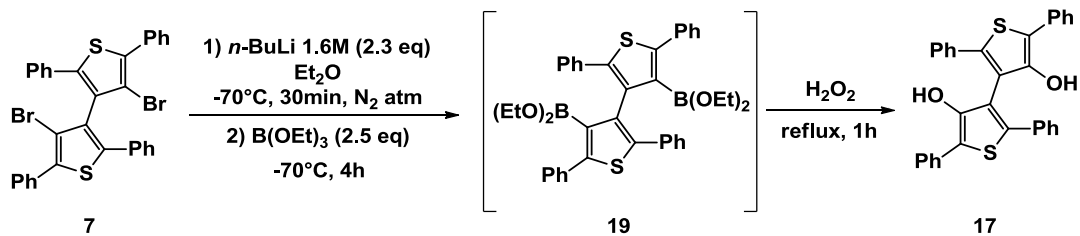
Scheme 4.1

Despite low yields, this approach allowed us to achieved material enough to carry out its analytical and spectroscopic characterization and ^{1}H and ^{13}C NMR spectrum confirmed the presence of signals attributable to the sole enol tautomer, as shown in Figure 4.4.
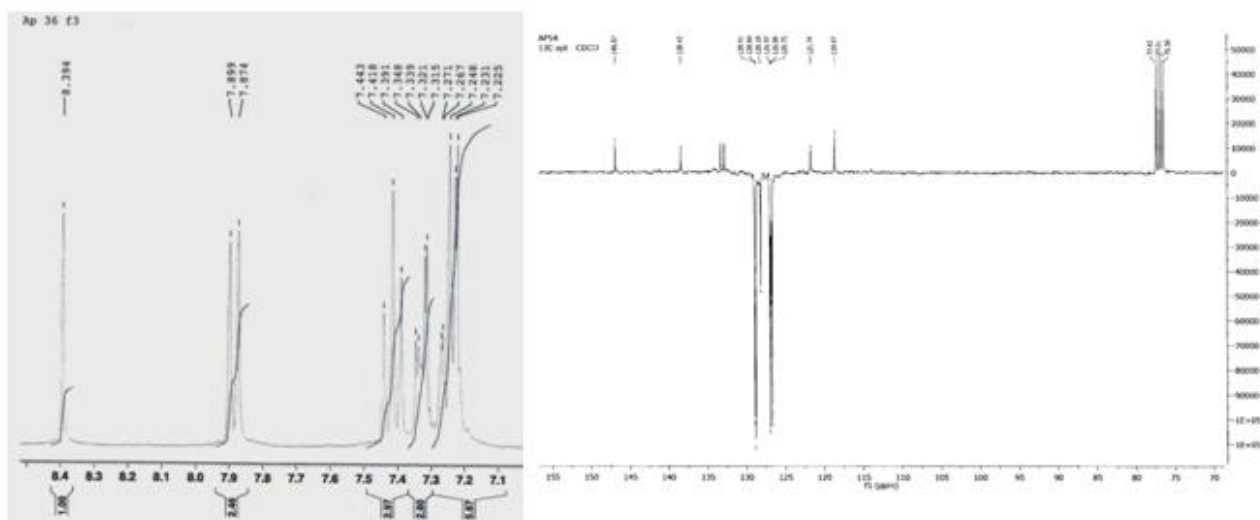
Figure 4.4

To improve the yields of the synthesis of **17**, we decided to pass through the formation of the dimethoxyderivative, according to "strategy 1". The introduction of methoxy groups on the dibromoderivate **7** was carried out by nucleophilic substitution with an excess of sodium methoxide in presence of catalytic amounts of copper (I) bromide, following a procedure reported in literature for aromatic and heteroaromatic halides.[92] The reaction led to the formation of an equimolar mixture of monomethoxy derivative **20** and dimethoxy derivative **21**, each one in 25% yields (Scheme 4.2).
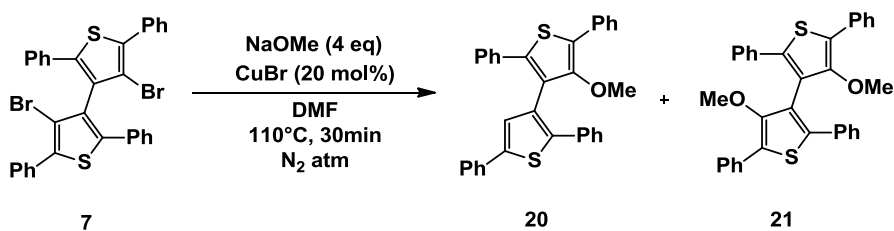
Scheme 4.2

Demethylation reaction was carried out with BBr$_3$ in dichloromethane at room temperature. The non-isolable intermediate **22** was decomposed with water to give bithienol **17** in quantitative yields (Scheme 4.3).
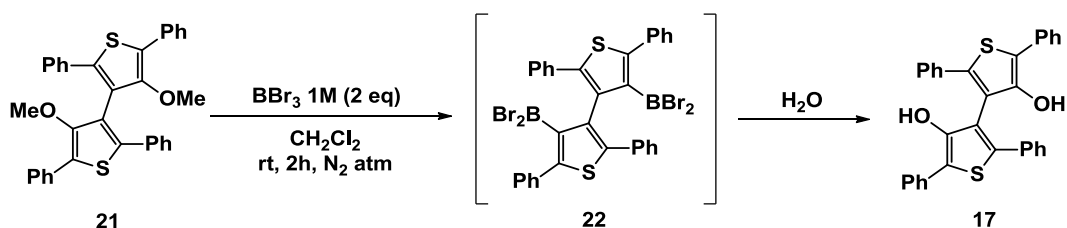
Scheme 4.3

However, also this synthetic scheme wasn't satisfactory since the introduction of the second methoxy group was difficult to achieve and we decided to follow the strategy 2, starting from 2,5-diphenyl-3-bromothiophene. The substitution of the bromine atom with NaOMe and CuBr led to 2,5-diphenyl-3-methoxythiophene in 60% yields (Scheme 4.4).
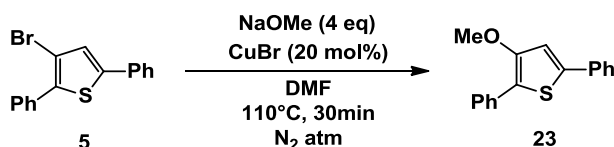
Scheme 4.4

The subsequent bromination, which should led to the formation of the intermediate necessary to build the interanular bond, was a failure: in fact the bromination, conducted both with NBS at 0°C and Br$_2$ at room temperature, didn't lead to the desired product **24** but rather to a mixture consisting of 2-(4-bromophenyl)-3-methoxy-5-phenylthiophene and 4-bromo-2-(4-bromophenyl)-3-methoxy-5-phenylthiophene (Scheme 4.5), which were analytically and spectroscopically recognized and characterized.
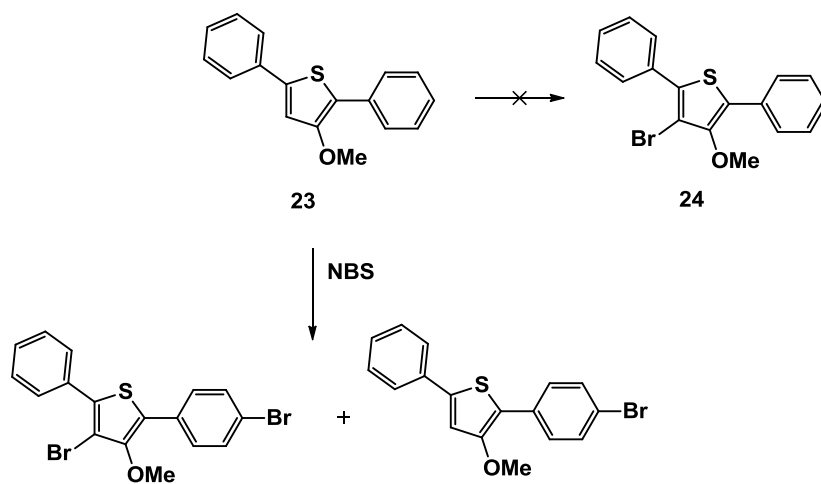
Scheme 4.5

It wasn't possible to isolate the product of bromination of the thiophene ring also carrying out the reaction with NBS at -20°C, being the only product isolated the 2-(4-bromophenyl)-3-methoxy-5-phenylthiophene.

This result could be explained considering the activation of the para position of the closed phenyl ring, induced by the methoxy group (Figure 4.5).
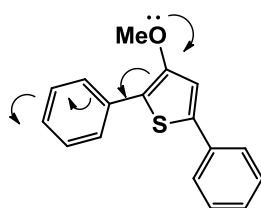
Figure 4.5

We attempted direct metallation of the β-position, which should be quite acidic due to the presence of the methoxy group, in according with what widely verified for anisole.[93]

We started the investigation employing *tert*-BuLi as base, considering that the use of a strong base for the deprotonation would be indispensable. The progressive addition of the base to the solution of **23** in ether produced a strong blue coloration. ^{1}H-NMR spectrum of a sample quenched with D$_2$O, showed the absence of the thiophenic proton.

However, coupling of the lithium derivative, mediated by copper (II) chloride, didn't produce the expected results: in fact the desired product **21** was isolated only in traces (8% yields), while the starting reagent and 2,5-diphenyl-3-chloro-4-methoxythiophene were the main products of the reaction (Scheme 4.6).

Scheme 4.6

71
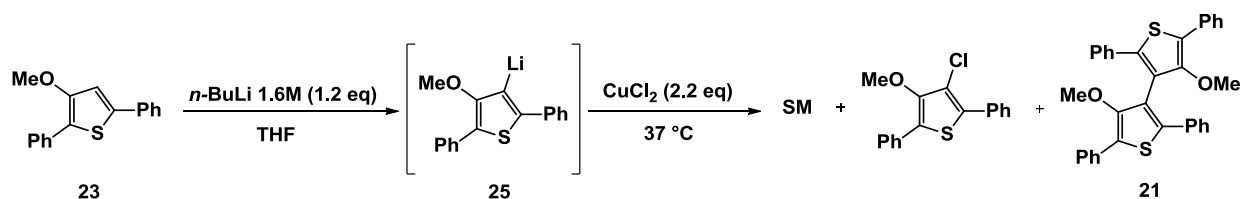
Unfortunately, it was no possible to improve this result, both by changing temperature reaction and by increasing oxidant equivalents; the scarce reactivity of the anion **25** can be ascribe to the fact that lithium derivative is a intimate ion pair stabilized by the methoxy group that, through the coordination with lithium, makes the reactive site less accessible to the oxidant.

To solve this inconvenience, we decided to employ *n*-BuLi in presence of TMEDA that should increase the reactivity of the base and allow the carbanion to be less shielded. Surplisingly, the addition of *n*-BuLi didn't produce a blue coloration, but a slight yellow coloration; however, also in this case, the ^{1}H-NMR spectrum of a sample quenched with D$_2$O, showed the absence of the thiophenic proton.

This result led us to think that the species generated with *tert*-BuLi was a radical anion, which could justify the failure of the reaction previously mentioned. The addition of the oxidant at -10°C allowed to obtain a mixture similar to that isolated in the precedent reaction, but where the dimer **21** was present in a slightly higher amount (12% yields).

Encouraged by this result, we carried out the oxidation reaction at 35°C, considering that an increase of the temperature could facilitate the coupling reaction. Analysis of the crude by TLC showed a significant increase of the intensity of the spot, displaying the RF of the dimeric product **21**. Surprisingly, ^{1}H-NMR spectrum of the isolated product showed the presence, in equal quantities, of a second coupling product characterized by two non equivalent methoxy groups (Scheme 4.7).
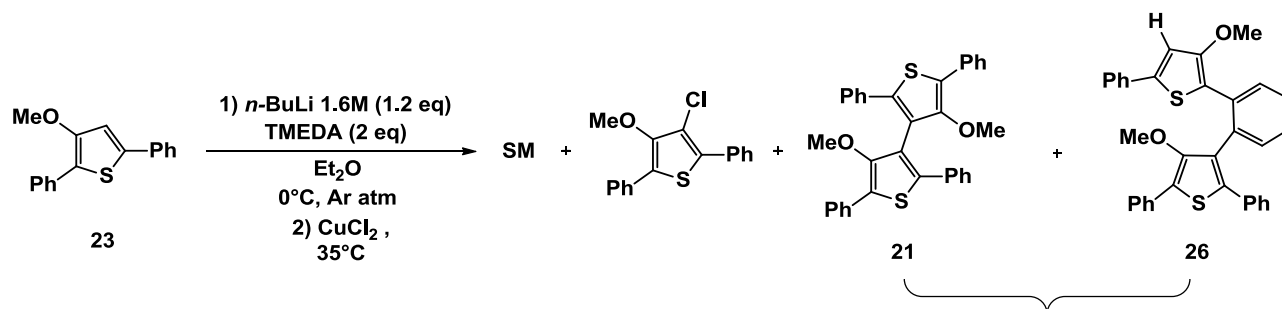
Scheme 4.7

The formation of **26** must be ascribe to the presence of two different lithium derivative in solution, both stabilized by the methoxy group (Figure 4.6), which could react generating a non symmetrical coupled derivative.
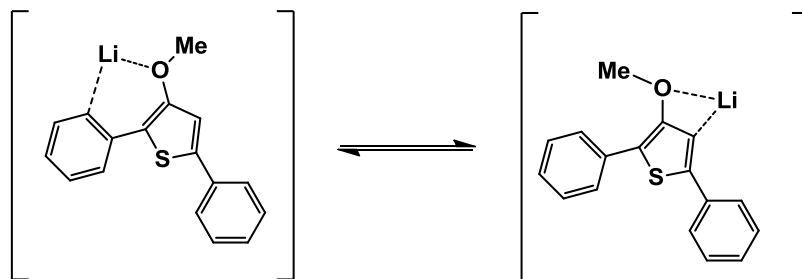
Figure 4.6

Unfortunately, we couldn't separate the two dimeric products neither by column chromatography nor by

fractional crystallization.

We performed different texts in order to inhibit the formation of the undesired product. By performing the reaction at room temperature we observed a reduction of undesired product until 12% yields, combined with a decrease of the overall coupling yields (18%).

The by-product wasn't observed in the crude when the reaction was carried out at 0°C, but the result wasn't satisfactory since the yield of **21** dropped to 15%, an unsatisfactory result.

A decisive improvement was realized when THF was employed as solvent; the reaction was carried out at 37°C in the presence of two equivalents of TMEDA; in these conditions **21** was isolated in 45% yields, beside the starting material which can be reutilized (Scheme 4.8).
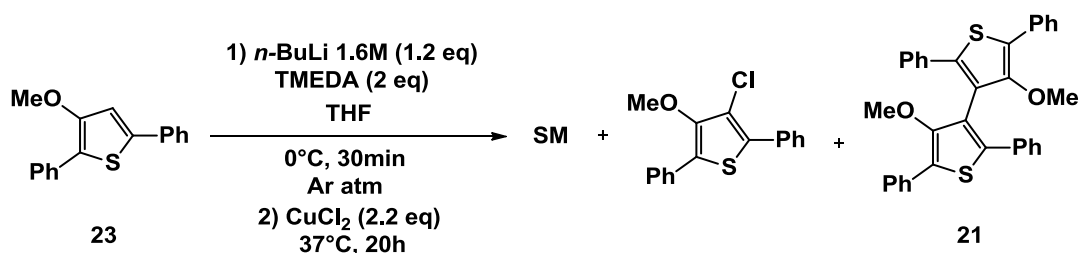
Scheme 4.8

We were able to obtain crystals suitable for the determination of the structure by X-ray diffraction, using pentane as solvent.

An important information that we obtained from the X-ray structure is the dihedral angle value between the two thiophene rings, which is 79°, being 111° in the case of the 2,2'-dimethoxy-1,1'-binaphthyl (Figure 4.7).[94]

This data underlined the geometrical difference of bithiophene derivatives in comparison with carbocyclic analogues. A similar geometry should be maintained into the corresponding diol, even if the intramolecular hydrogen bonds could produce some differences.
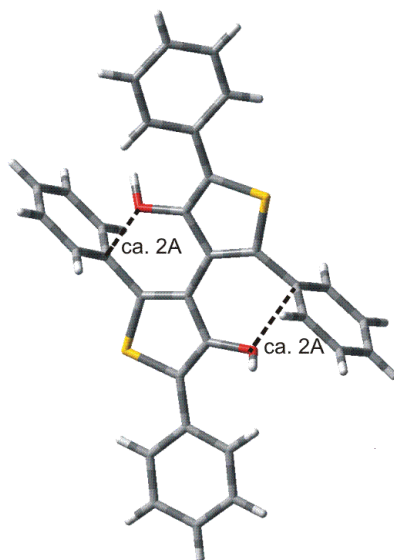
Figure 4.7

4.2 *2,2',5,5'-Tetramethyl-4,4'-diol-3,3'-bithiophene (18)*

We followed the same synthetic approach for the synthesis of bithienol **17** (Scheme 4.9) and we introduced the methoxy group on the thiophenic ring before the formation of the interanular bond.
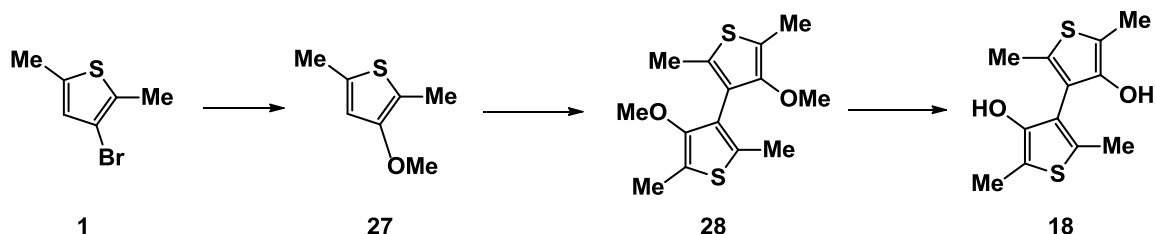
Scheme 4.9

Nucleophilic substitution with sodium methoxyde and copper (I) bromide on the 2,5-dimethyl-3-bromothiophene, carried out in the same experimental conditions described for the synthesis of 3-methoxy-2,5-diphenylthiophene, led to the methoxyl derivative **27** in 60% yields.

Unfortunately, direct metallation of **27** did't take place; in fact, the use of *tert*-BuLi as a base led to the opening of the thiophenic ring, meanwhile *n*-BuLi wasn't strong enough as base to deprotonate the β-position (Scheme 4.10) and we recovered the starting material unreacted.
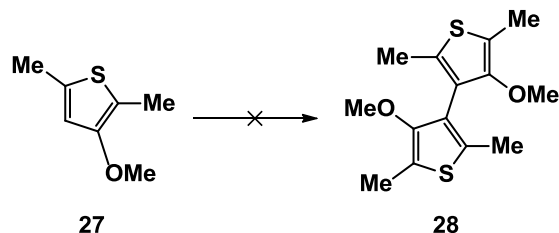
Scheme 4.10

Therefore we considered reasonable to perform a transmetallation on the 2,5-dimethyl-3-bromo-4-methoxythiphene and we investigated the bromination of **27** (Scheme 4.11).
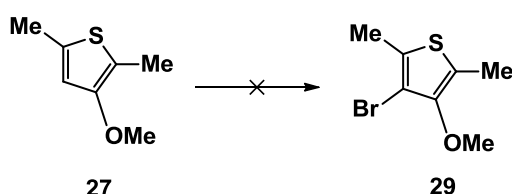
Scheme 4.11

Unfortunately we couldn't obtained the bromoderivative using both NBS in the presence of hydroquinone and Br$_2$ as brominating agents. We varied the equivalents of brominating agent and the reaction temperature,

but in any case we obtained a polymerization product, probably derived from the methyl-quinone that, in turn, could be formed by introduction of a bromine atom on a methyl group and subsequent elimination of HBr, as shown in Scheme 4.12.
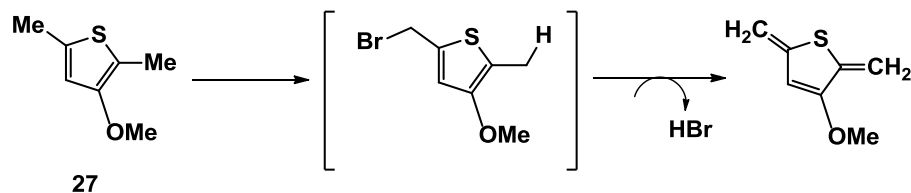
Scheme 4.12

Due to the failure of this synthetic strategy, we investigated the alternative approach, in which the functionalization of the thiophene ring with the oxygen atoms is the last step. The functionalization of the key intermediate **3** can be realized following the two synthetic pathways reported in Scheme 4.13.
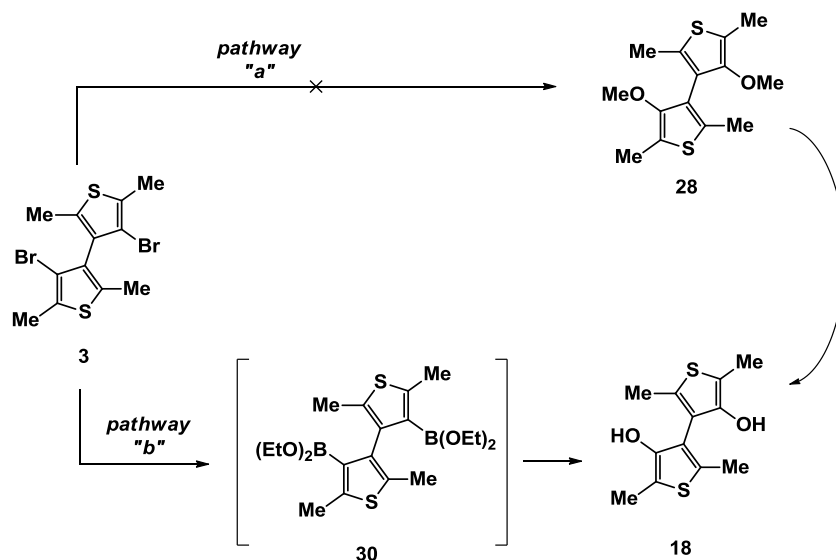
Scheme 4.13

The introduction of methoxy groups with sodium methoxyde in the presence of copper (I) bromide (pathway "a") was unsuccessful: although different experimental conditions were employed, in each case we observed the formation of reduction products **31**, in which one bromine atom was replaced with a methoxyl group and the other one was reductively removed and **2**, in which both bromine atoms were reductively removed (Scheme 4.14).
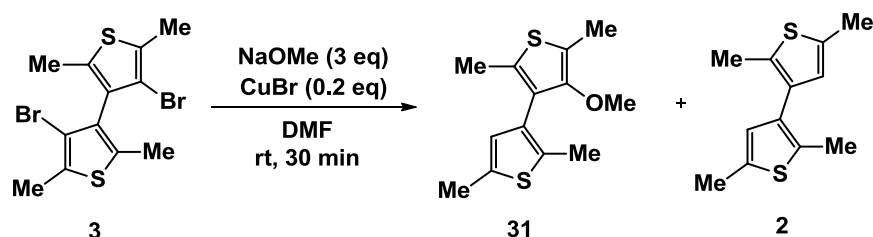
Scheme 4.14

The introduction of the hydroxy groups following pathway "b" was carried out one pot; the formation of the anion was performed employing *tert*-BuLi as a base at -60°C and the following reaction with triethyl borate was carried out at room temperature for 4 hours. Finally, the temperature was increased to reflux in order to allowed the oxidation of the borate with H_2O_2 (Scheme 4.15).

TLC of the reaction crude showed the presence of only one product, that presented on the plate an elongated spot; mass spectrum clearly showed the peak at 253 mass units, relative to the tetramethyl bithienol **18**.
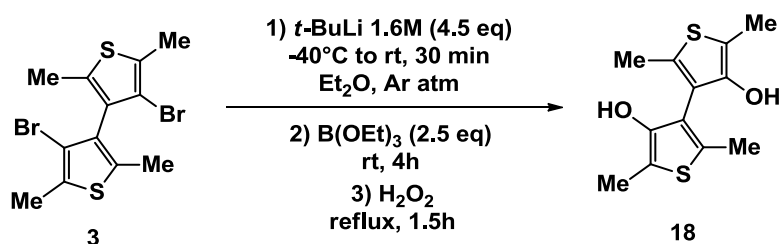
Scheme 4.15

However, ^{1}H-NMR spectrum is rather complex and suggested the presence of different tautomers in solution, being present signals at 1.75 ppm and 2.40 ppm, corresponding to methyl groups on saturated carbons and on aromatic rings, respectively. The presence of different methyl groups should be ascribed to the formation of the tautomers **32** and **33** shown in Scheme 4.16. The frame is further complicated by the fact that each tautomer can exist in the form of various diastereoisomers, taking into consideration the presence of stereocenters and stereogenic axis.
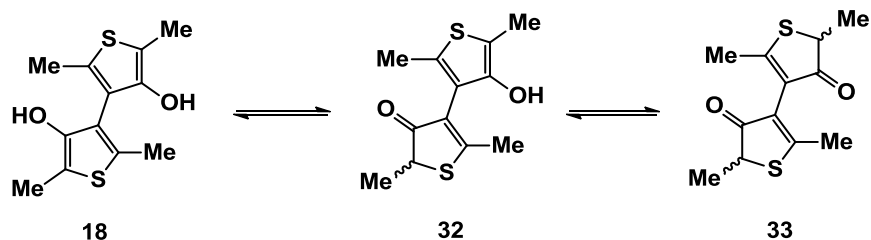
Scheme 4.16

4.3 Resolution of Bithienol 17

In order to establish if the resolution of **17** on a preparative scale would be possible, we started to resolve bithienol on an analytical level by HPLC on a chiral stationary phase. This preliminary study allowed to get important information about the configurational stability of the enantiomers at room temperature and was necessary in order to find a method to check the enantiomeric purity after the resolution process.

The chromatogram of racemic bithienol, carried out using a Daicel AD column and hexane:isopropanol 8:2 (flow: 0.8 mL/min, pressure: 17 bar) shows two distinct peaks, confirming the non-interconversion of the two enantiomers, at least at room temperature during the separating process (Figure 4.8).
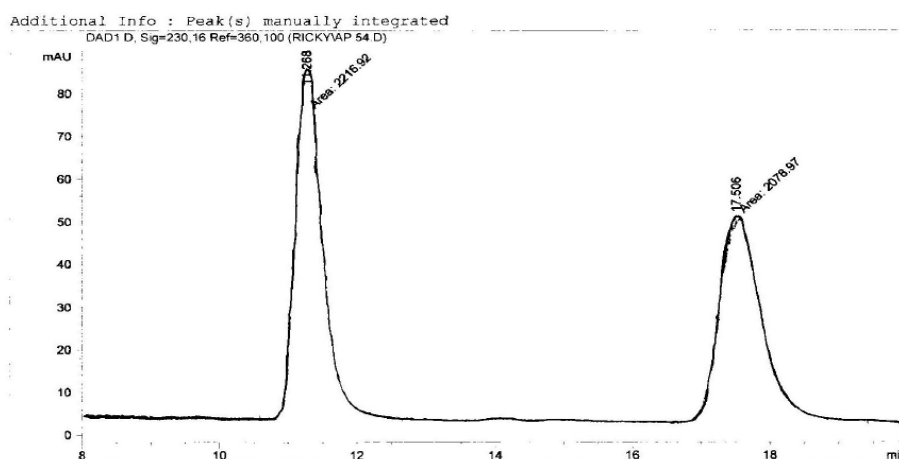
Figure 4.8

4.4 Chiroptic characterization of (+)- and (-)-17

The two enantiomers were separated into antipodes by semipreparative HPLC on a chiral stationary phase, by Dr. Cirilli of the Istituto di Sanità di Roma; separative process was carried out employing a Chiralpack IA column (250mm x 4.6 mm ID), with *n*-hexane:isopropanol 7:3 as eluent (T° = 25°C, flow rate = 1 mL/min, UV detector at 254 nm).
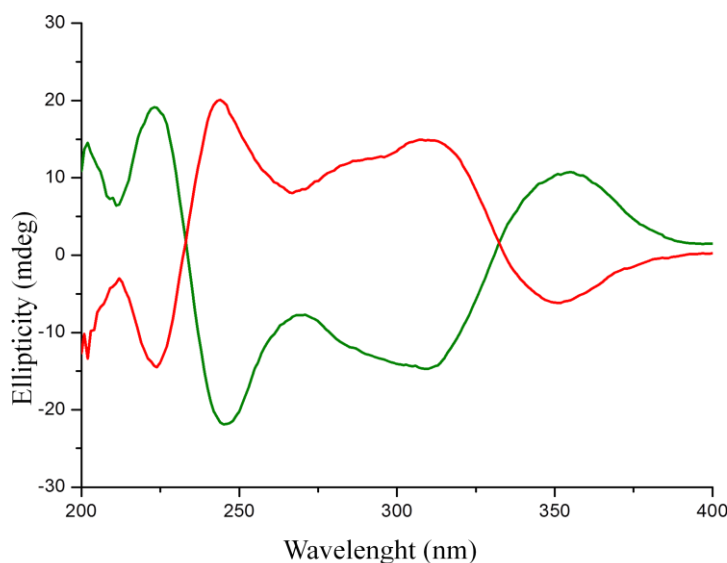
Green curve: first enantiomer eluted, levorotatory

Red curve: second enantiomer eluted, destrorotatory

Figure 4.9

The enantiomers were characterized by chiroptical analysis; circular dichroism curves were recorded at 5°C in ethanol and were perfectly specular (Figure 4.9).

4.5 *Configurational stability of Bithienol 17*

After this encouraging results, in order to have a more detailed idea of the configurational stability of **17**, the rotation barrier was evaluated both by computational calculation by Dr. Sergio Rossi of the Università degli Studi di Milano, and by HPLC on chiral stationary phase by Dr. Roberto Cirilli of the Istituto Superiore di Sanità di Roma.

4.5.1 Theoretical determination of the configurational stability

Conformational analysis was performed using molecular mechanics calculations with MonteCarlo techniques in order to determinate the conformation with minimum energy. For this purpose, two different force fields were employed: MMFFs,[95] and OPLS_2005,[96] with the employment of Macromodel program.[97]

The most stable conformation calculated for **17** shows a dramatic reduction of the dihedral angle between the two thiophene rings in comparison with the corresponding dimethoxy derivative **21**, from 79° to 50.5°.

The explanation of this variation is related to the formation of an intramolecular hydrogen bond between the two hydroxy groups, that forces the two heterocyclic rings to assume a conformational model for the establishment of such additional bond.

In fact, O---H-O distances are 1.8 Å, a classical value for this kind of interaction (Figure 4.10).

After identifying the most stable conformation, the energy was evaluated depending on the

dihedral angle value. The rotation barrier resulted 27.98 kcal/mol, based on MMFFs calculations and 31.72 kcal/mol, based on OPLS_2005 calculations; in both cases the energy barrier is higher than 22 kcal/mol, that means the racemization is not a rapid process, at least at room temperature.
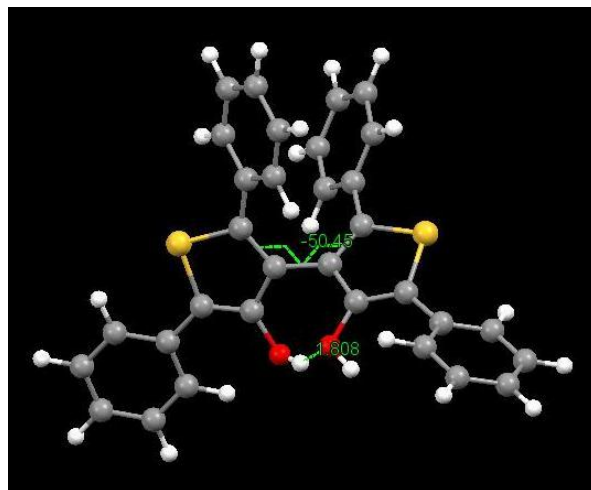
Figure 4.10

Furthermore, the rotational barrier was calculated by DFT analysis (B3LYP-631G basis set[98], with Gaussian 09[99]) and, in this case, the geometry of the transition state, relative to the coplanarity of the heterocyclic rings, was evaluated to be 29 kcal/mol (Figure 4.11).
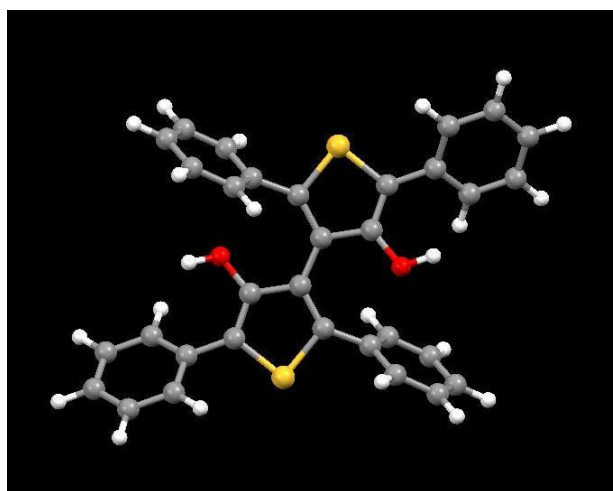
Figure 4.11

4.5.2 Experimental determination of the configurational stability

Configurational stability of **17** was determined by R. Cirilli of Istituto Superiore di Sanità di Roma through an HPLC analysis on chiral stationary, following the racemization of levorotatory enantiomer over time.

Off column experiments, showed in Figure 4.12, were carried out evaluating, at regular intervals, the

mutation of the enantiomeric excess of the first eluted enantiomer, which was maintained at 60°C in a solution of isopropanol.

$$k_{rac} = 5.06 \times 10^{-4} \text{ sec}^{-1}$$

$$\Delta G^{\#} = 24.6 \text{ Kcal/mol}$$

Elution time (min)
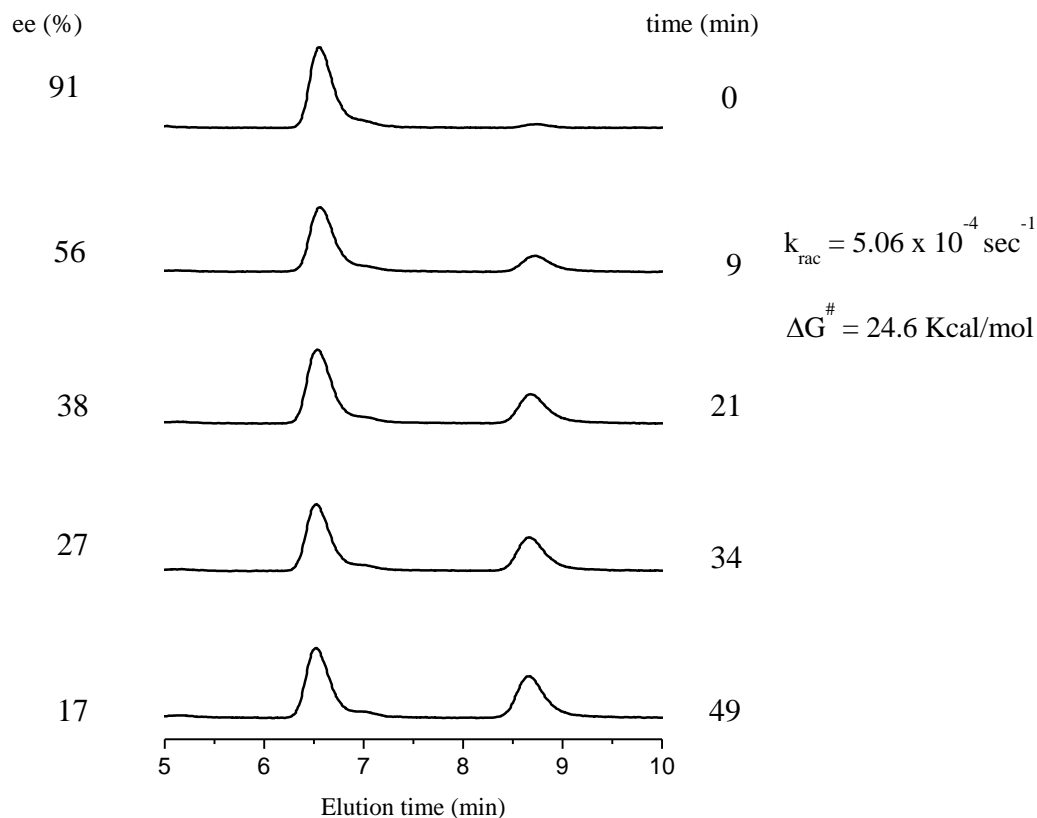
Figure 4.12

The barrier of racemization was calculated by plotting the natural logarithm of the enantiomeric excess as a function of time: the energy of racemization was traced back from the value of the angular coefficient and resulted to be 24.6 kcal/mol. (Figure 4.13).

$$y = -5.0589x + 4.2977$$
$$R^2 = 0.9985$$
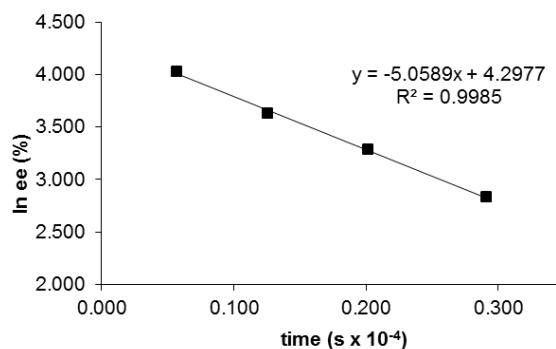
Figure 4.13

Enantiomerization barrier was also determined through an on column experiments: chiral dynamic HPLC

analysis (eluent: *n*-hexane:isopropanol 8:2; rate flow: 0.2 mL/min) of racemate were carried out at increasing temperatures, from 30°C to 45°C, evaluating the kinetic of peak coalescence (Figure 4.14).

Chromatograms show a plateau zone between the peaks of the two enantiomers, due to the partial enantiomerization of both antipodes during the separation process at these temperatures.
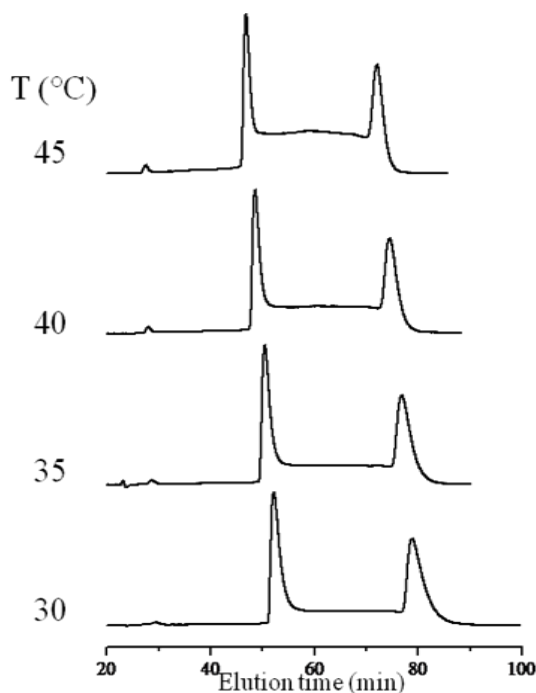
Figure 4.14

Chromatograms were investigated by Professor M. Pierini of the Università "La Sapienza" who, employing simulation methods, acquired a racemization energy of 24.6 kcal/mol smaller than that obtained with by Dr. S. Rossi through computational methods.

This results could be explained considering that the experimental conditions employed in the analytical resolution inhibits the formation of hydrogen bond that stabilized the diol **17** in the theoretical approach.

4.5.3 Computational calculations on differently substituted bithienols

The low configurational stability shown by bithienol prompted us to perform a computational analysis in order to identify possible substituents capable of increasing the racemization barrier. The computational work was carried out by Dr. Sergio Rossi of the Università degli Studi di Milano, who investigated the conformational analysis through molecular mechanics (OPLS_2005) to identify the structure with the lowest energy and subsequent refined geometry with semi-empirical methods (PM6) and finally evaluated the energy by DFT with different basis-sets.

Different substituents were introduced in different positions on the phenyl rings and the racemization

barriers of the corresponding bithienol derivatives were calculated. From the results reported in Figure 4.15 it is clear that the functionalization withf different subsituents of the aromatic rings doesn't lead to a raising of the racemization barrier, as we expected being steric hindrance increased.

In fact, the more the steric hindrance of the substituents increases the more th aromatic rings tend to orientate so that the steric interactions diminish with a decrease of the configurational stability of the compound.

Instead alkyl substituents as isopropyl on thiophene rings increase the energy barrier, but they couldn't be utilized since the keto-enol equilibrium in this case should be shifted towards the formation of a mixture of keto-isomers.

However, the equilibrium could be shifted towards the formation of the enol derivative through the transformation into a suitable cyclic derivative.
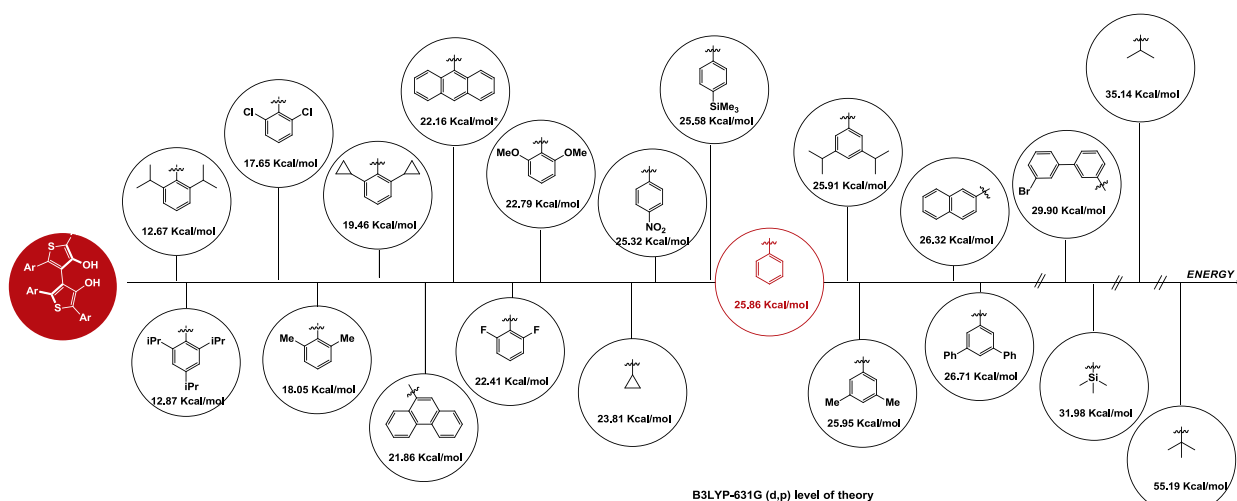
Figure 4.15

4.6 Derivatives of 2,2',5,5'-Tetraphenyl-4,4'-diol-3,3'-bithiophene (17)

The low configurational stability of bithienol **17** prompted us to investigate the corresponding chiral phosphorous ligands, especially phosphoric acids, phosphoramidites and phosphites. These derivatives were designed to restrict the rotation around the interanular bond and being cyclic structures, could ensure an higher configurational stability to the system.

Furthermore, these derivatives could be employed as organic catalyst or as chiral ligand of transition metals in asymmetric catalysis and their ability as chiral promoter could be evaluated.

In fact, phosphoric acids, derived from BINOL, were widely employed as bifunctional catalysts, being characterized both from a Brønsted acidic site and from a Lewis basic site, as shown in Figure 4.16.
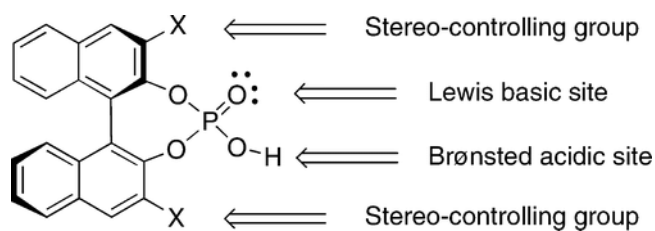
Figure 4.16

The appropriate choice of the substituents at the 3,3'-position is crucial for observing high enantioselectivity[100] (Figure 4.17).

a: X=H
b: X=Ph
c: X=4-NO$_2$C$_6$H$_4$
d: X=4-β-naph-C$_6$H$_4$
e: X=4-ClC$_6$H$_4$
f: X=3,5-(CF$_3$)$_2$C$_6$H$_3$
g: X=3,5-dimesitylphenyl

h: X=1-naphthyl
i: X=2,4,6-(i-Pr)$_3$C$_6$H$_2$
j: X=9-anthryl
k: X=9-phenanthryl
l: X=biphenyl
m: X=2-naphthyl
n: X=SiPh$_3$

Figure 4.17

Phosphoric acids derived from BINOL was used by Terada in the Mannich reaction of 2,4 pentadione with aldimines, furnishing the corresponding adducts with excellent enantioselectivities[112] (Scheme 4.17).

Ar = Ph, p-MeC$_6$H$_4$, p-BrC$_6$H$_4$, p-FC$_6$H$_4$, o-MeC$_6$H$_4$, 1-naphthyl
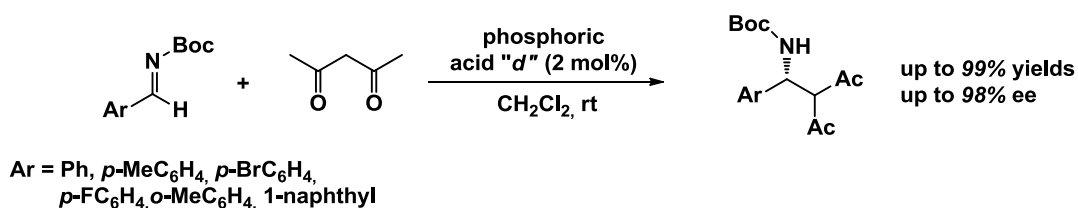
Scheme 4.17

Terada also reported the aza Friedel-Crafts alkylation of furan with aldimines by means of 2 mol% of phosphoric acid *"g"* [101] (Scheme 4.18).
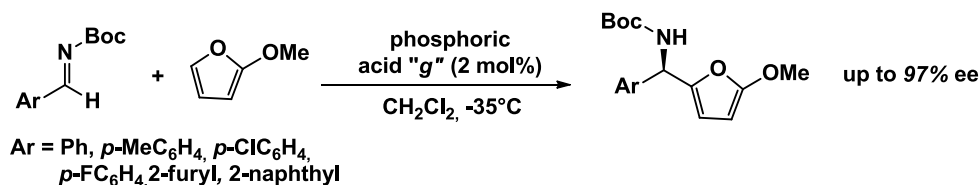
Scheme 4.18

You and co-worker demonstrated that indoles are also suitable nucleophiles for the addition to aldimines catalyzed by phosphoric acid "*h*" (Scheme 4.19); high yields and excellent enantiomeric excesses were achieved for a wide range of aromatic aldimines[110].
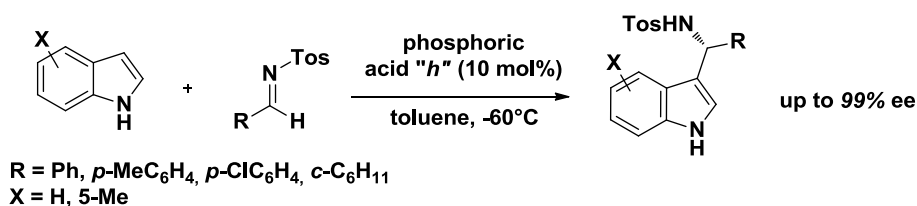
Scheme 4.19

The aza Diels-Alder reaction of dienes with aldimines, derived from aliphatic as well as aromatic aldehydes in the presence of phosphoric acid "*j*", gave the corresponding cycloadducts, after acidic treatment, with excellent enantioselectivity[102] (Scheme 4.20).
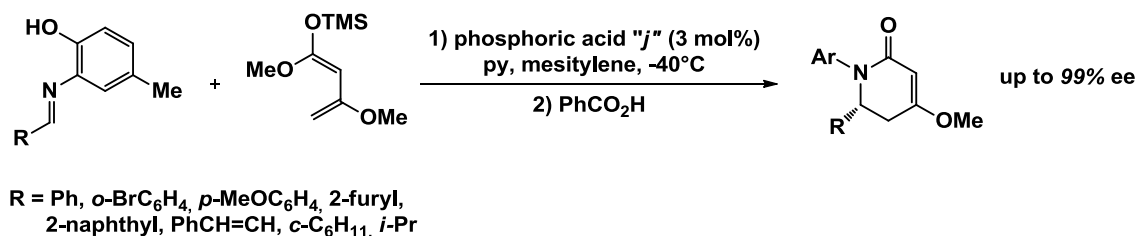
Scheme 4.20

Rueping reported the enantioselective reduction of imines catalyzed by phosphoric acid "*f*" as Brønsted acid, employing Hantzsch ester as hydrogen source; good enantiomeric excesses were obtained[111] (Scheme 4.21).
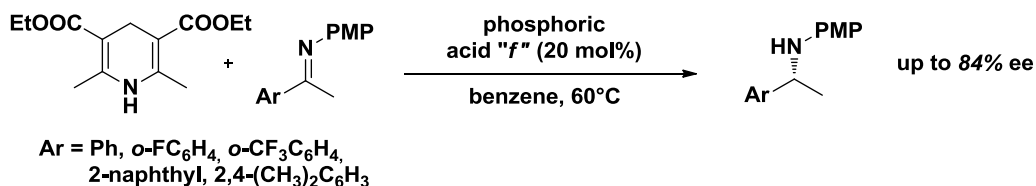
Scheme 4.21

Feringa introduced phosphoramidites as ligands for asymmetric catalysis; in particular, he developed an efficient catalytic system for enantioselective carbon-carbon formation by 1,4-addition of organozinc reagents to enones, obtaining excellent stereocontrol.[103]

Best results were obtained when sterically demanding substituent were introduced at nitrogen atom and the catalyst was prepared in situ from $Cu(OTf)_2$; with this catalyst, enantioselectivities up to 90% for chalcones and >98% for cyclohexanones were obtained (Scheme 4.22).
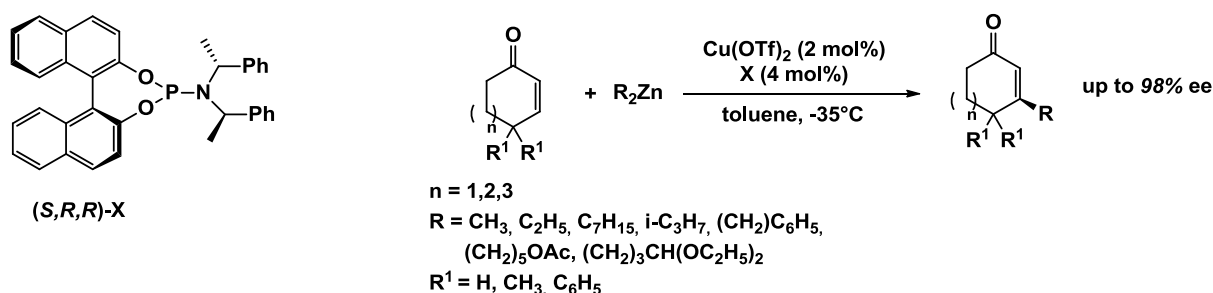
Scheme 4.22

Phosporamidites were also employed as ligands in the Rh-catalyzed asymmetric hydrogenations of substituted olefins; enantioselectivities between 95 and 99% were obtained in the asymmetric hydrogenation of protected α- and β-dehydroamino acids and esters, methylensuccinic acid and esters, aromatic enamides, aromatic enol esters, aromatic and aliphatic enol carbamates, and α-substituted cinnamic acids.[104]

Rh-catalyzed asymmetric hydrogenation of enol acetates and enol carbamates using MonoPhos and PipPhos is shown in Scheme 4.23 as example.
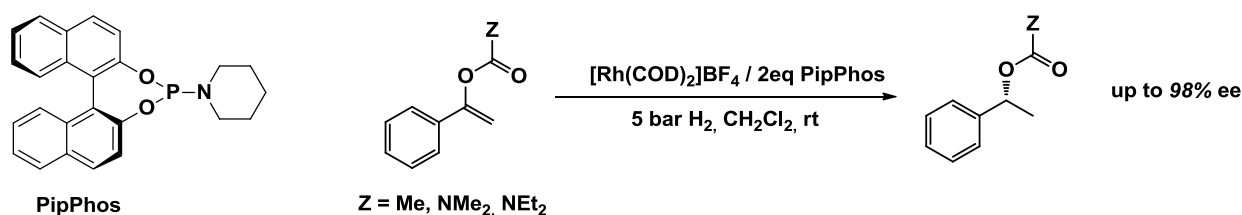
Scheme 4.23

Wolfe reported the enantioselective synthesis of substituted pyrrolidines via Pd-catalyzed carboamination reactions between aryl/alkenyl bromides and γ-aminoalkene derivatives;[105] employing (R)-Siphos-PE as ligand, different pyrrolidines were obtained with enantioselectivities between 72 and 94% (Scheme 4.24). These compounds are particularly interesting since many natural products and pharmaceutical compounds are based on their backbone.
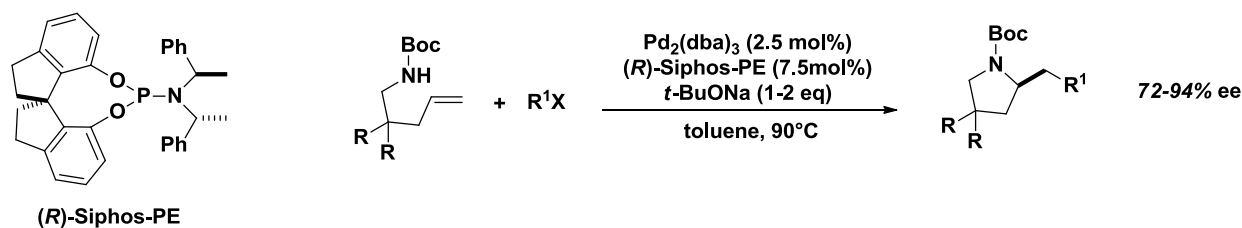
Scheme 4.24

Reetz established the basis for the development of monodentate phosphate ligands: in particular, enantioselective Rh-catalyzed hydrogenation reactions using enantiopure BINOL and the dianhydro-D-mannite of itaconic acid dimethyl ester (Scheme 25) led to ee of 88% for the (*S*)-derivative and 95% for the (*R*)-derivative, an indication that the chiral information in the P heterocycle is decisive and that the combination of (*R*)-BINOL and dianhydro-D-mannite represented the matched case.[106]
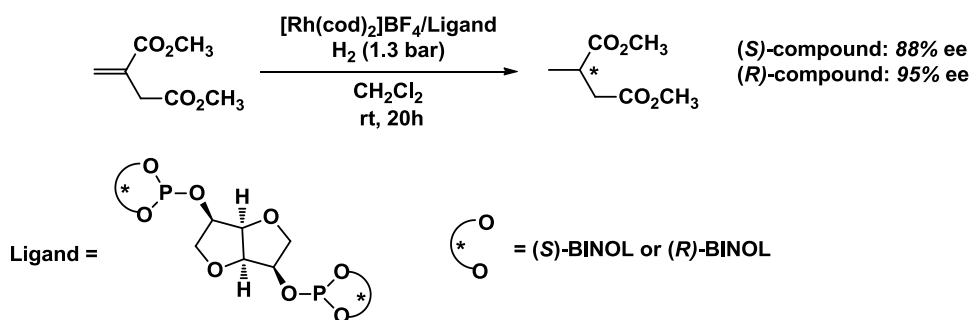
Scheme 4.25

The same research group synthesized numerous binaphthyl-based phosphite ligands, using different achiral or chiral alcohols, functionalized with alkyl or aryl chains and applied them in rhodium-catalyzed hydrogenation reactions achieving excellent enantioselectivities.[107] As an example, hydrogenation of 2-acetamido acrylic ester to the corresponding alanine derivative is reported in Scheme 4.26.
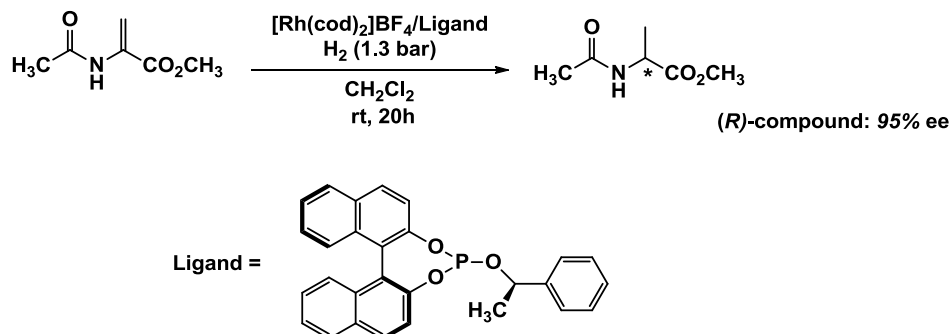
Scheme 4.26

Gennari and Piarulli reported the synthesis of a series of methoxyaryl and methoxybenzyl-based

phosphites: mixtures of these ligands were investigated in the formation of non-covalent supramolecular bidentate rhodium complexes, wherein cooperative synergetic effects were proved by an excellent catalytic enantiodiscrimination in the hydrogenation of acrylic acid derivatives, using appropriate combinations[108] (Scheme 4.27).
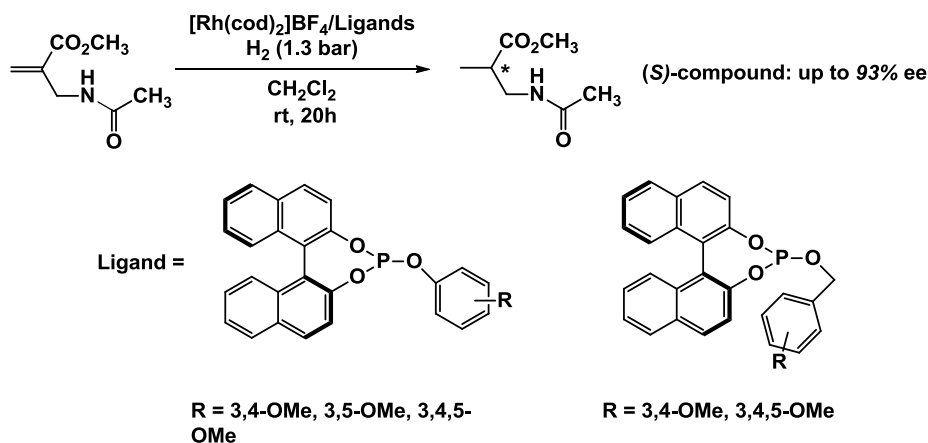
Scheme 4.27

4.6.1 Synthesis of the phosphoric acid (34)

The synthesis of phosphoric acid **34** was carried out in two steps, in order to isolate and characterize the chloride intermediate, which could be employed as starting material to obtain the corresponding amides or esters (eventually using chiral amines or alcohols).

The chloride intermediate was obtained in quantitative yields, employing pyridine as solvent and $POCl_3$ as phosphorylating agent, as reported in literature for BINOL;[109] the conversion was observed by ^{31}P NMR spectroscopy and was complete after only 4 hours.

Conversion of intermediate **35** into the acid **34** by hydrolysis was completed after 2 hours and the desired product was obtained for simple treatment of the crude with *n*-hexane (Scheme 4.28).
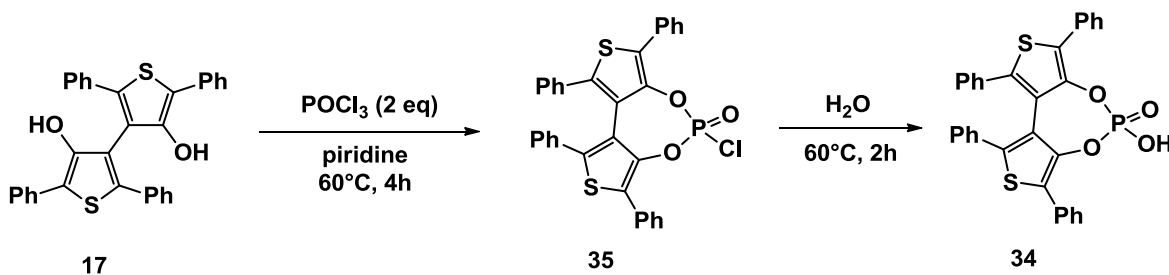
Scheme 4.28

In collaboration with the research group of Professor M. Benaglia of Università degli Studi di Milano,

racemic phosphoric acid **34** was employed as organic catalyst in the nucleophilic addition of indole to aldimines[110] (*a*), reduction of imines with Hantzsch dihydropiridine[111] (*b*), and Mannich reactions[112] (*c*), in order to test its catalytic activity, which was good in the first two reactions and outstanding in the last one (Scheme 4.29).
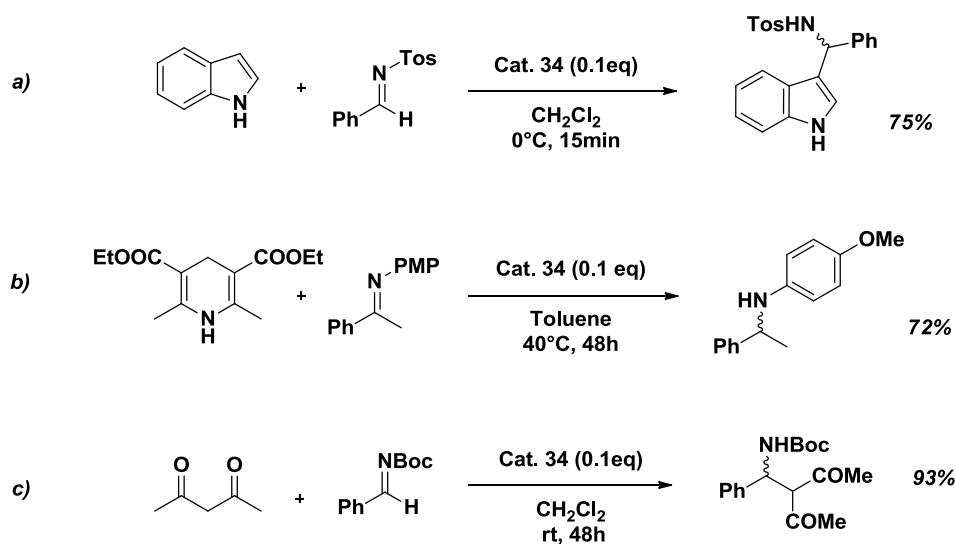
Scheme 4.29

These promising results prompted us to investigate its resolution into antipodes through the formation of diastereomeric esters, with chiral alcohols that could be easily separated by chromatography and the enantiopure acid recovered after hydrolysis (Scheme 4.30).
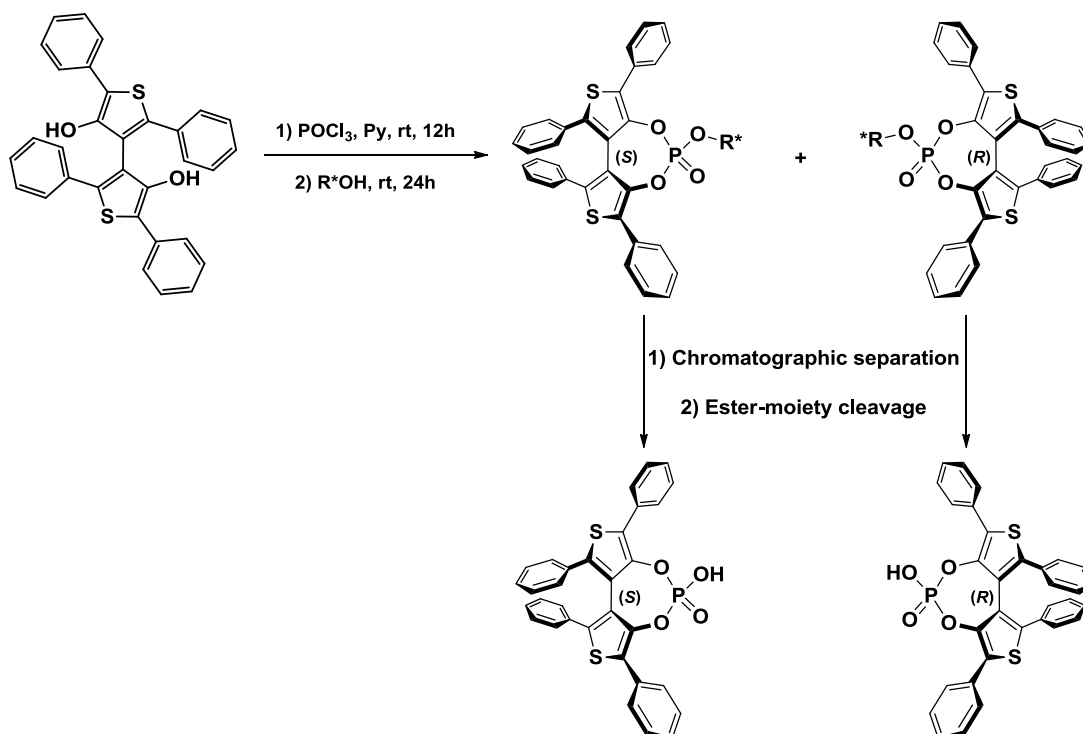
Scheme 4.30

(1*R*,2*S*)-(-)-*N*-Methylephedrine and (2*R*)-2-octanol were employed as chiral alcohols (Figure 4.18); with the former alcohol, only one diastereisomer was formed, whereas with the latter a 2:1 diastereoisomeric mixture was observed. These experiments confirmed the configurational lability of the phosphoric acid; in fact a 1 to 1 mixture of diastereomeric esters would has formed if the phosphoric acid had been configurationally stable. A different ratio of the diastereomeric esters proved the existence of an equilibrium between the two antipodes of the phosphoric acid at room temperature.
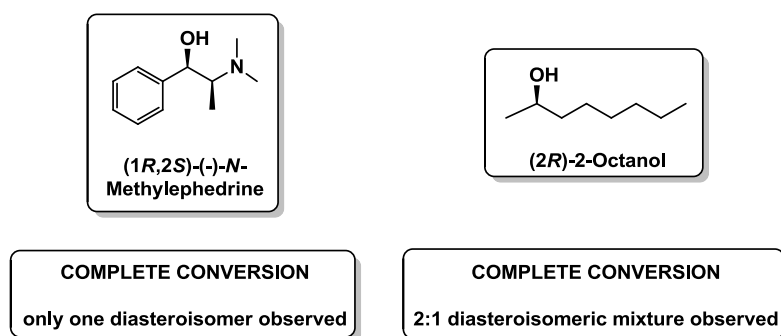
Figure 4.18

The low configurational stability of the phosphoric acid was further confirmed by computational calculations by Dr. S. Rossi, who found a racemization barrier of 25.9 kcal/mol (Figure 4.19).
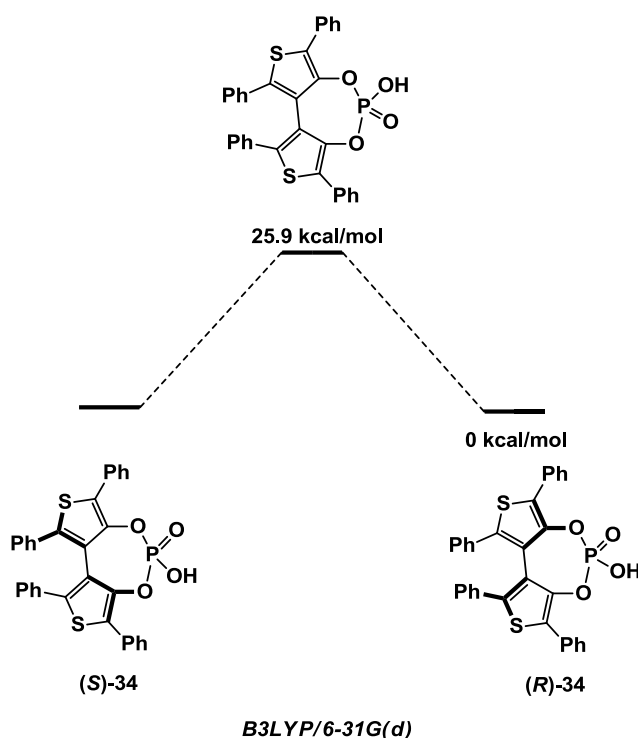
Figure 4.19

4.6.2 Synthesis of the phosphoramidites with (R,R)- and (S,S)- bis[1-phenylethyl]amine (36) and (37)

We decided to utilize the bithienol **17** to synthesize some phosphoramidites and we employed as amine both the enantiomers of the bis[1-phenylethyl]amine. These derivatives were synthesized in order to compare their catalytic activity and enantioselection ability with those of the corresponding carbocyclic analogues, based on the binaphtylic backbone.

The phosphoramidites **36-37** were synthesized one pot following a scheme generally carried out in two steps: in the first step, the PCl_3 was converted into a dichloro-dialkylaminophosphane by treatment of the suitable enantiomer of the amine, at 70°C and in the presence of triethylamine. This intermediate was directly converted into **36** or **37** by cooling at -78°C and adding a mixture of bithienol and triethylamine in a toluene/THF 4:1 solution. The resulting mixture was allowed to warm at room temperature overnight and then purified by flash chromatography (Scheme 4.31).
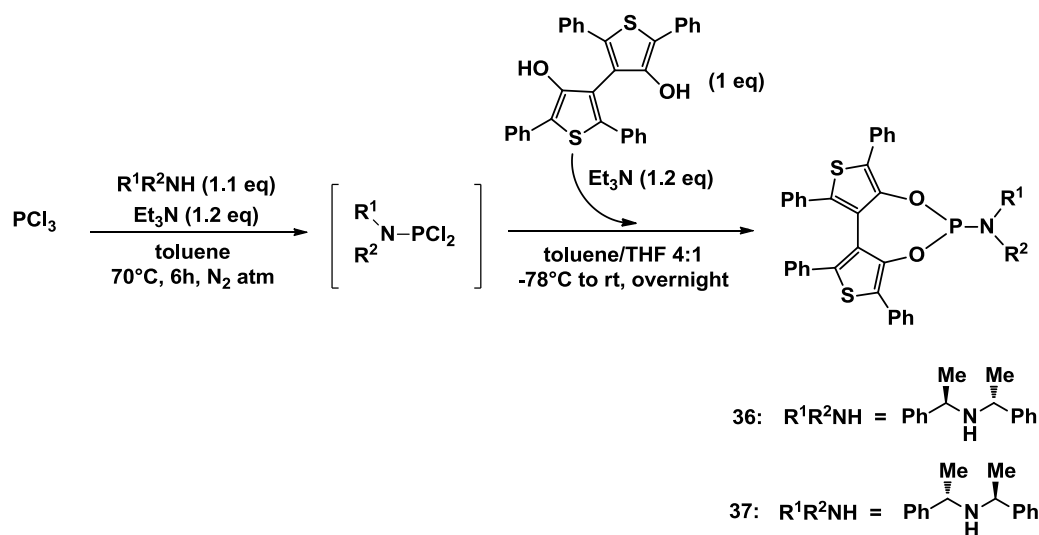
Scheme 4.31

Following this procedure, **36** and **37** were obtained respectively in 33% and 36% yields.

The ^{31}P-NMR spectrum in CD_2Cl_2 of the both compounds are identical and showed the presence of two diastereoisomers in 6:1 ratio, as shown in Figure 4.20.
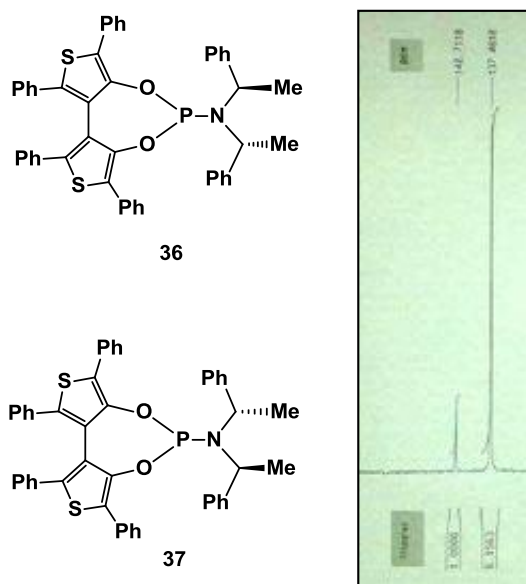
Figure 4.20

Due to the impossibility to separate the two diastereoisomer by column chromatography, both the phosphoramidites were separated at an analytical level through HPLC analysis on chiral stationary phase by Dr. Cirilli (Figure 4.21).
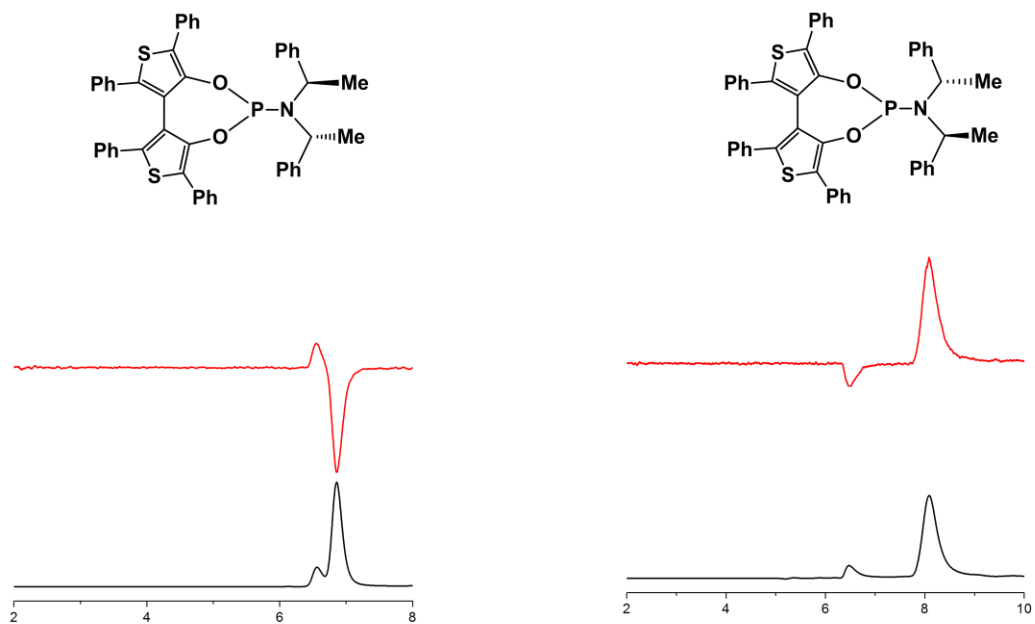
CSPs: Chiralpak IC 250 mm x 4.6 mm I.D.
    + Chiralpak IC 150 mm x 4.6 mm I.D.
Eluent: n-hexane-dichloromethane-ethanol-DEA
    100-1-1-0.2
Flow rate: 1 ml/min
Temperature: 8.3°C
Detector: UV (black) and CD (red) at 280 nm

CSPs: Chiralpak IA-3 250 mm x 4.6 mm I.D.
    + Chiralpak IA-3 100 mm x 4.6 mm I.D.
Eluent: n-hexane-dichloromethane-ethanol-DEA
    100-5-1-0.2
Flow rate: 1 ml/min
Temperature: 8.2°C
Detector: UV (black) and CD (red) at 280 nm

Figure 4.21

We couldn't separate the diastereomeric mixture on a semipreparative scale level since they slowly interconverted at room temperature. In fact, on-column experiment, carried out under the experimental conditions reported in Figure 4.22, confirmed that the diastereomerization process already takes place at room temperature
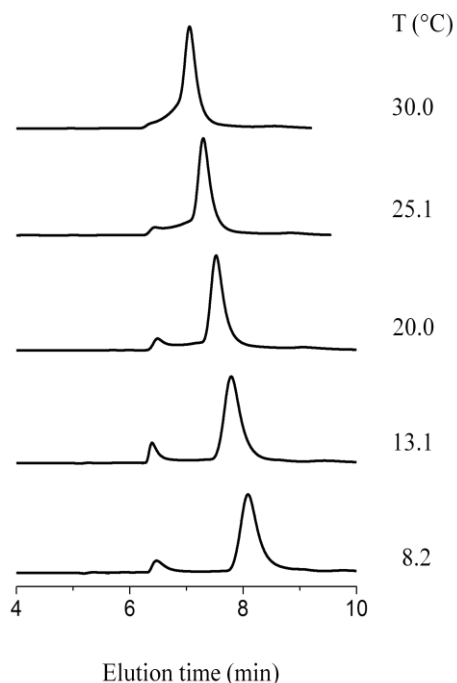
CSP: Chiralpak IA-3 (250 x 4.6 mm i.d.)+ Chiralpak IA-3 (100 x 4.6 mm i.d.);
Eluent: n-hexane–dichlorometane–ethanol-DEA 100:5:1:0.2 (v/v/v);
Flow-rate: 1 mL/min; Detector: UV at 280 nm.

Figure 4.22

Moreover ^{1}H-NMR spectrum of phosphoramidite **36** in toluene-d_8 carried out at variable temperatures, showed that the diastereomerization process deeply depends on the solvents. In fact, in a dipolar solvent the two diasteroisomers appeared to be more stable and their ratio was modified from 5:1 at 27°C to 3:1 at 92°C (Figure 4.23).

| 27°C | 40°C | 60°C | 80°C | 92°C |
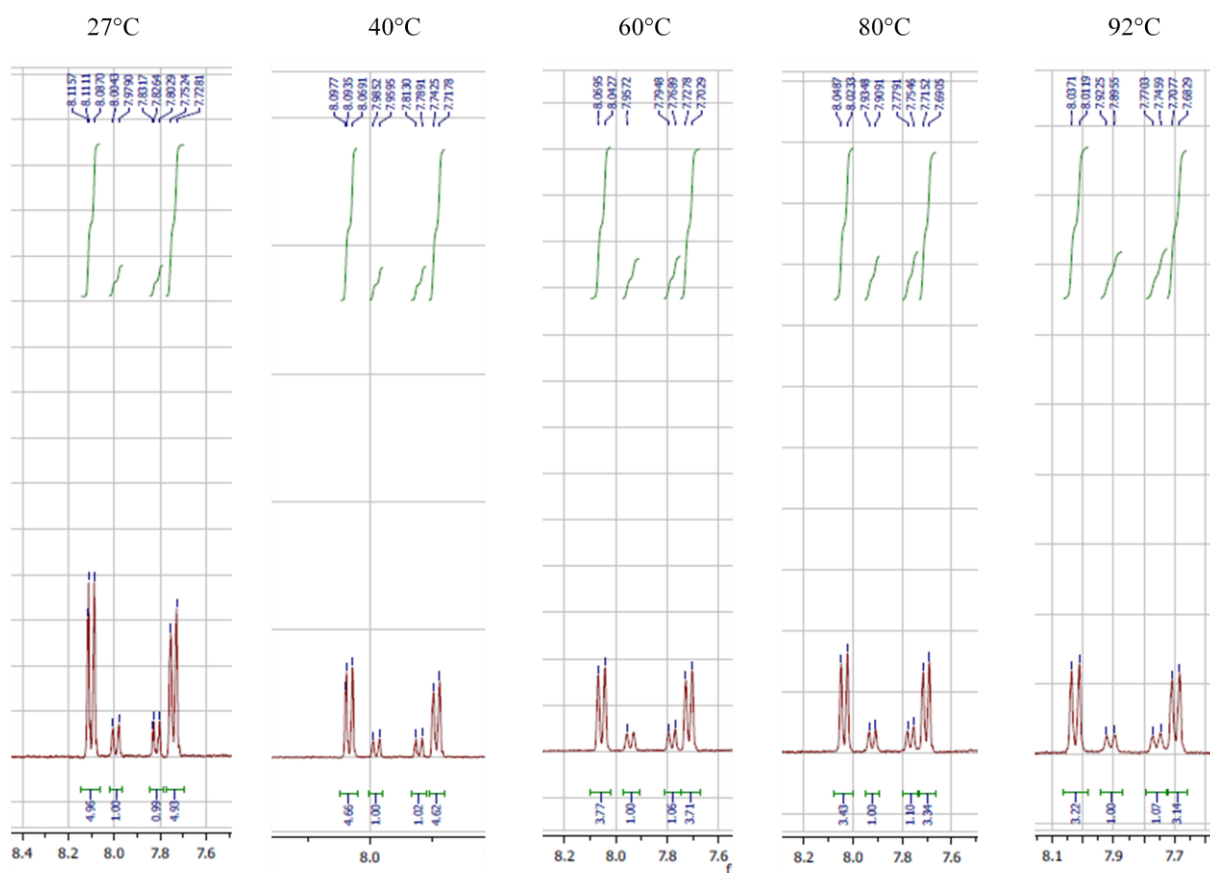
Figure 4.23

4.6.3 Synthesis of the phosphite with trans-2-phenyl-1-cyclohexanol (38)

The synthesis of phosphite **38** was carried out following the procedure analogous to that described before for the preparation of the phosphoramidites. The *trans*-2-phenyl-1-cyclohexanol was treated at room temperature with slight excess of PCl$_3$ in dichloromethane to give a dichloroalkoxyphospane that was converted into phosphite by slow addition of a solution of bithienol and triethylamine in THF (Scheme 4.32).
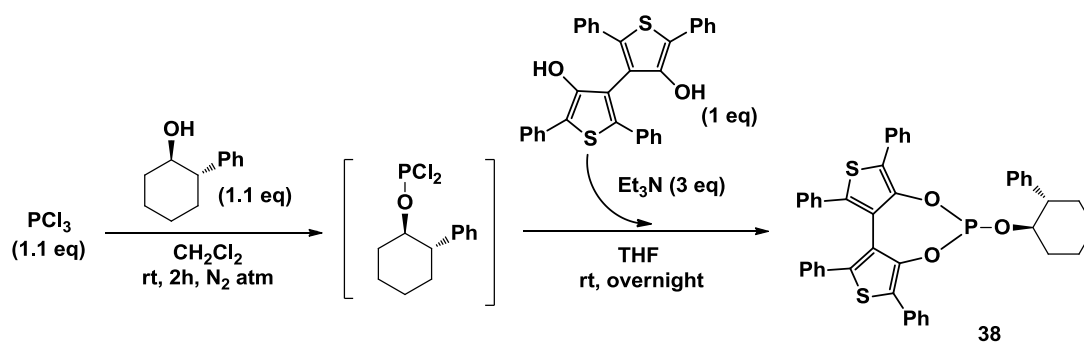
Scheme 4.32

After purification by column chromatography, the ^{31}P NMR spectrum in CD$_2$Cl$_2$ showed the presence of

two peaks at 139 and 130 ppm respectively, correspondind to the two diastereoisomers in approximately a 2.5:1 ratio and few signals corresponding to degradation products, as shown in Figure 4.24.

Figure 4.24

Unfortunately, also in this case we couldn't separate the two diastereisomers through column chromatography. Moreover, the computational calculations showed the low configuration stability of the compounds, being the racemization barrier 25.97 kcal/mol (Figure 4.25).

Figure 4.25

4.7 Computational calculations on the derivatives of differently substituted bithienols

The same theoretical analysis, developed to calculate the racemization barrier of diols, was performed on some phosphoric acids. Surplisingly, when atropoisomeric backbone was functionalized with aryl substituents the racemization barrier is very similar to that calculated for the corresponding diols. Unfortunately, the isopropyl group, that seemed to be a good candidate to obtain configurationally stable diols, produced a decrease of the energy barrier in the case of the corresponding phosphoric acid.

In order to obtain configurationally stable derivatives, *t*-butyl and trimethylsilyl groups must be introduced on the 3,3'-bithiophene scaffold.

Figure 4.26

The synthesis of these derivatives is not trivial since in the case of the trimethylsilyl substituents the functionalization of the atropoisomeric backbone must be effected at the end of the synthetic scheme, due to their lability.

As for the synthesis of the tetra-*t*-butyl derivative, we verified that the synthetic scheme followed for the preparation of the tetramethyl derivative is not expoitable since the bromination of the 2,5-di-*t*-butylthiophene, carried out both with Br_2 and NBS, produces a complex mixture of products.

In order to overlap the cited problems, we envisaged a synthetic scheme, reported below, based on the 4,4'-dimethoxy-3,3'-bithiophene, which could be functionalized with the trimethylsilyl groups through the formation of a tetraanion.

In addition, the four *tert*-butyl groups could be introduced taking advantage of an electrophilic substitution of the carbocation derived from the protonation of isobutene.

Scheme 4.33

Theoretical calculations were performed on **37** and phosphoramidites derived from bithienol and bis[(*S*)-1-naphthylethyl]amine or bis[(*S*)-1-cyclohexylethyl]amine, in order to evaluate their diastereomerization barrier and to search for a compound less configurationally labile than **37**.

From this investigation, the best candidate appeared to be the phosphoramidite derived from bis[(*S*)-1-naphthylethyl]amine, that was characterized by an energy barrier of 32.95 Kcal/mol.

(*S*)-*SS*	1.04 Kcal/mol	5.60 Kcal/mol	9.81 Kcal/mol
(*R*)-*SS*	0 Kcal/mol	0 Kcal/mol	0 Kcal/mol
TS	30.03 Kcal/mol	27.73 Kcal/mol	32.95 Kcal/mol

level of theory: B3LYP-631g (d,p)
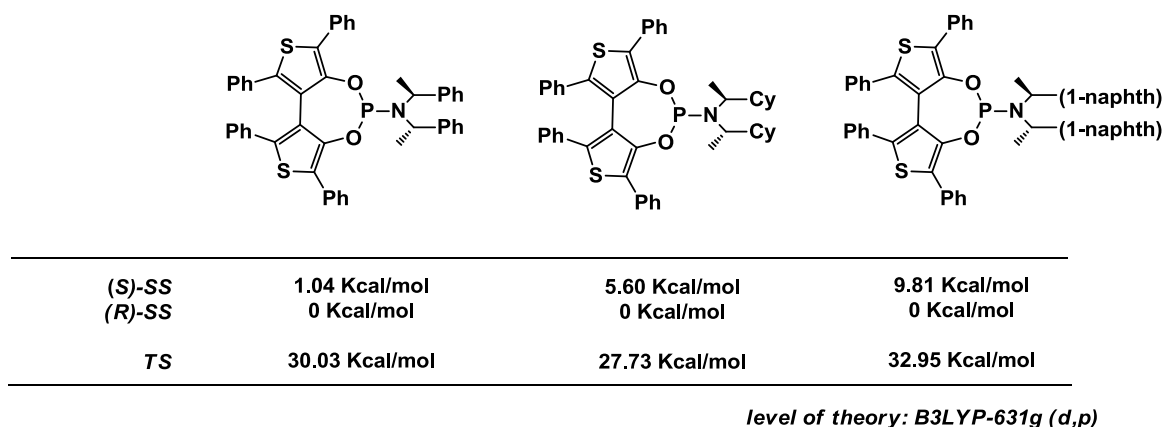
Figure 4.27

4.8 Conclusions

A new class of atropoisomeric diols were synthesized, characterized by two connected heteroaromatic pentatomic rings, instead of hexatomic carbocyclic rings.

In particular, we synthesized the 3,3'-bithiophen-4,4'-diols functionalized with methyl or phenyl groups in α-position of the thiophenic ring.

In the case of bithienol **17**, we demonstrated that it is possible to shift the keto-enol equilibrium to the enol tautomer by extending the conjugation of the molecule. This result was confirmed in the case of bithienol **18**, in which the lack of aromatic substituents led to the formation of different tautomers.

The antipodes of **17** were obtained by semipreparative HPLC on a chiral stationary phase and the racemization barrier was evaluated, both through computational calculations and by experimental methods

(on column and off column experiments).

We transformed bithienol **17** in its corresponding derivatives such as the phosphoric acid **34**, the phosphoramidites **36** and **37** and the phosphites **38**, in order to restrict the rotation around the interanular bond and to test their ability as chiral promoters.

Phosphoric acid **34**, tested in three types of reactions, showed good catalytic ability; the configurational lability of the compound was demonstrated both by computational calculations and through the formation in a ratio different from 1 to 1 of the diastereomeric esters with a chiral alcohol.

Concerning phosphoramidites **36** and **37**, studies on their configurational stability exhibited the dependence of the diasteromeric ratio on the solvent; their ability as a chiral ligand will be tested in hydrogenation reactions.

The synthesis of phosphites **38** led to the formation of the two diastereoisomers, in 5:2 ratio, beside to some degradation products.

Investigation of the racemic barrier of diols and of the corresponding phosphoric acids, functionalized with different aromatic and aliphatic substituents, showed that the former are unsuitable to obtain configurationally stable compounds, while the latter could increase the configurational stability.

The phosphoramidites showed an higher diastereomerization barrier, even if we are still looking for an appropriate amine capable of further increasing the configurational stability.

4.9 EXPERIMENTAL SECTION

4.9.1 General information

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen or argon. Dry solvents were used as received and stored under inert gas. All reagents, if not otherwise specified, were used as received and, if necessary, stored under inert gas.

For thin layer chromatography analysis, pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV254were used. Visualization was accomplished by irradiation with a UV lamp and/or staining with potassium permanganate alkaline solution. Column chromatography was performed on 230-400 mesh Sigma-Aldrich silica gel.

Melting point determinations were performed by using a Buchi B-540 instrument.

^{1}H NMR, ^{13}C NMR were measured on a Brucker FT 300 or a Brucker AMX 300 instrument. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling costants are reported as Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet.

Mass analysis were performed using a VG 7070 EQ-HF instrument.

4.9.2 Synthetic procedures

- **Synthesis of 2,2',5,5'-tetraphenil-4,4'-diol (17) from dibromoderivative 7**
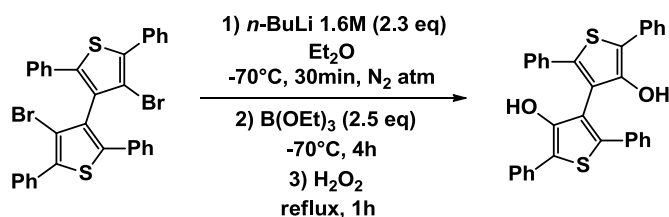
n-BuLi (1.6M solution in hexane, 0.7mL, 2.3 eq) was added dropwise to a stirred solution of 4,4'-dibromo-2,2',5,5'-tetraphenil-3,3'-bithiophene (0.30g, 0.48mmol, 1 eq) in dry diethyl ether (1mL), at -70°C and under N_2 atmosphere; after 30 minutes, triethylborate (0.2mL, 1.2mmol, 2.5 eq) was added and the mixture was stirred for 4 hours at -70°C. The reaction was warmed up at room temperature and a solution 10% of H_2O_2 (0.5mL) was added dropwise; at the end of the addition, the reaction was stirred at reflux for 1 hour, then cooled down. Sodium metabisulphite was added to reduce H_2O_2 unreactive; the aqueous phase was extracted with diethyl ether (2 x 5mL) and the organic layer was dried over Na_2SO_4 and concentrated in vacuo.

Flash chromatography (hexane/CH_2Cl_2 1:1) afford the compound **17** as a yellow solid, isolated in 21% yield.

mp: 165°C.

^{1}H NMR (acetone-d$_6$, 300 MHz) δ 8.39 (s, 1H), 7.90 (d, 4H, *J* = 7.5 Hz), 7.40 (t, 4H, *J* = 7.5 Hz), 7.31-7.26 (m, 4H) 7.24-7.21 (m, 8H).

^{13}C NMR (acetone-d$_6$, 75.4 MHz) δ 118.7, 121.7, 127.0, 129.0, 132.9, 132.5, 138.4, 146.9.

MS (EI): 502 (M$^+$)

- **Synthesis of 4,4'-dimethoxy-2,2',5,5'-tetraphenyl-3,3'-bithiophene (21) from 7**
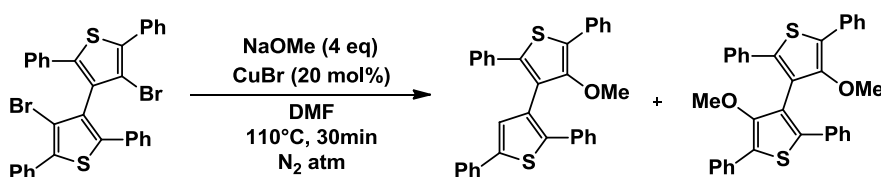
Sodium methoxide was prepared by dissolving metallic sodium (0.016g, 0.72mmol, 3 eq) in dry methanol (2mL), under inert atmosphere, at room temperature; the solvent was partially removed at reduced pressure and a white solid, suspended in methanol, was obtained and dissolved in DMF (2mL).

4,4'-Dibromo-2,2',5,5'-tetraphenil-3,3'-bithiophene (0.15g, 0.24mmol, 1 eq) and copper(I) bromide (0.007g, 0.048mmol, 20 mol%) were added and the reaction mixture warmed at 110°C; after 30 minutes the reaction crude was filtered on celite with hexane (20mL). Then the filtered was extracted with water (15mL), and the aqueous phase was extracted with hexane (2 x 15mL); the organic layer was dried and concentrated in vacuo.

Flash chromatography (hexane/CH_2Cl_2 8:2) led to compound **21** as a white solid, isolated in 50% yield.

mp: 148°C.

^{1}H NMR (CDCl₃, 300 MHz) δ 7.81 (d, 4H, *J* = 7.2 Hz), 7.42 (t, 4H, *J* = 7.5 Hz), 7.29-7.18 (m, 12H), 3.52 (s, 6H).

^{13}C NMR (CDCl₃, 75.4 MHz) δ 60.5, 125.9, 126.9, 127.0, 128.0, 133.0, 134.5, 137.7, 152.7.

MS (EI): 530 (M⁺).

- *Synthesis of 2,2',5,5'-tetraphenil-3,3'-bithiophen-4,4'-diol (17) from methoxy 21*
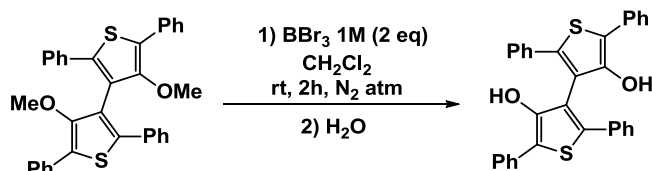
BBr₃ (1.0M solution in methylene chloride, 9.4mL, 2 eq) was added to a stirred solution of 4,4'-dimethoxy-2,2',5,5'-tetraphenil-3,3'-bithiophene (2.5g, 4.7mmol, 1 eq) in dry CH₂Cl₂ (60mL), under N₂ atmosphere; after 2 hours water (50mL) was added and the reaction mixture was stirred for further 30 minutes. The organic layer was dried over Na₂SO₄ and concentrated in vacuo.

Flash chromatography (hexane/CH₂Cl₂) afforded compound **17** in quantitative yield.

- *Synthesis of 3-methoxy-2,5-diphenylthiophene (23)*
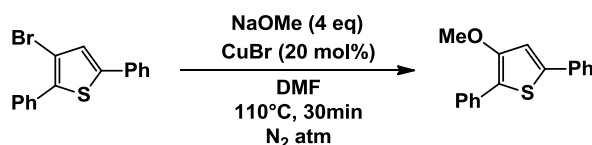
Sodium methoxide was prepared by dissolving metallic sodium (2g, 87mmol, 4 eq) in dry methanol (20mL), under inert atmosphere, at room temperature; the solvent was partially removed at reduced pressure and a white solid, suspended in methanol, was obtained and dissolved in DMF (10mL). To this mixture 2,5-diphenyl-3-bromothiophene (6.3g, 20mmol, 1 eq) and copper(I) bromide (0.57g, 4.0mmol, 20 mol%) were added and the reaction mixture warmed at 110°C; after 30 minutes the reaction crude was filtered on celite with hexane (40mL). Then the filtered was extracted with water (40mL), and the aqueous phase was extracted with hexane (2 x 40mL); the organic layer was dried and concentrated in vacuo.

Gravimetric column chromatography (hexane/CH₂Cl₂ 8:2) led to compound **23** as yellow solid, isolated in 90% yield.

^{1}H NMR (CDCl₃, 300 MHz) δ 7.81 (d, 2H, *J* = 7.8 Hz), 7.65 (d, 2H, *J* = 7.8 Hz), 7.45-7.39 (m, 4H), 7.34 (d, 1H, *J* = 7.2 Hz), 7.27 (d, 1H, *J* = 6.6 Hz), 7.20 (s, 1H), 3.99 (s, 3H).[113]

- *Synthesis of 2,2',5,5'-tetraphenil-3,3'-bithiophen-4,4'-dimethoxy (21) from 23*
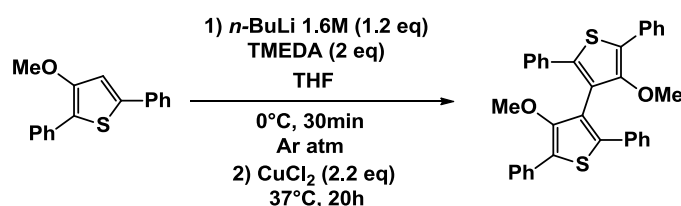
n-BuLi (1.6M solution in hexane, 16mL, 1.2 eq) was added dropwise to a mixture of 2,5-diphenil-3-methoxythiophene (5.75g, 21.4mmol, 1 eq) and TMEDA (6.5mL, 42.8mmol, 2 eq) in dry THF (40mL), at 0°C and under Ar atmosphere; after 30 minutes, CuCl$_2$ dry (6.3g, 47.8mmol, 2.2 eq) was rapidly added at 10°C and the reaction mixture was warmed up at 37°C for 20 hours. The solvent was removed under reduced pressure and the crude was diluted with CH$_2$Cl$_2$ (30mL) and extracted with a 5% HCl solution (30mL), saturated solution of NaHCO$_3$ (30mL) and water (30mL); the organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo.

Flash chromatography (hexane/CH$_2$Cl$_2$ 8:2) led to compound **21** in 45% yield.

- *Synthesis of 3-methoxy-2,5-dimethylthiophene (27)*
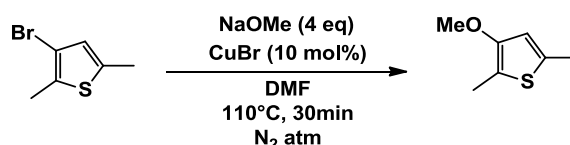
Sodium methoxide was prepared by dissolving metallic sodium (0.36g, 15.6mmol, 1.5 eq) in dry methanol (5mL), under inert atmosphere, at room temperature; the solvent was partially removed at reduced pressure and a white solid, suspended in methanol, was obtained and dissolved in DMF (2.6mL). To this mixture 2,5-dimethyl-3-bromothiophene (2g, 10.4mmol, 1 eq) and copper(I) bromide (0.150g, 1.04mmol, 10 mol%) were added and the reaction mixture warmed at 110°C; after 30 minutes the reaction crude was filtered on celite with dichlorometane (20mL). Then the filtered was extracted with water (15mL), and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 20mL); the organic layer was dried and concentrated in vacuo.

Distillation under reduced pressure (b.p. 125°C, 12 torr) afforded compound **27** as colourless oil, isolated in 60% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.49 (s, 1H), 3.77 (s, 3H), 2.38 (s, 3H), 2.21 (s, 3H).

Characterization of the compound is according with the literature[114].

- *Synthesis of 2,2',5,5'-tetramethyl-3,3'-bithiophen-4,4'-diol (18)*
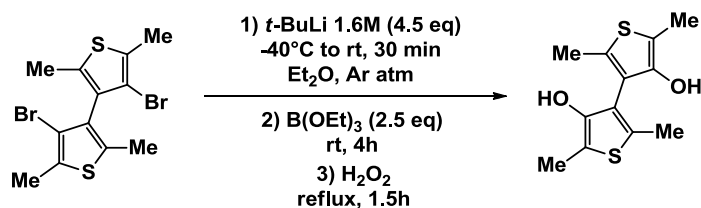
t-BuLi (1.6M solution in hexane, 2mL, 4.5 eq) was added dropwise at -40°C, under Ar atmosphere, to a

stirred solution of 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene (0.25g, 0.65mmol, 1 eq) in dry diethyl ether (5mL); the reaction mixture was warmed up at room temperature and stirred for 30 mintes, then triethylborate (0.28mL, 1.6mmol, 2.5 eq) was added. The reaction mixture was stirred for 4 hours at room temperature; after that, a solution 10% H_2O_2 (0.6mL) was added and the reaction was stirred at reflux for 1.5 hours. The aqueous phase was extracted with diethyl ether (5mL) and the organic layer was washed with sodium metabisulphite, dried and concentrated in vacuo.

Flash chromatography (CH_2Cl_2/MeOH 9.5:0.5) afforded the compound **18** as brown oil, isolated in quantitative yield. The impossibility to characterize this compound by ^{1}H NMR spectroscopy was due to the presence of various tautomers.

MS (EI): 254 (M[+]).

- *Synthesis of phosphoric acid of bithienol 34*
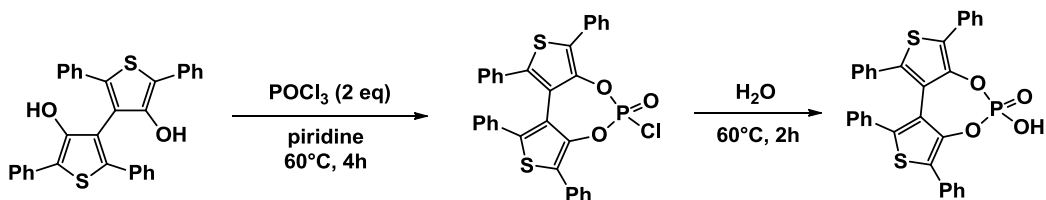
POCl$_3$ (0.073mL, 0.78mmol, 2 eq) was added dropwise to a solution of 2,2',5,5'-tetraphenil-3,3'-bithiophen-4,4'-diol (0.195g, 0.39mmol, 1 eq) in pyridine (1mL) and the reaction mixture was stirred for 2 hours at 60°C. The formation of the chloride intermediate **35** was confirmed by ^{31}P NMR and mass spectrum spectroscopy [**^{31}P NMR (CDCl$_3$, 300 MHz)** δ 3.37 (s); **MS (EI):** 582 (M[+])]. Water (1mL) was added to the mixture and the biphasic suspension was stirred at the same temperature for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (5mL) and extracted with 1N HCl solution (5mL); the organic layer was dried over Na_2SO_4 and concentrated at reduced pressure. The product **34** was obtained as green solid, isolated in quantitative yield.

^{1}H NMR (acetone-d$_6$, 300 MHz) δ 7.84 (d, 4H, *J* = 9 Hz), 7.39 (t, 4H, *J* = 9 Hz), 7.28 (d, 2H, *J* = 9 Hz), 7.07-6.98 (m, 6H), 6.87 (d, 4H, *J* = 6 Hz).

^{31}P NMR (CDCl$_3$, 300 MHz) δ -3.22.

MS (EI): 564 (M[+]).

- *General procedure for the synthesis of phosphoramidites with (R,R)- and (S,S)- bis[1-phenylethyl]amine (36) and (37)*
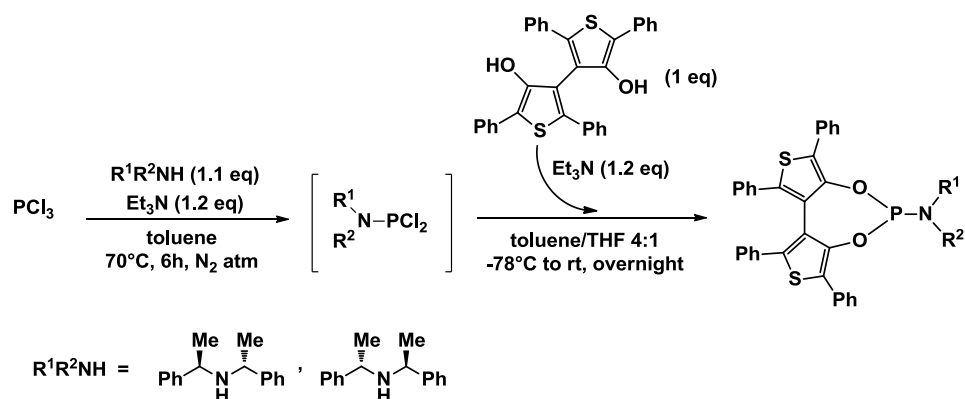
A solution of the enantiopure bis[1-phenylethyl]amine (60μL, 0.263mmol, 1.1 eq) and triethylamine (44μL, 0.316mmol, 1.2 eq) in dry toluene (2.5mL) was added to a solution of PCl_3 (23μL, 0.263mmol, 1.1 eq) in toluene (0.7mL), under nitrogen; the reaction mixture was heated to 70°C for 6 hours, and allowed to cool to room temperature.

Triethylamine (84μL, 0.605mmol, 2.3 eq) was added and the mixture was cooled to -78°C; a solution of bithienol (0.120g, 0.239mmol, 1 eq) in dry toluene/THF 4:1 (0.6mL) was added slowly. The reaction mixture was stirred overnight, allowing to warm slowly to room temperature. The mixture was filtered over a pad of celite with ethyl acetate (50mL), and the solvent was removed under reduced pressure.

Flash chromatography afforded compound **36** and **37**.

phosphoramidite with bis[(*R*)1-phenylethyl]amine 36: white solid, isolated in 33% yield.

^{1}**H NMR (CD$_2$Cl$_2$, 300 MHz)** *minor diastereomer*: δ 7.97 (m, 2H), 7.75-7.71 (m, 2H), 7.49-7.44 (m, 2H), 7.26-7.24 (m, 4H), 7.10-6.88 (m, 20H), 4.68-4.60 (m, 2H), 1.70 (d, 6H, *J* = 7.13 Hz);

major diastereomer: δ 8.00 (d, 2H, *J* = 7.23 Hz), 7.64-7.59 (m, 2H), 7.49-7.44 (m, 2H), 7.26-7.24 (m, 4H), 7.10-6.88 (m, 20H), 4.78-4.69 (m, 2H), 1.43 (d, 6H, *J* = 7.07 Hz).

^{31}**P NMR (CD$_2$Cl$_2$, 300 MHz)** δ 137.44 (s, major diastereomer), 142.68 (s, minor diastereomer).

MS (EI): 755 (M$^+$).

phosphoramidite with bis[(*S*)1-phenylethyl]amine 37: white solid, isolated in 36% yield.

^{1}**H NMR (CD$_2$Cl$_2$, 300 MHz)** *minor diastereomer*: δ 7.95 (d, 2H, *J* = 7.62 Hz), 7.81-7.78 (m, 2H), 7.54-7.49 (m, 4H), 7.38-7.28 (m, 4H), 7.13-6.92 (m, 18H), 4.68-4.64 (m, 2H), 1.76 (d, 6H, *J* = 7.05 Hz);

major diastereomer: δ 8.07 (d, 2H, *J* = 7.44 Hz), 7.71-7.68 (m, 2H), 7.54-7.49 (m, 4H), 7.38-7.28 (m, 4H), 7.13-6.92 (m, 18H), 4.78-4.68 (m, 2H), 1.49 (d, 6H, *J* = 7.02 Hz).

^{31}**P NMR (CDCl$_3$, 300 MHz)** δ 137.48 (s, *major diastereomer*), 142.71 (s, *minor diastereomer*).

MS (EI): 755 (M$^+$).

- ***Synthesis of phosphite 38***
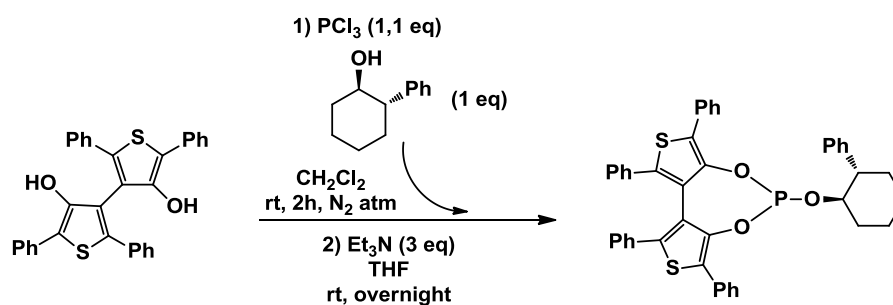
PCl$_3$ (35μL, 0.4mmol, 2 eq) was added to a solution of the *trans*-2-phenyl-1-cyclohexanol (35mg, 0.2mmol, 1 eq) in dry dichlorometane (1.2mL) at room temperature, under nitrogen; after stirring 2 hours, the solvent and excess of PCl$_3$ were removed under reduced pressure and the resulting residue was dissolved in dry THF (0.6mL) and a solution of bithienol (100mg, 0.2mmol, 1 eq) and triethylamine (83 μL , 0.6mmol, 3 eq) in dry THF (0.6mL) was slowly added. The reaction mixture was left under stirring overnight, then filtered on silica pad with CH$_2$Cl$_2$ (50mL) and the solvent was removed under reduced pressure.

Flash chromatography (petroleum ether/CH$_2$Cl$_2$ 1:1) afforded compound **38** as yellow solid in 45% yield.

^{1}H NMR (CD$_2$Cl$_2$, 300 MHz) *major diastereomer* : δ 7.76 (d, 2H, *J* = 8.3 Hz), 7.46-7.32 (m, 8H), 7.21-7.14 (m, 7H), 7.00-6.82 (m, 8H), 4.13-4.10 (m, 1H), 2.53-2.50 (m, 1H), 1.79-1.75 (m, 1H), 1.61-1.56 (m, 1H), 1.49-0.99 (m, 5H), 0.86-0.84 (m, 1H)

minor diastereomer : δ 7.61 (d, 2H, *J* = 8.2 Hz), 7.46-7.32 (m, 8H), 7.21-7.14 (m, 7H), 7.00-6.82 (m, 8H), 4.41-4.37 (m, 1H), 2.56-2.53 (m, 1H), 1.79-1.75 (m, 1H), 1.61-1.56 (m, 1H), 1.49-0.99 (m, 5H), 0.86-0.84 (m, 1H)

^{31}P NMR (CD$_2$Cl$_2$, 300 MHz) δ 139.35 (s, *major diastereomer*), 130.20 (s, *minor diastereomer*).

MS (ESI): 755 (M+Na)$^+$.

5. ATROPOISOMERIC BIHETEROAROMATIC BISOXAZOLINES

We designed new bisoxazolines with the scope to enlarge the families of bisoxazolines based on the backbone of the tetramethyl-3,3'-bithiophene and to investigate new atropoisomeric scaffolds, in particular the tetraphenyl-3,3'-bithiophene.

The energy barrier to rotation around the bond interconnecting the heteroaromatic rings is a crucial parameter for the performance of these ligands: if rotation is not allowed, a new configurationally stable axial stereogenic element is generated in addition to the stereocenters present on the oxazoline rings, and consequently, two diastereoisomers, differing in the configuration of the stereogenic axis, are formed.

5.1 *Synthesis of bisoxazolines 42, 44, 47 and 48*

The synthesis of all the ligands started from the suitable dicarboxylic acid, that was obtained in turn by *in situ* carbon dioxide treatment of the 4,4'-dilithium derivative, synthesized by transmetallation of the corresponding dibromoderivative with *t*-BuLi (Scheme 5.1).

Following this procedure, the diacids were obtained in moderate yields.
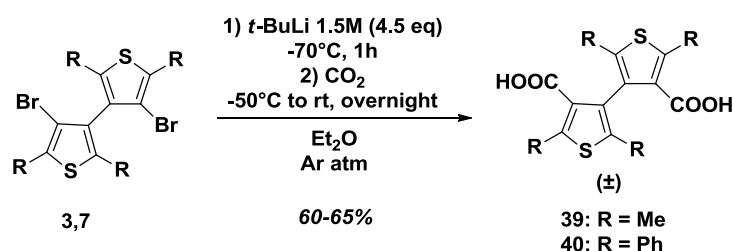
Scheme 5.1

The preparation of the diamides and the their conversion into the corresponding oxazoline rings were effected through different strategies.

In particular, to obtain the bisoxazoline ligands based on the tetramethyl substituted scaffolds, the dicarboxylic acid **39** was converted into the corresponding acid chlorides, using thionyl chloride in excess, and then into the diamides **41** by reaction with (*R*)-phenyl glycinol. The two diastereomeric diamides were easily separated by column chromatography and separately cyclized to the corresponding bisoxazolines by reaction with the Burgess reagent, in THF solution. The desired products were obtained in modest yields (Scheme 5.2).
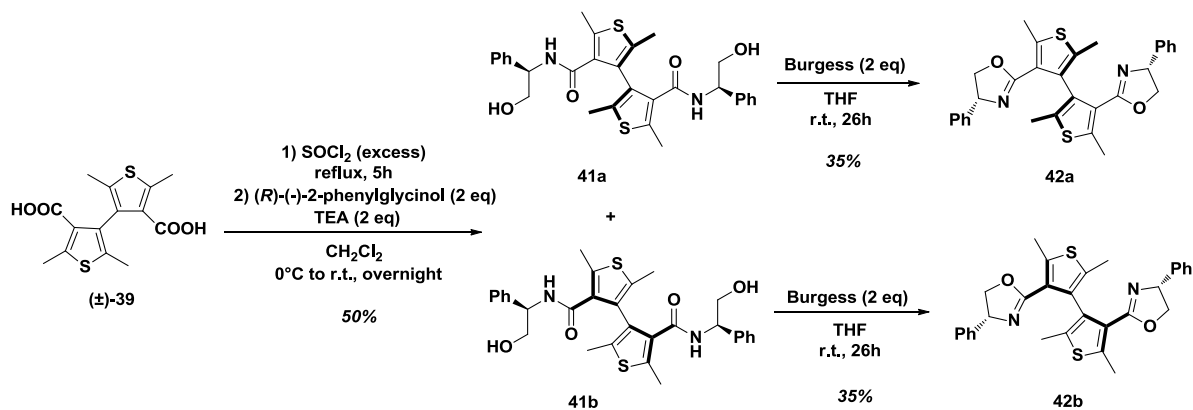
Scheme 5.2

For the synthesis of the bisoxazolines based on the tetraphenyl scaffold, first we followed the procedure mentioned above; in this case we obtained the diamides in scarce yields and the results weren't reproducible. When the reaction with Burgess reagent was carried out at room temperature, only the mono-cyclised products were obtained; the main obstacle to the formation of the second could be the steric hindrance of the phenyl groups on the bithiophene backbone. To improve the formation of bisoxazoline rings, the reaction was carried out at higher temperatures: in this conditions, one of the two amides reacted easily and the bisoxazoline was obtained after 8 hours; while the cyclisation of the second amide didn't occurr.

In order to improve yields, we changed experimental procedure and we decided to form the amidic bond directly from the carboxylic acid, using HOAt and HATU as coupling reagents, in the presence of DIPEA as base. Following this synthetic scheme, we obtained both the diamides in good yields after separation by column chromatography. The subsequent cyclisation using DAST as reactive led to the formation of **44a** and **44b** in 40% and 30% yields respectively (Scheme 5.3).
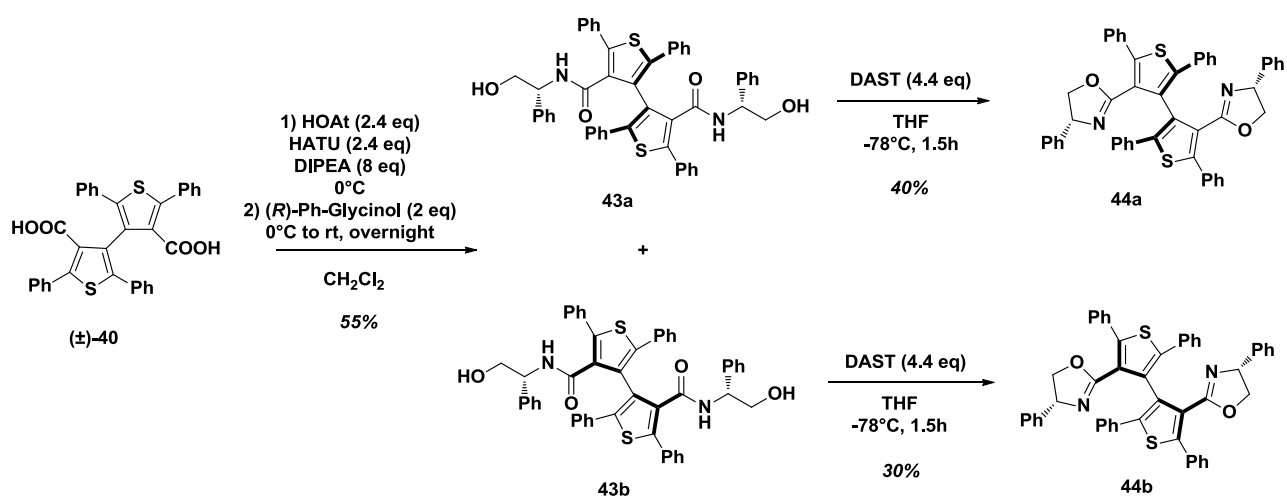
Scheme 5.3

We synthesized bisoxazoline with different substituents at the stereocenters: in particular we used *L*-valinol

as enantiopure aminoalcohol; since the isopropyl substituent on the oxazoline moiety exhert a different hindrance respect to the phenylic group, that is free to vary its arrangement from coplanar to perpendicular to the thiophene ring.

The amide formation was carried out starting from the suitable dicarboxylic acids following the procedure describe above. The two diastereomeric diamides **45a** and **45b** were obtained in 26% and 39% yields respectively and the diastereomeric diamides **46a** and **46b** both in 28% yields.

To form the oxazoline ring, we took inspiration from a literature procedure that describes the cyclisation of *N*-(β-hydroxy)amides with diisopropylcarbodiimide (DIC), in presence of catalytic amounts of Cu(OTf)$_2$ as a method to obtain the 2-oxazolines in good yields.[115]

Unfortunately,this procedure wasn't efficient and we isolated the bisoxazolines **47a** and **47b** in 15% and 20% yields and **48a** and **48b** in 60% and 83% yields.

Furthermore, the products couldn't been obtained in a pure state due to the presence of the diisopropylurea.

Scheme 5.4
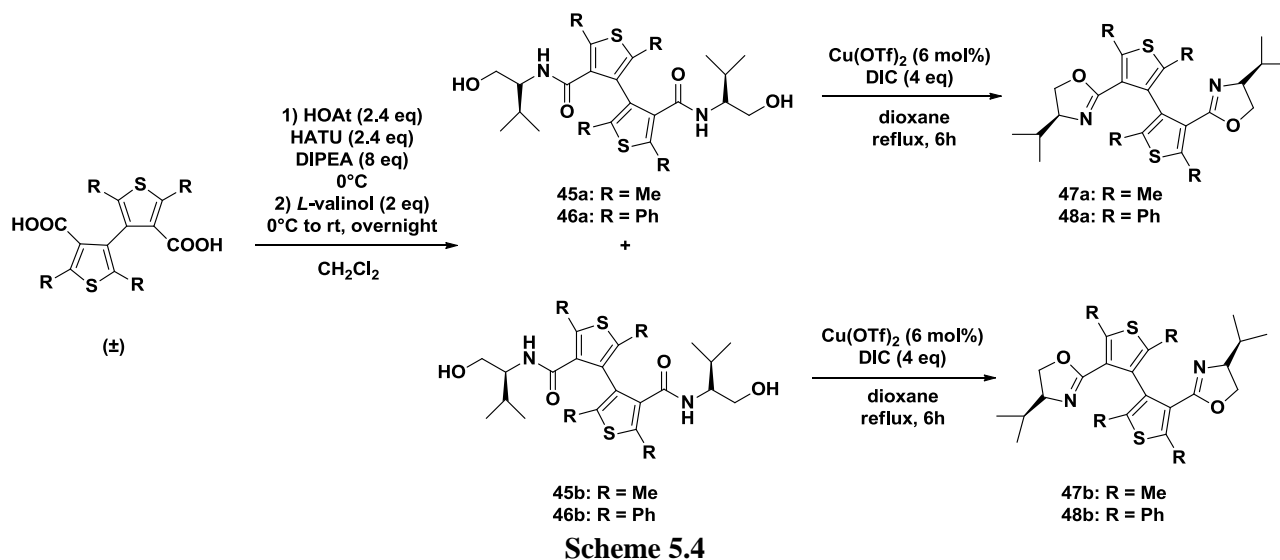
5.2 *Determination of absolute configuration by chiroptical spectroscopies*

The determination of the absolute configuration of chiral organic molecules often poses a challenging problem in structure elucidation; there are various approaches to the solution of the problem, e.g. X-ray, crystallography, chiroptical methods, and NMR anisotropy methods, each with its own advantages and limitations.

The determination of a structure by using X-ray diffraction requires that the sample should be characterized by a crystal (not always possible) and NMR spectroscopy reveals only information on the relative configuration of the compound. Chiroptical spectroscopies characterizations allow to analyze the sample in solution and usually provide accurate informations absolute configuration, comparing experimental property with the one obtained by quantum-mechanics methods.

For these reasons, the most applied technique is circular dichroism (CD) that detects the absorption

difference between left- and right-circularly polarized light for individual transition. CD techinques include both the traditional electronic CD (ECD), that determines the electronic transitions and the vibrational CD (VCD), developed in the seventies, that brought about the possibility to study the vibrational transitions, usually more numerous and better resolved that the electronic ones.

Additionally, the calculation VCD is often easier than ECD since only the electronic ground state needs to be modeled.

The assignment of the absolute configuration was effected by comparison of the calculated and experimental ECD and VCD spectra (Figure 5.1).
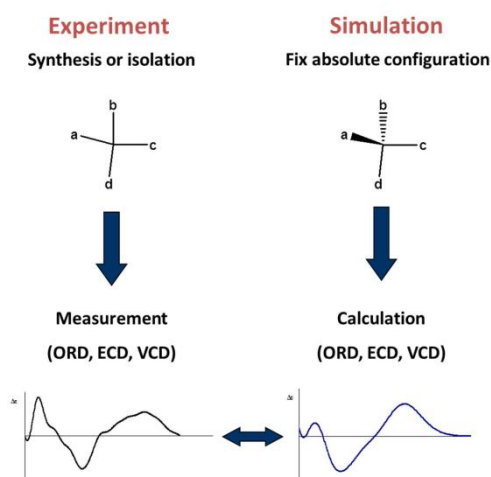
Figure 5.1

In order to obtain reliable results, it is very crucial to have as much an accurate structural description of the system geometry.

A fundamental step is to get all the possible conformations by a conformer distribution search at molecular mechanics level.

All the conformers found or, to a reasonable approximation, only the conformers which differ from the most stable one less than 4 Kcal/mol have to be taken into account. The geometry is optimized and the free energy for all the above conformers is calculated by means of Density Functional Theory (DFT). The software package used during this work are Spartan02[116] for conformational MM searches and Gaussian09[117] for DFT calculations.

Only the optimized conformers which differ from the most stable one less than 2 Kcal/mol in relative free energy are taken into account; these are appreciably populated in the Boltzmann distribution.

Chiroptical properties are then calculated for each conformer found and total property is given as weighted average over the Boltzmann conformers distribution.

It is obvious why it is important to get accurate calculated geometries and energies in order to achieve a correct simulation of chiroptical properties, especially for flexible systems which possess a large number of

conformers even with opposite chiroptical response. In fact an inaccurate estimation of structure or energy could lead to an incorrect AC assignment.

The absolute configuration assignment of bisoxazolines was performed by Dr. Giuseppe Mazzeo of the Università degli Studi di Brescia.

Concerning bisoxazolines **42a** and **42b**, the computational approach is applied to assign their axial absolute configuration since central chirality is known by stereo controlled synthetic pathway.

Experimental ECD spectra of the two diastereomeric bisoxazolines **42a** and **42b** are quite weak and show little differences, hardly attributable to the axial chirality: in fact in this case ECD spectra likely gave us information about the central chirality, due to the perturbation of the phenyl group chromophore on the oxazoline ring stereocenter (Figure 5.2).
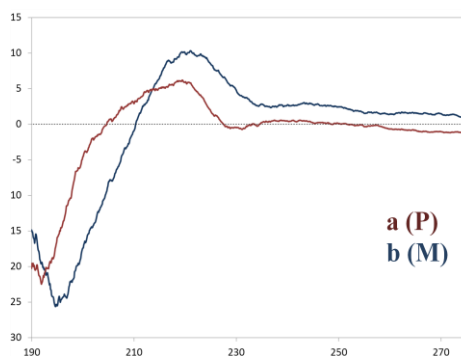
Figure 5.2

On the contrary, VCD spectra of **42a** and **42b** are almost mirror images, as shown in Figure 5.3.

VCD spectra gave us information both about central and axial chirality: from qualitative analysis of the superimposed spectra, it's possible to observe which bands inverts its sign, and therefore which band is pertinent to the axial chirality, and which maintain the same sign and therefore applicable to central chirality. These observations led us to conclude that VCD relates to axial chirality and appears to be an excellent means to monitor R_{ax} vs S_{ax}.
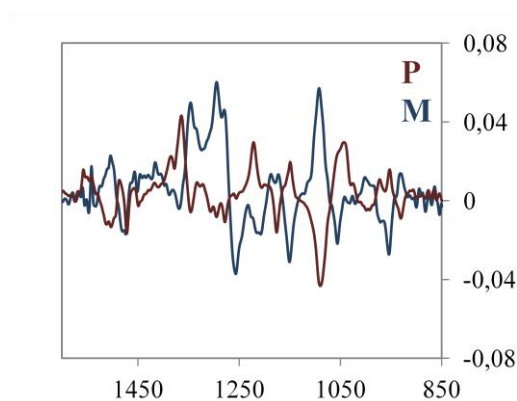
Figure 5.3

As anticipated, for the assignment of the absolute configuration, VCD experimental measurements were compared to theoretical VCD spectra. For the achievement of calculated VCD spectra, a conformational search with molecular mechanics (MMFF94 force field) was carried out and all MM diastereomeric conformations were fully optimized at DFT/B3LYP/TZVP level of theory: 6 most populated conformers displaying *M* torsion (*S* configuration) and 4 conformers exhibiting *P* torsion (*R* configuration) were found (Figure 5.4).
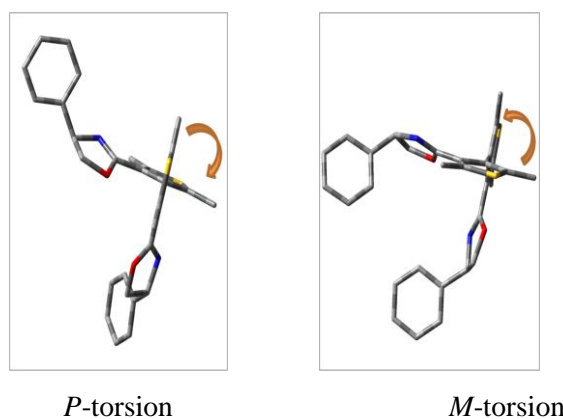
P-torsion   *M*-torsion

Figure 5.4: most populated conformers for *P* and *M* torsion

Comparison between theoretical and experimental spectra showed good agreement in sign, position and intensity of the main VCD bands leading to a safe absolute configuration assignment for each diastereomer (Figure 5.5).

42b   **42a**
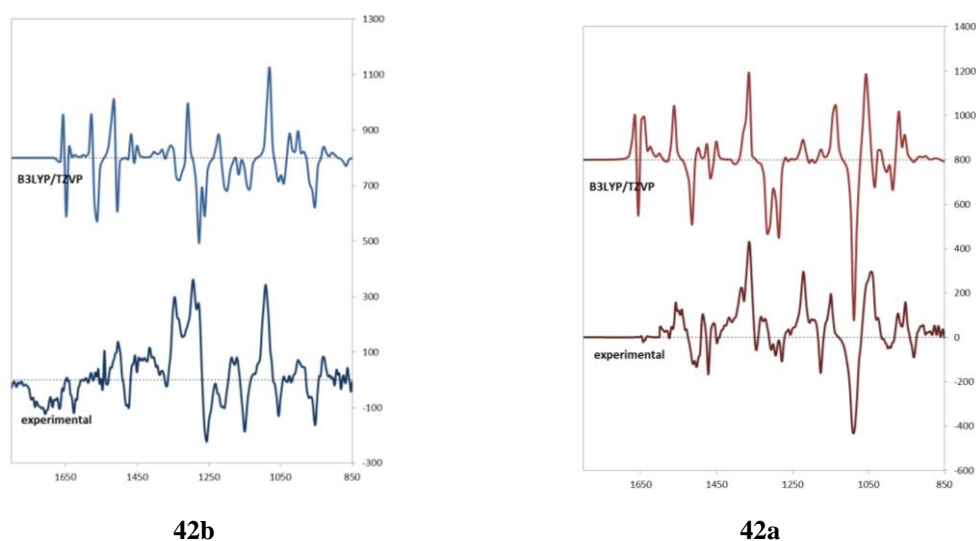
Figure 5.5

A more detailed investigation of the signature analysis of the spectra highlighted the presence of a triplet (" + - + " for the *P* torsion and "- + -" for the *M* torsion) between 1050 and 1150 cm^{-1}, relative to C-H bendings

of methyl groups can be considered a diagnostic feature of axial chirality. On the other hand, the negative bands at 1250-1260 cm^{-1}, present in both spectra, are referred to the central chirality and due to C*-H bendings of the stereocenter of the oxazoline moiety (Figure 5.6)

Figure 5.6: in yellow rectangle the triplet bands relative to the axial chirality, in green elliptical the bands relative to the central chirality

Therefore, we can certainly affirm that the triplet at ca. 1100 cm^{-1} is characteristic of the vibrations of the methyl groups on the bithiophene scaffold and thus they can be safely used to determine the absolute configuration of the chiral axis of the tetramethyl bithiophene core by a simple comparison between the signs of the triplet.

This hypothesis could be confirmed by the comparison with the tetraMe-BITIOPO[71] that is characterized by an analogous atropoisomeric scaffold.

In fact, the analysis of its VCD spectrum showed the presence of the characteristic triplet around 1200 cm^{-1} (Figure 5.7).
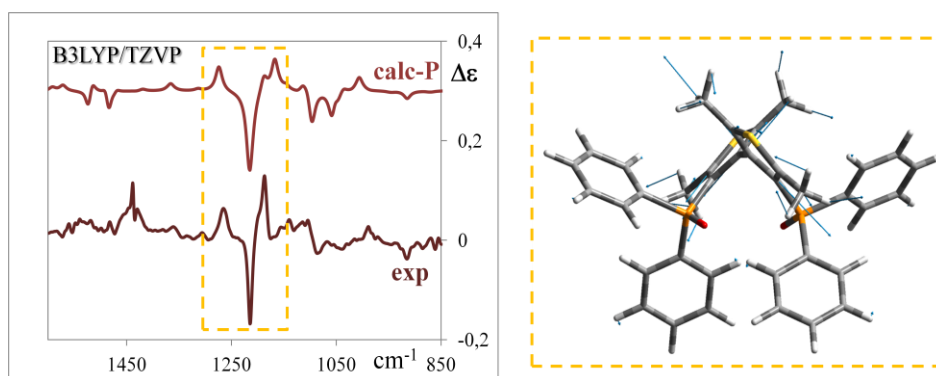
Figure 5.7: in yellow rectangle the triplet bands relative to the axial chirality

Also in the case of the bisoxazolines characterized by the presence of the phenyl groups, the absolute configuration of the stereocenters on the oxazoline rings was *R*.

In this case ECD spectra showed an almost enantiomere behavior between the two diastereomers (Figure 5.8). The extension of the bithiophenic chromophore, due to the presence of the four phenyl groups on the skeleton, involve an extended conjugation of the core which induces the atropoisomeric system driving ECDs with respect to the central chirality.

We focused on the calculation of VCD spectra, being VCD already full of informations.
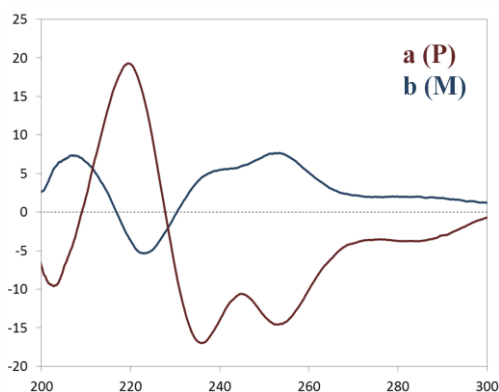
Figure 5.8

A conformational search with molecular mechanics (MMFF94 force field) was carried out. All MM diastereomers conformations were fully optimized at DFT/B3LYP/TZVP level of theory showing 4 conformers with *M* torsion and 7 with *P* torsion (Figure 5.9).
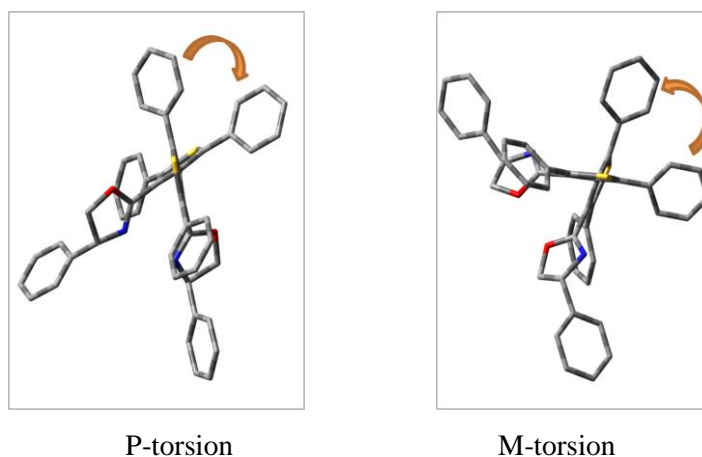
P-torsion   M-torsion

Figure 5.9: most populated conformers for *P* and *M* torsion

Absolute configuration was assigned to compounds **44a** and **44b** by comparison of their experimental VCD curves with the calculated ones (Figure 5.10 and 5.11) obtained as weighed Boltzmann's populations over all significant conformations.

Also in this case, VCD characterization allowed to discriminate axial and central chirality.
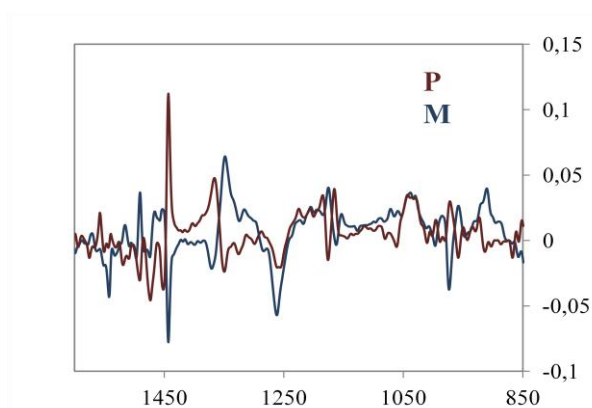
Figure 5.10

As in the case of tetramethyl derivatives **42a** and **42b**, all VCD bands which invert sign with respect to the two diastereomers VCD spectra refer to axial chirality. The bands at about 1450 cm-1 (Figure 5.11, experimental spectra) are in fact allied to C-H phenyl in-plane bendings (Figure 5.11, calculated spectra).

The bands at ca. 1275 cm^{-1} preserved the negative sign in both the diastereoisomers confirming that these bands are related to the carbon stereocenters that exhibit the same absolute configuration.

The computational study showed that these modes refer to bisoxazolines C*-H bendings (Figure 5.11).
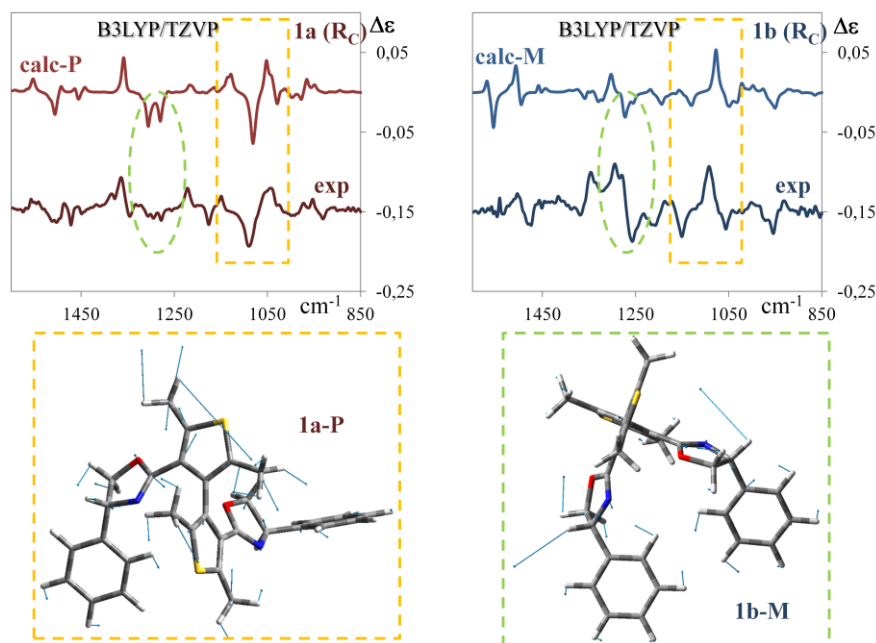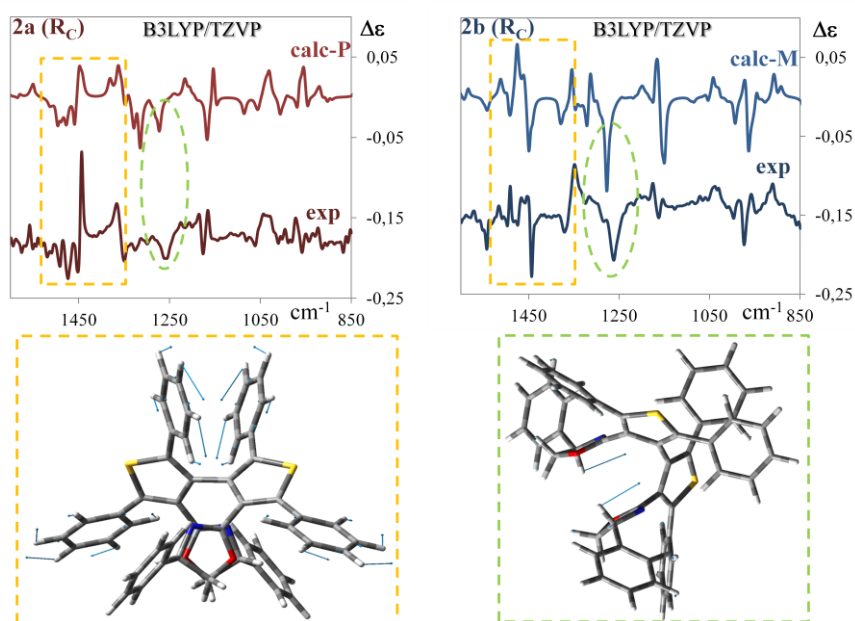

Figure 5.11: in yellow rectangle the triplet bands relative to the axial chirality, in green elliptical the bands relative to the central chirality

5.3 *Catalytic applications*

Lewis acid-catalyzed Friedel-Crafts alkylation reaction is a powerful carbon-carbon bond forming process in organic chemistry; the asymmetric version of this reaction can provide a very useful approach to the enantiomerically enriched alkylated arene products. In particular, asymmetric Friedel-Crafts alkylation of indoles has shown promise as a synthetic methodology toward functionalized indoles;[118] optically active indole derivatives have attracted significant attention in organic synthesis for their importance as building blocks in a variety of interesting natural products and potential medicinal agents.

α,β-Unsaturated carbonyl compounds are very suitable subtrates for this reaction and they have been widely investigated over the last years. The use of nitroalkanes is more recent but the easy transformation of nitro group into a range of different functionalities makes their use even more attractive; nitroalkenes are very reactive Michael acceptors[119] and the products of the alkylations of indoles with nitroalkenes can be applied to the synthesis of many biologically active compounds.

In 2001 Jørgensen reported the first example of this reaction using a C_2-symmetric chiral bisoxazolines-copper(II) complex as catalyst;[120] subsequently, other Authors employed bisoxazolines-complexes to promote the reactions and, later on, Reiser examined the oxazoline/metal ratio influence on the enantioselectivity.[121]

Reactions with α,β-unsaturated carbonyl compounds, such as alkylidene malonate, are almost completely confined to the use of Cu(II)-bisoxazolines complexes. However, recently, the knowledge that these substrates are able to chelate a series of Lewis acids in many asymmetric reactions[122] has led to the employment of different Lewis acids in the reactions; in the case of nitroalkenes, Zn(II)-complexes gave excellent yields and high enantioselectivities.[123]

In view of the above considerations, we decided to screen our ligands in the Friedel-Crafts alkylation of indole.

We started with the Friedel-Crafts alkylation of indole with *trans*-β-nitrostyrene; the screening results are reported in Table 5.1.
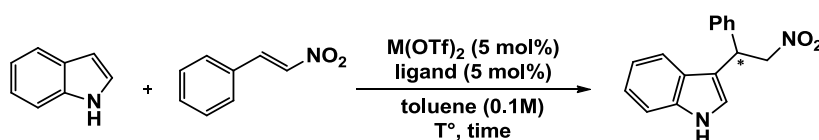
Table 5.1:

Ligand	Metal	Time (h)	T° (°C)	Yield(%)	ee(%)
42b	Zn	19	rt	92	2
42a	Zn	19	rt	77	13
42b	Cu	42	rt	7	26
42a	Cu	96	rt	24	1

42b	Zn	14	0	97	11
44a	Zn	23	rt	87	3
44a	Cu	24	rt	27	4

Zn(II)-bisoxazoline **42** showed a good catalytic activity, but very low enantioselection ability.

A contrary behavior was observed by using copper(II)-complexes; in fact drop in the yields was observed while a slightly increase of the enantiomeric excess was observed. These results couldn't been improved also operating at lower temperatures.

The bisoxazolines characterized by the presence of the phenyl substituents didn't allow to improve the enantioselectivity; however the same behavior, observed in the case of the tetramethyl substituted ligands, was noticed being the Zn(II)-complex more active than the copper one.

We undertook experiments on Friedel-Crafts alkylation with benzylidenmalonate (Table 5.2).

Firstly, the reaction was carried out using ethanol as solvent, but the reaction didn't occur. Carrying out the reaction in toluene, and using zinc(II)-complexes, moderate yields and low enantiomeric excesses were obtained.

The levels of the enantioselection reached couldn't be considered satisfactory and it appeared evident that our ligands are not suitable for this kind of reactions.
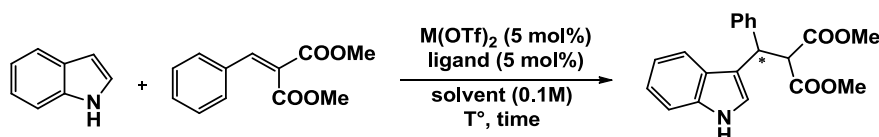
Table 5.2:

Ligand	Metal	Solvent	Time (h)	T° (°C)	Yield(%)	ee(%)
42b	Cu	EtOH	96	rt	-	-
42b	Zn	Toluene	120	rt	72	23
42a	Zn	toluene	96	rt	63	22

5.4 *Conclusions*

The class of the atropoisomeric bisoxazolines based on the scaffold of the 3,3'-bithiophene has been extended by varying both the substituents on the thiophene and on the oxazoline rings.

Some of them were fully characterized from a chiroptical point of view and their absolute configuration

were determined through the comparison of their experimental and theoretical VCD curves.

Furthermore they were tested in some asymmetric Friedel-Crafts reactions showing good catalytic activity but low enantioselection ability.

5.5 <u>EXPERIMENTAL SECTION</u>

5.5.1 General information

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry nitrogen or argon. Dry solvents were used as received and stored under inert gas. All reagents, if not otherwise specified, were used as received and, if necessary, stored under inert gas.

For thin layer chromatography analysis, pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV254were used. Visualization was accomplished by irradiation with a UV lamp and/or staining with potassium permanganate alkaline solution. Column chromatography was performed on 230-400 mesh Sigma-Aldrich silica gel.

Melting point determinations were performed by using a Buchi B-540 instrument.

^{1}H NMR, ^{13}C NMR and ^{31}P NMR were measured on a Brucker FT 300 or a Brucker AMX 300 instrument. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling costants are reported as Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, br d = broad doublet.

Mass analysis were performed using a VG 7070 EQ-HF instrument.

5.5.2 Synthetic procedures

- *General procedures for the synthesis of 2,2',5,5'-tetrasubstituted-3,3'-bithiophene-4,4'-dicarboxylic acids 39 and 40*

R = Me, Ph
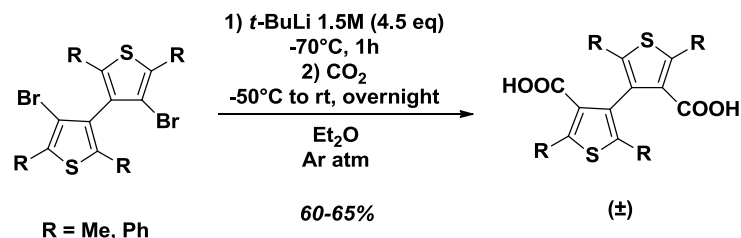
t-BuLi (1.5M solution in hexane, 24mL , 4.5 eq) was slowly added to a solution of dibromoderivative **3** or **7** (8mmol, 1 eq) in dry diethyl ether (30mL), at -70°C under Ar atmosphere; after 1 hour dry $CO_{2(g)}$ was bubbled into the reaction mixture at -50°C and after warming to room temperature and stirred overnight. The solvent was removed in vacuo; water (30mL) and dichlorometane (30mL) were added to the residue, the aqueous layer was separated and the organic phase was extracted with an aqueous K_2CO_3 solution (30mL). The combined aqueous layers were acidified with a HCl solution (30mL) until the product precipitated, it was collected and dried to give the desired products.

2,2',5,5'-tetramethyl-3,3'-bithiophene-4,4'-dicarboxylic acid (39):
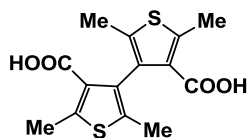
white solid, isolated in 77% yield.

1H NMR (CD3OD, 300 MHz) δ 2.62 (s, 6H), 2.04 (s,6H).

MS (EI): 310 (M+).[124]

2,2',5,5'-tetraphenyl-3,3'-bithiophene-4,4'-dicarboxylic acid (40):
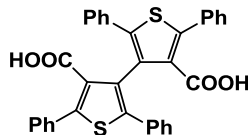
pale yellow solid, isolated in 62% yield.

mp >240°C.

1H NMR (CDCl3, 300 MHz) δ 7.56-7.53 (m, 4H), 7.41-7.39 (m, 6H), 7.15-7.05 (m, 6H), 6.69-6.67 (m, 4H).

13C NMR (CDCl3, 75.4 MHz) δ 127.4, 128.1, 128.3, 128.6, 128.7, 129.4, 132.4, 133.1, 133.3, 142.2, 168.8, 207.

MS (EI): 558 (M+).

- *Synthesis of N,N'-bis[(R)-2-hydroxy-1-phenylethyl]-2,2',5,5'-tetramethyl-3,3'-bithiophene-4,4'-dicarboxamide (41a and 41b)*
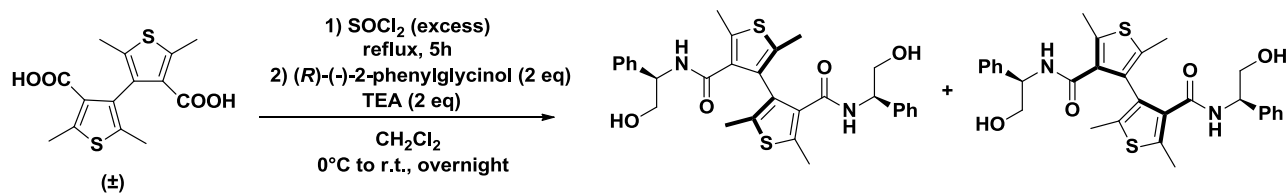
SOCl$_2$ (4mL) was slowly added to a solution of diacid **39** (1g, 3.23mmol, 1 eq) in dry CH$_2$Cl$_2$ (15mL); the reaction mixture was stirred at reflux for 5 hours, then the excess of thionyl chloride was removed under reduced pressure.

The solution of the dicarboxylic acid dichloride (3.23mmol, 1eq) in dry CH$_2$Cl$_2$ (6mL) was dropped, under nitrogen, at 0°C into a stirred solution of TEA (0.9mL, 6.46mmol, 2 eq) and (R)-phenylglycinol (0.89g, 6.46mmol, 2 eq) in dry CH$_2$Cl$_2$ (6mL). The reaction mixture was stirred at room temperature overnight and then washed with 1N HCl solution (10mL) and then with water (10mL). The organic layer was separated and dried over Na$_2$SO$_4$ and the solvent removed under reduced pressure. The crude was purified by flash chromatography (AcOEt/hexane 7:3) and the two diastereomeric diamides were obtained as first and second fraction.

First fraction (**41 b**): brown solid, isolated in 29% yield.

mp 175-176°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30-7.28 (m, 6H), 7.09-7.07 (m, 4H), 6.75 (br d, 2NH), 5.07-5.02 (m, 2H), 3.69 (t, 4H, J = 5.1 Hz), 2.51 (s, 6H), 2.17 (s, 6H).

^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 13.2, 14.1, 55.6, 65.6, 126.7, 127.5, 128.5, 130.9, 134.5, 134.7, 137.9, 139.1, 166.3.

MS (EI): 548 (M$^+$).

Second fraction (**41a**): brown solid, isolated in 29% yield.

mp 104-106°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29-7.25 (m, 6H), 7.06-7.03 (m, 4H), 6.65 (br s, 1H), 5.06-5.00 (m, 2H), 3.83 (dd, 2H, J = 11.7, J = 3.3), 3.60 (dd, 2H, J = 11.7, J = 5.7), 2.61 (s, 6H), 2.14 (s, 6H).

^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 13.2, 14.8, 56.0, 65.8, 126.6, 127.5, 128.5, 130.8, 133.0, 134.4, 139.0, 140.7, 165.6.

MS (EI): 548 (M$^+$).

- ***General procedures for the synthesis of diamides43a, 43b, 45a, 45b, 46a and 46b***
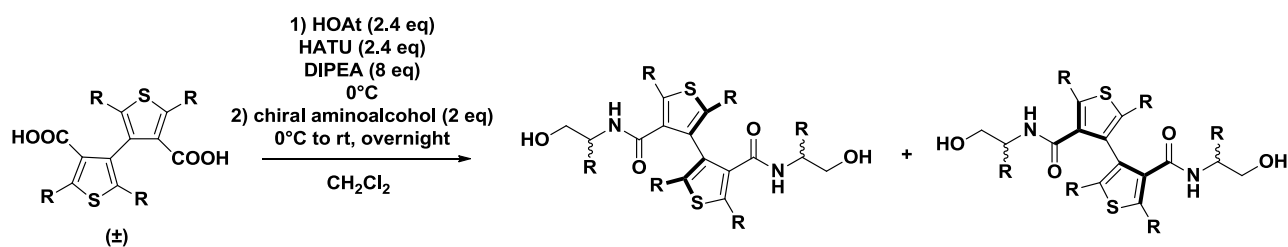
Diacid (0.69mmol, 1 eq) was dissolved in dry dichloromethane (8 mL) and stirred under N_2 atmosphere; at 0°C, HATU (0.627g, 1.65mmol, 2.4 eq), HOAt (0.225g, 1.65mmol, 2.4 eq) and DIPEA (0.9mL, 5.51mmol, 8 eq) were added. After 30 minutes, the enantiopure aminoalcohol (1.38mmol, 2 eq) was added and the reaction mixture was stirred overnight. The reaction mixure was washed with 1N HCl solution (10mL) and the organic layer was dried and concentrated at reduced pressure.
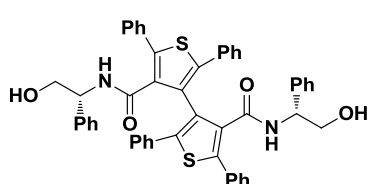
N,N′-bis[(R)-2-hydroxy-1-phenylethyl]2,2′,5,5′-tetraphenyl-3,3′-bithiophene-4,4′-dicarboxamide (43a) and (43b): the two diastereomers were obtained by flash chromatography using CH_2Cl_2/AcOEt 9:1 as eluent. **43a** and **43b** were collected as second and fourth fraction.

Second Fraction (43a): pale yellow solid, isolated in 28% yield.

mp: 195-198°C;

^{1}H NMR (CDCl₃, 300 MHz) δ 7.56-7.53 (m, 4H), 7.35-7.30 (m, 10H), 7.25-7.22 (m, 6H), 7.20-7.18 (m, 6H), 7.08 (br d, 2NH), 7.01-6.98 (m, 4H), 5.03 (dt, 2H, J = 10.5 Hz, J = 5.4 Hz), 3.61 (d, 4H, J = 5.4 Hz).

^{13}C NMR (CDCl₃, 75.4 MHz) δ 55.1, 56.1, 65.7, 127.0, 127.7, 128.1, 128.8, 130.7, 132.6, 133.1, 136.1, 138.5, 141.35, 142.0, 166.7.

MS (EI): 796 (M⁺).

Fourth fraction (43 b): pale yellow solid, isolated in 28% yield.

mp: 127-131°C;

^{1}H NMR (CD₂Cl₂, 300 MHz) δ 8.01 (br d, 2NH), 7.38-7.35 (m, 4H), 7.27-7.24 (m, 8H), 7.18-7.15 (m, 10H), 7.08-7.06 (m, 4H), 6.88 (d, 4H), 6.50 (br s, 2OH), 4.92 (q, 2H), 3.65 (d, 4H, *J* = 5.6 Hz).

^{13}C NMR (CD₂Cl₃, 75.4 MHz) δ 57.2, 65.9, 127.1, 128.1, 128.3, 129.0, 129.2, 129.6, 130.5, 132.3, 133.1, 138.4, 167.3.
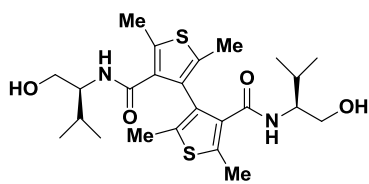
N,N′-bis[(S)-1-hydroxy-3-methylbutan-2-yl]-2,2′,5,5′-tetramethyl-3,3′-bithiophene-4,4′-dicarboxamide (45a) and (45b) : the two diastereomers were obtained by flash chromatography using AcOEt/petroleum ether 9:1 as eluent. **45a** and **45b** were collected as third and fourth fraction.

Third fraction (**45a**): brown solid, isolated in 26% yield.

mp: >230°C

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.93 (br d, 2NH), 3.75-3.71 (m, 2H), 3.51-3.50 (m, 4H), 2.51 (s, 6H), 2.10 (s, 6H), 1.85-1.78 (m, 2H), 0.90-0.83 (m, 12H).

MS (EI): 480 (M$^+$).

Fourth fraction (**45b**): brown dense oil, isolated in 39% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.29 (br d, 2NH), 3.72-3.67 (m, 2H), 3.52 (dd, 2H, *J* = 11.7 Hz, *J* = 3 Hz), 3.35 (dd, 2H, *J* = 11.4 Hz, *J* = 6 Hz), 2.56 (s, 6H), 2.14 (s, 6H), 1.65 (q, 2H, *J* = 6.6 Hz), 0.79 (d, 6H, *J* = 6.6 Hz), 0.69 (d, 6H, *J* = 6.9 Hz).

MS (EI): 480 (M$^+$).
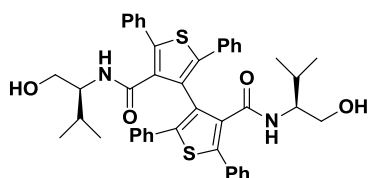
N,N'-bis[(*S*)-1-hydroxy-3-methylbutan-2-yl]-2,2',5,5'-tetraphenyl-3,3'-bithiophene-4,4'-dicarboxamide (46a) and (46b): the two diastereomers were obtained by flash chromatography using AcOEt/petroleum ether 6:4 as eluent. **46a** and **46b** were collected as first and second fraction

First fraction (**46a**)*:* white solid, isolated in 28% yield.

mp: 76-77°C.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.65-7.61 (m, 4H), 7.41-7.38 (m, 10H), 7.25-7.21 (m, 6H), 6.62 (br d, 2NH), 3.68-3.61 (m, 2H), 3.40 (d, 4H, *J* = 4.2 Hz), 1.98 (br s, 2OH), 1.67 (q, 2H, *J* = 6.9 Hz), 0.75 (d, 6H, *J* = 6.8 Hz), 0.61 (d, 6H, *J* = 6.8 Hz).

^{13}C NMR (CD$_2$Cl$_2$, 75.4 MHz) δ 18.7, 19.4, 28.8, 57.5, 63.2, 127.4, 127.5, 127.7, 128.0, 128.3, 128.6, 130.6, 132.8, 133.1, 136.7, 140.5, 141.9, 166.9.

MS (EI): 728 (M$^+$).

Second fraction (**46b**)*:* pale yellow solid, isolated in 28% yield.

mp: 85-86°C.

^{1}H NMR (CD$_2$Cl$_2$, 300 MHz) δ 7.69-7.61 (m, 4H), 7.42-7.36 (m, 10H), 7.33-7.26 (m, 6H), 6.97 (br d, 2NH), 3.69-3.62 (m, 2H), 3.47 (d, 2H, *J* = 5.1 Hz), 1.85 (br s, 2OH), 1.64 (q, 2H, *J* = 6.6 Hz), 0.66 (d, 6H, *J* = 6.6 Hz), 0.56 (d, 6H, *J* = 6.9 Hz).

^{13}C NMR (CD$_2$Cl$_2$, 75.4 MHz) δ 18.5, 19.3, 29.3, 58.1, 64.2, 127.6, 128.2, 128.3, 128.5, 128.9, 129.1, 129.3, 131.2, 133.1, 133.5, 137.2, 141.7, 167.

MS (EI): 728 (M$^+$).

- *General procedure for the synthesis of 2,2',5,5'-Tetramethyl-4,4'-bis[(S)-4,5-dihydro-4-phenyloxazol-2-yl]-3,3-bithiophene (42a) and (42b)*
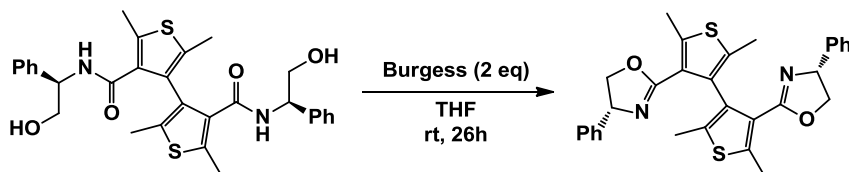
The Burgess reagent (methyl N-[[(triethylammonio)sulphonyl]carbamate] (0.313g,1.31mmol, 2 eq) was added to the solution of the enatiopure dicarboxamide (0.36g, 0.656mmol, 1 eq) in dry THF (4mL). The reaction mixture was stirred for 26 hours. The solvent was removed at reduced pressure. Flash chromatography (AcOEt/hexane 4:6) afforded the desired compounds **42a** and **42b**

(*R*)-2,2',5,5'-Tetramethyl-4,4'-bis[(S)-4,5-dihydro-4-phenyloxazol-2-yl]-3,3-bithiophene (42a): dense colourless oil, isolated in 35% yield.

^{1}H NMR (CDCl_3, 300 MHz) δ 7.33-7.25 (m, 6H), 7.18-7.15 (m, 4H), 5.24 (dd, 2H, J = 10.2 Hz, J = 8.1 Hz), 4.50 (dd, 2H, J = 10.2 Hz, J = 8.4 Hz), 3.92 (t, 2H, J = 8.1 Hz), 2.69 (s, 6H), 2.25 (s, 6H).

^{13}C NMR (CDCl_3, 75.4 MHz) δ 13.7, 15.0, 29.7, 69.9, 126.1, 126.2, 126.6, 127.3, 128.5, 133.1, 139.4, 142.9, 162.1.

MS (EI): 512 (M$^+$).

(*S*)-2,2',5,5'-Tetramethyl-4,4'-bis[(S)-4,5-dihydro-4-phenyloxazol-2-yl]-3,3-bithiophene (42b):
dense colourless oil, isolated in 35% yield.

^{1}H NMR (CDCl_3, 300 MHz) δ 7.29-7.18 (m, 10H), 5.25 (dd, 2H, J = 10.2 Hz, J = 8.1 Hz), 4.46 (dd, 2H, J = 10.2 Hz, J = 8.4 Hz), 3.96 (t, 2H, J = 8.4 Hz), 2.71 (s, 6H), 2.18 (s, 6H).

^{13}C NMR (CDCl_3, 75.4 MHz) δ 13.9, 15.2, 29.4, 70.1, 126.4, 126.6, 126.8, 127.3, 128.3, 133.4, 139.6, 143.1, 162.2.

MS (EI): 512 (M$^+$).

- *General procedure for the synthesis of 2,2',5,5'-tetraphenyl-4,4'-bis[(S)-4,5-dihydro-4-phenyloxazol-2-yl]-3,3-bithiophene (44a and 44b)*
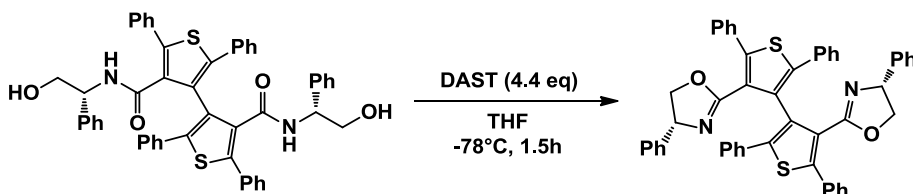
Pure diamide (0.64g, 0.8mmol, 1 eq) was dissolved in THF (6.5mL) and cooled at -78°C, then DAST (0.5mL, 3.52mmol, 4.4 eq) was added dropwise and the reaction stirred at the same temperature for 90 minutes. The mixture was filtered and the solvent evaporated under reduced pressure. The product was

purified by flash chromatography using AcOEt/hexane 3:7 as eluent.

(4R,4'R)-2,2'-(2,2',5,5'-tetraphenyl-[3,3'-bithiophene]-4,4'-diyl)bis(4-phenyl-4,5-dihydrooxazole)
(44a): brown solid, isolated in 40% yield.

^{1}H NMR (MeOD, 300 MHz) δ 7.64-7.57 (m, 4H), 7.45-7.38 (m, 6H), 7.15-6.97 (m, 20H), 5.22 (t, 2H, $J =$ 9.9 Hz), 4.62 (t, 2H, $J = 9.9$ Hz), 4.02 (t, 2H, $J = 8.7$ Hz).

- *General procedures for the synthesis of the bisoxazolines 47a, 47b, 48a and 48b*
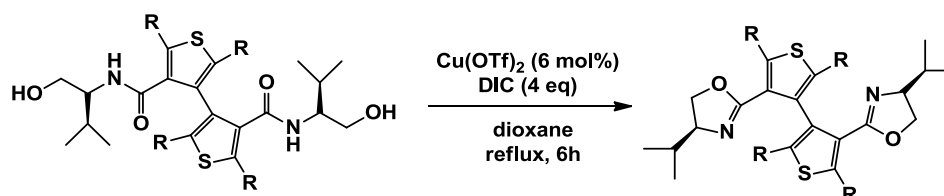
DIC (84μL, 0.543mmol, 4 eq) was added to a solution of pure amide **46** or **47** (0.136mmol, 1 eq) and Cu(OTf)$_2$ (3mg, 0.008mmol, 6 mol%) in anhydrous 1,4-dioxane (0.8mL) and the reaction was heated at reflux for 6 hours. The resulting white precipitate was filtered, washed with ethyl acetate (10mL), and the solution evaporated under reduced pressure. The residue was purified by flash chromatography (AcOEt/petroleum ether).
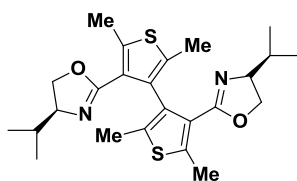
2,2',5,5'-Tetramethyl-4,4'-bis[(S)-4,5-dihydro-4-isopropyloxazol-2-yl]-3,3-bithiophene (47a) from diamide 45a: pale yellow solid, isolated in 15% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 4.09-4.03 (m, 2H), 3.86-3.76 (m, 4H), 2.56 (s, 6H), 2.16 (s, 6H), 1.69-1.63 (m, 2H), 0.85-0.79 (m, 12H).

2,2',5,5'-Tetramethyl-4,4'-bis[(S)-4,5-dihydro-4-isopropyloxazol-2-yl]-3,3-bithiophene (47b) from diamide 45b: pale yellow solid, isolated in 20% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.88-3.79 (m, 2H), 3.57-3.49 (m, 4H), 2.57 (s, 6H), 2.04 (s, 6H), 1.65-1.58 (m, 2H), 0.88 (d, 6H, $J = 6.7$ Hz), 0.80 (d, 6H, $J = 6.7$ Hz).
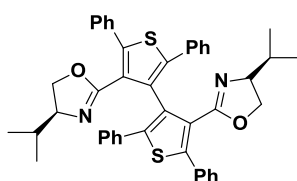
2,2',5,5'-Tetraphenyl-4,4'-bis[(S)-4,5-dihydro-4-isopropyloxazol-2-yl]-3,3-bithiophene (48a) from diamide NUM (46a): pale yellow solid, isolated in 60% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.65-7.62 (m, 4H), 7.38-7.28 (m, 6H), 7.16-7.03 (m, 10H), 4.19-4.12 (m, 2H), 3.94-3.84 (m, 4H), 1.67-1.60 (m, 1H), 0.77 (d, 6H, $J = 2.1$ Hz), 0.74 (d, 6H, $J = 1.8$ Hz).

2,2',5,5'-Tetraphenyl-4,4'-bis[(S)-4,5-dihydro-4-isopropyloxazol-2-yl]-3,3-bithiophene (48b) from diamide 46b: pale yellow solid, isolated in 83% yield.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.66-7.64 (m, 4H), 7.42-7.39 (m, 6H), 7.15-7.07 (m, 10H), 4.18-4.15 (m, 2H), 3.93-3.91 (m, 4H), 1.68-1.61 (m, 2H), 0.78 (d, 6H, $J = 1.8$ Hz), 0.76 (d, 6H, $J = 1.8$ Hz).

- *General procedures for the asymmetric Friedel-Crafts alkylation of 1H-indole with trans-β-nitrostirene*
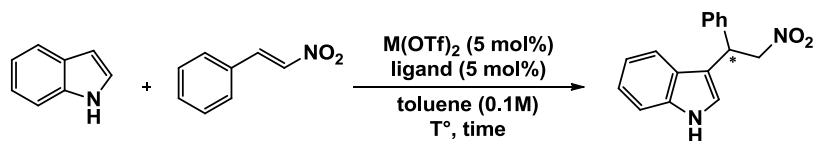
M(OTf)$_2$ (0.015mmol, 5 mol%) and the ligand (0.015mmol, 5 mol%) were dissolved in the solvent (1.3mL) and stirred at room temperature for 30 minutes. *Trans*-β-nitrostirene (0.045g, 0.3mmol, 1 eq) was added, the reaction was stirred for 30 minutes, then 1H-indole (0.035g, 0.3mmol, 1 eq) was added at 0°C and stirred.

After the reaction was complete (monitored by TLC), the solvent was removed under vacuum; flash chromatography (AcOEt/petroleum ether 2:8) afford the final product. Spectroscopical data of the product were in agreement with the literature[123] and enantiomeric excesses were determined by chiral HPLC equipped with chiral column Chiracel OD-H.

- *General procedures for the asymmetric Friedel-Crafts alkylation of 1H-indole with dimethyl-2-benzylidenmalonate*
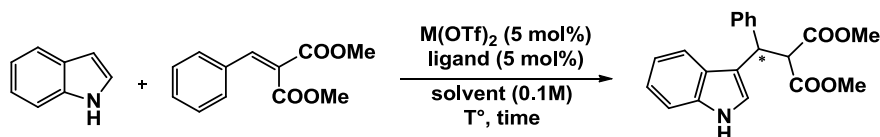
M(OTf)$_2$ (0.015mmol, 5 mol%) and the ligand (0.015mmol, 5 mol%) were dissolved in the solvent (1.4mL) and stirred at room temperature for 30 minutes. Dimethyl-2-benzylidenmalonate was added (0.066g, 0.3mmol, 1 eq), the reaction was stirred for 30 minutes, then 1H-indole (0.042g, 0.36mmol, 1.2 eq) was added at 0°C and stirred.

After the reaction was complete (monitored by TLC), the solvent was removed under vacuum; flash chromatography (CH$_2$Cl$_2$/petroleum ether 8:2) afford the final product. Spectroscopical data of the product were in agreement with the literature[125] and enantiomeric excesses were determined by chiral HPLC equipped with chiral column Chiracel OD-H.

Palladium-Catalyzed Allylic Aminations of β,γ-Unsaturated Acid Derivatives

This following part of this Ph.D. thesis was conducted at *Université Pierre et Marie Curie (Paris 6)*, in the Institut Parisien de Chimie Moléculaire (IPCM), under the supervision of Professors G. Poli and J. Oble (*ROCS* team).

The main research domain of this team deals with the study of innovative organometallic transformations for organic synthesis, with a particular focus on the development of new Pd-catalyzed domino reactions for the synthesis of heterocyclic scaffolds, catalytic allylic C-H activations and selective transition-metal-catalyzed transformations

6.1 Introduction

The direct conversion of C-H bonds into C-O, C-X (X = halogen), C-N, C-S, and C-C bonds represents a challenging transformation in organic chemistry. Indeed, the traditional approaches for the formation of such carbon-carbon or carbon-heteroatom bonds rely on the use of pre-functionalized substrates, which adds at least one steps as well as consequent costs to the overall construction of a molecule. Bypassing this issue would not only improve atom economy but also increase the overall efficiency of multistep synthetic sequences. This is the reason why direct C-H bond functionalization reactions have recently emerged as a field of intense research. Nonetheless, such transformations are difficult due to the inert nature of most carbon-hydrogen bonds and the requirement to control site selectivity, as usually molecules contain several C-H groups.

Transition metals can react with C-H bonds to produce C-M bonds through a process called "C-H activation". The resulting C-M bonds are more reactive than their C-H counterparts and they can be converted into new functional groups, in many cases in mild conditions.

Many different transition metals are used for this purpose. In particular, C-H functionalization reactions catalyzed by palladium(II) catalysts are particularly attractive for different reasons:

a) palladium can participate in metallation with a variety of ligand-directing groups and readily promotes C-H activation both at sp^2 and sp^3 C-H sites;

b) the prospect to install many different types of bonds (few other metal-catalysts allow such diverse bond construction), due to the compatibility of Pd(II) catalysts with various oxidants and the ability to selectively functionalize palladated intermediates;

c) the opportunity to perform reactions in the presence of air and moisture, making palladium catalysts exceptionally practical for applications in organic synthesis.[126]

In particular, allylic C-H positions are activated easier than other inactivated positions. Therefore, a special interest for the direct functionalization of these positions arose in the past years. Although various metals are able to promote such activation, palladium remains one of the most attractive metals when taking into account both the cost of the metal salt and its reactivity.

C-N bond are present in a wide range of natural substances as well as in pharmaceutical products, and in

the last decades a number studies have been consecrated to the development of the amination reaction. The most classical methods for installing a nitrogen-based group into an organic framework via N-C bond formation rely on S_N2 substitution reactions using K-phthalimide (Gabriel reaction) or Na azide.[127] While these methods are reliable, they require oxidation of the precursor of the electrophilic substrate in order to install the appropriate leaving group. Thus, reactions that directly and selectively convert C-H bonds into C-N bond would significantly simplify synthetic sequences avoiding preparation and handling of pre-oxidized materials.

Although a few Pd-catalyzed allylic amination reactions have been recently reported, this reaction is still underdeveloped, and several challenging variations are still waiting to be discovered. For example, the direct intermolecular allylic amination starting from an β,γ-unsaturated acid derivatives is so far an unknown transformation.

This chapter reports a brief survey of the state of the art of the Pd-catalyzed direct allylic aminations, followed by disclosure of our the preliminary studies in the intermolecular allylic amination of β,γ-unsaturated amides.

6.2 *Pd-catalyzed allylic aminations*

Alkenes, easily available from petrochemical sources, are suitable starting materials to be functionalized into more complex structure. Such transformations can usually be run under catalytic conditions, and palladium chemistry allows accomplishing a handful of variations. In particular, the direct oxidative allylic amination of alkenes allows the one-step generation of an N-C bond of an alkene with formation of an allylic amine. Although synthetically very powerful, this transformation is still rather underdeveloped and the degree of mechanistic understanding of the reported transformations has not reached a satisfactory degree of maturity, yet.

The interaction between a Pd(II) complex and an alkene modifies the π-system generating a transient complex. Two different reactivities may subsequently take place: a) the addition of a nucleophile to the activated alkene, usually followed by a dehydropallaation reaction (Scheme 6.1, top line), b) the activation of an allylic C-H position to generate an electrophilic η³-allylpalladium complex, whose in situ trapping by a nucleophilic species delivers the final allylated compound and a Pd(0) complex. The global sequence is called "direct Pd-catalyzed allylation", and allows the direct functionalization of an allylic C-H bond (Scheme 6.1, bottom line). Worthy of note, in both cases, an external stoichiometric oxidizing agent is needed to bring the zerovalent Pd back to the original Pd(II) state. In the following lines we will focus on the allylic amination reaction, starting with quoting a selection of the most relevant reported examples.
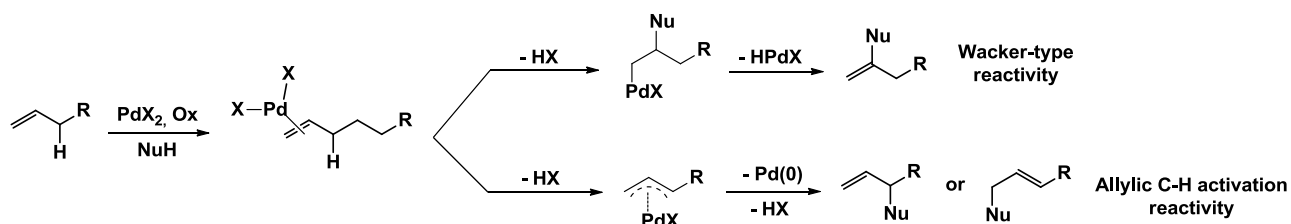
Scheme 6.1

6.2.1 Intermolecular allylic aminations

Recently, White *et al.* developed a protocol for the direct allylic amination of terminal alkenes with *N*-tosyl methylcarbamate, using catalytic amounts of the system [Pd(OAc)$_2$/PhSO(CH$_2$)$_2$SOPh], in the presence of benzoquinone (BQ) and diisopropyl ethyl amine (DIPEA).[128] A range of terminal alkenes were successfully oxidized under these conditions to give the corresponding protected linear allylic amines in good yields (Scheme 6.2).
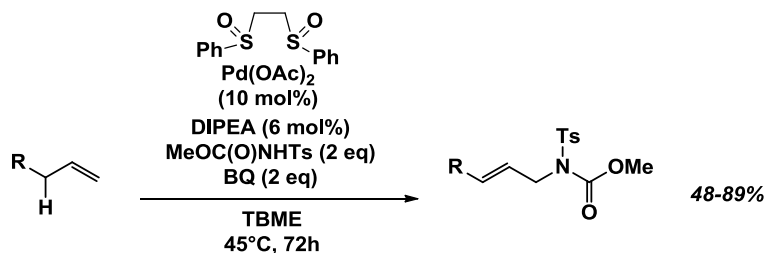
Scheme 6.2

Similarly, Ishii reported the direct allylic amination by employing a molybdovanadophosphate salt as oxydant, namely NPMoV, in the presence of palladium (II) trifluoroacetate. However, the reaction was limited in its scope to the use of diaryl amines as nucleophile[129] (Scheme 6.3).
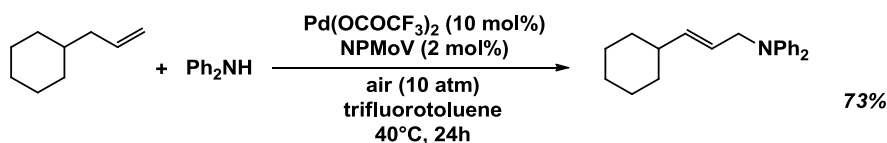
Scheme 6.3

Even though, as shown above, a few intermolecular direct Pd-catalyzed allylic aminations have already been reported, this field is still in its infancy and its development is highly desirable and a challenge for future investigations.[130]

6.2.2 Intramolecular allylic aminations

In 2004, Broggini reported the intramolecular amination of tosylated *N*-allyl-anthranilamides with catalytic amounts of Pd(OAc)$_2$. Depending on the reaction conditions, it is possible to obtain either quinazolines or benzodiazepinones[131].
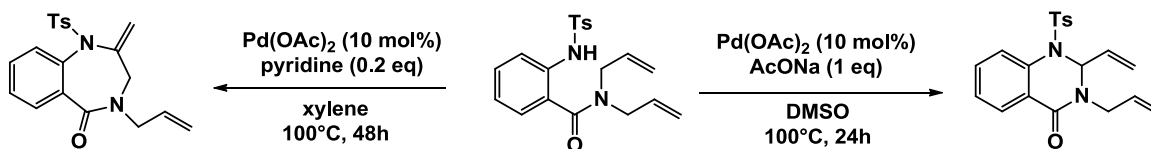
Scheme 6.4

The employment of a polar and aprotic solvent as DMSO, in the presence of AcONa as a base, favored the development of the η^3-allylPd-complex, and the following intramolecular amination of the internal carbon of the allylic complex afforded the quinazolines (Scheme 6.4, right). Instead using a non coordinationg solvent such as xylene, the formation of benzodiazepinones was preferred, and this cyclisation can be ascribed to a Wacker-type reactivity(Scheme 6.4, left).
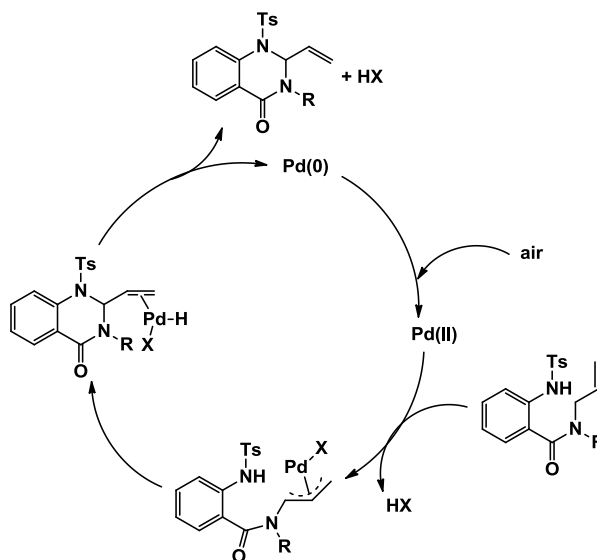
Scheme 6.5

Liu achieved the allylic cyclization of *N*-tosyl amides functionalized with terminal olefin to give five- or seven-membered lactams via the formation of an η^3-allylPd-complex. Depending on reaction conditions, azepinones were obtained using a Brønsted base (i.e. NaOBz) (Scheme 6.6, right), whereas pyrrolidones were formed in the presence of (salen)chromium (III) chloride[132] (Scheme 6.6, left).
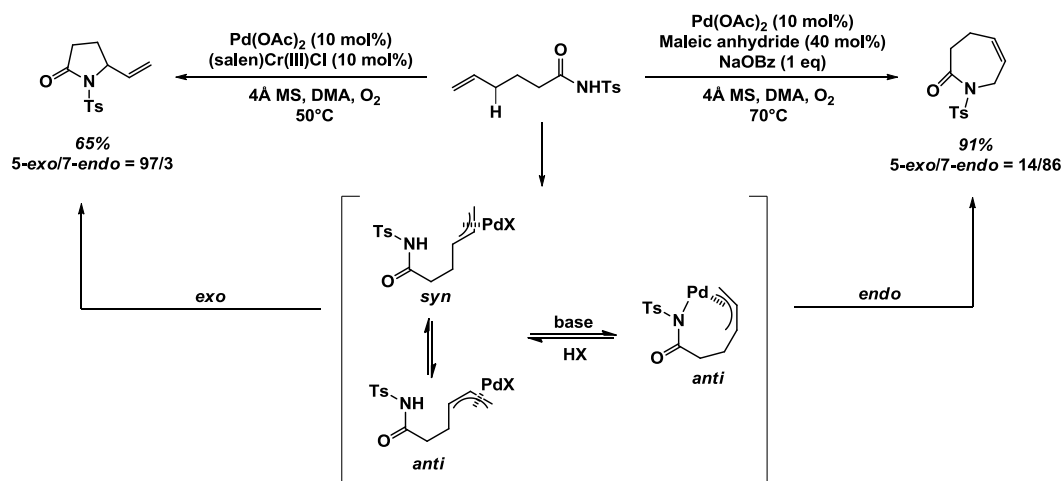
Scheme 6.6

Poli reported the different behavior of *N*-tosyl-amido-substituted alkenes under oxidative palladium(II) catalysis conditions:[133] the cyclic (5- or 6-membered) amminopalladate intermediate could evolve if conditions were complied with the presence of a strong terminal oxidant or employing a substrates that permit a distocyclic β-H elimination; otherwise the cyclic alkylpalladium complex was only a dormant species in equilibrium with the initial substrate and the C-H activation of the olefinic substrate took place, generating a η^3-complex followed by its interception by the nitrogen nucleophile (Scheme 6.7).
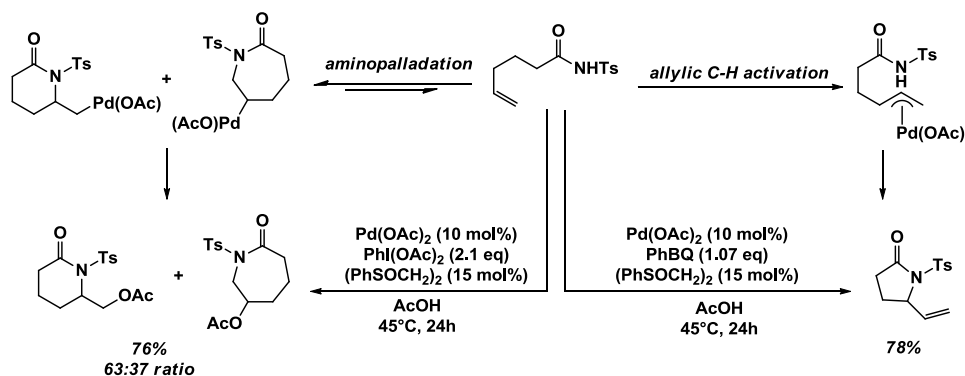
Scheme 6.7

6.3 *Aim of this project*

In the frame of dehydrogenative couplings, the direct allylic amination of but-3-enoic acid derivatives represents a thus far unknown and challenging synthetic transformation. Indeed, this reactivity, if possible, may allow the selective entry toward α- and/or γ-amino-acid derivatives. In particular, using Pd-catalysis, this transformation could be envisaged either through the oxidative PdX_2-catalyzed transformation of the butenoic derivative into a η^3-allyl complex, followed by direct trapping with an appropriate nitrogen nucleophile (Scheme 6.8, pathway I), or by the initial formation of the corresponding allylic acetate under

oxidative PdX$_2$ catalysis, followed by a Pd(0)-catalyzed allylic amination (Scheme 6.8, pathway II). Worthy of note, the first step of this second sequence, the Pd-catalyzed direct allylic acetoxylation of but-3-enoates, has been recently reported[136,139].
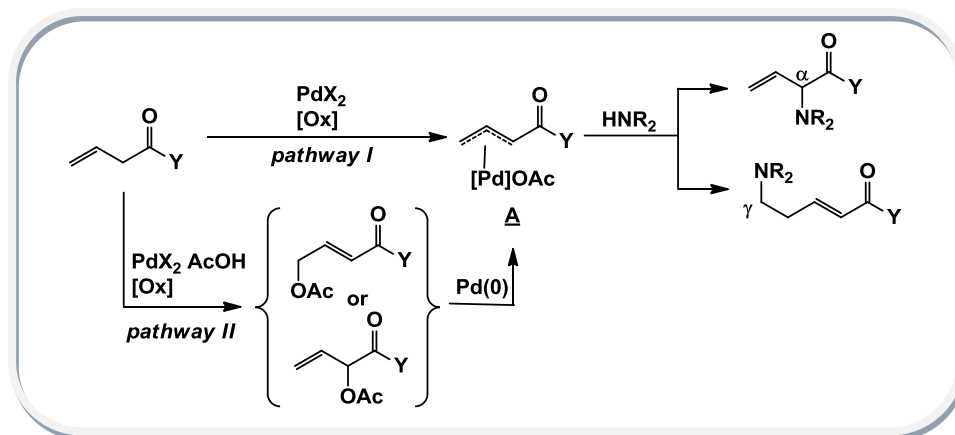
Scheme 6.8

Various factors are expected to influence the regioselectivity of the amination step of the η^3-allyl derivative, which, in principle, may afford α- or γ- selectivity. In particular, we reasoned that polarizing functional groups adjacent to the metal may direct the regioselectivity.[134] Accordingly, we decided to synthesize some amide derivatives of but-3-enoic acid bearing coordinating-groups. (Scheme 6.9). The synthesis of these β-γ-unsaturated amides will be first presented. Then, the preliminary results of intermolecular allylic amination will be discussed as a function of the followed strategy [direct Pd(II)-catalyzed oxidative amination *vs* sequential oxidative Pd(II)-cat. oxylation /Pd(0)-cat. amination].

6.3.1 Synthesis of β-γ-unsaturated amides

Amides **1a-e** were synthesized starting from but-3-enoic acid (Scheme 6.9).
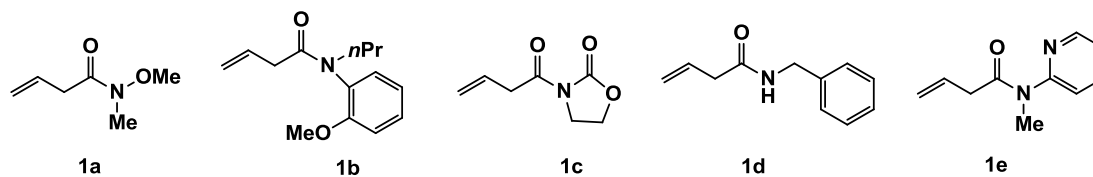
Scheme 6.9

On the one hand, amides **1a**, **1b** and **1c** could be prepared by treatment of 3-butenoic acid with thionyl chloride, followed by reaction of thus formed acyl chloride with the proper secondary amines (Scheme 6.10).
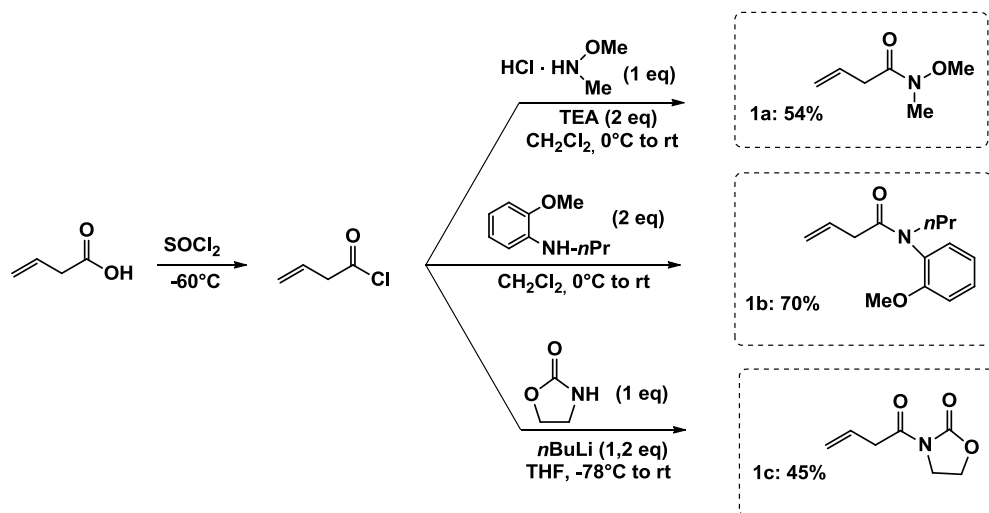
Scheme 6.10

On the other hand, amides **1d** and **1e** could be prepared via DDC coupling between 3-butenoic acid and the appropriate amine (Scheme 6.11).
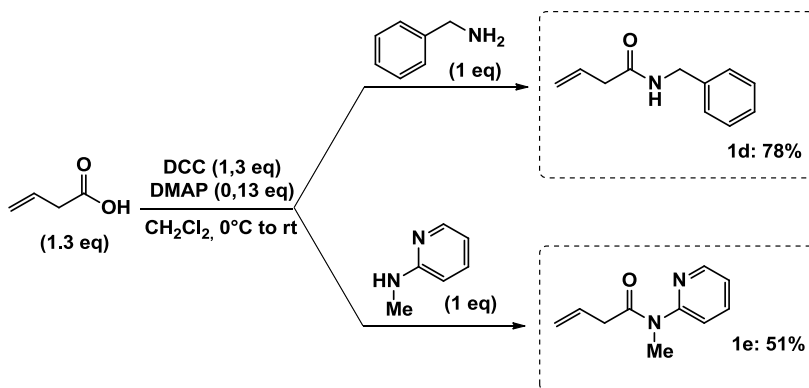
Scheme 6.11

6.3.2 Pd(II)-catalyzed direct allylic amination

As commented above, White developed an original Pd-catalyzed method for the direct dehydrogenative amination of terminal alkenes.[128] We thus decided to start our study of but-3-enamide amination testing her protocol, choosing amides **1a** and **1e** as the model substrates, and methyl *N*-tosyl carbamate as nucleophile. White's conditions (10 mol% Pd(OAc)$_2$, 10 mol% PhSO(CH$_2$)$_2$SOPh, 6 mol% DIPEA, 2 eq MeOC(O)NHTs, 2 eq BQ in THF) did not give the desired amination products, only starting material was recovered (Table 6.1, entry 1). Neither variation of the experimental conditions such as modifying the concentration of the middle (entry 2), nature of the ligand (entries 3 and 4), of the solvent (entry 5) and of the oxidant (entry 6), was efficient. Finally, degradation products were obtained using aerobic conditions in presence of AcONa, in DMSO at 100°C (entry 7).
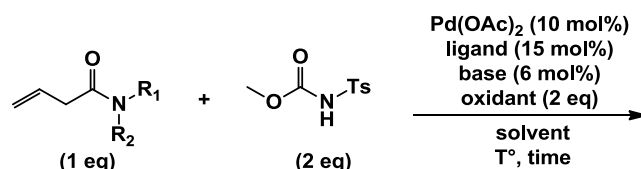
Table 6.1: screening conditions of direct amination

Entry	Substrate	Ligand	Base	Oxidant	Solvent	T° (°C)	Time (h)	Yield
1	1e	PhSO(CH$_2$)$_2$SOPh	DIPEA	BQ	THF (0,6M)	45	17	sm
2	1e	PhSO(CH$_2$)$_2$SOPh	DIPEA	BQ	THF (0,2M)	45	24	sm
3	1e	-	DIPEA	BQ	THF (0,2M)	45	24	sm
4	1e	PPh$_3$	DIPEA	BQ	THF (0,2M)	45	24	sm
5	1e	PhSO(CH$_2$)$_2$SOPh	-	BQ	AcOH (0,2M)	45	24	sm
6	1a	PhSO(CH$_2$)$_2$SOPh	DIPEA	BQ	THF (0,2M)	45	24	sm
7	1e	-	AcONa	O$_2$	DMSO (0,2M)	100	24	degrad.

Due to this failure of pathway I (direct allylic amination), we decided to investigate the alternative two-step pathway II,[135] involving Pd(II)-catalyzed oxidative allylic oxylation followed by Pd(0)-catalyzed allylic amination of this pre-functionnalized intermediate.

6.3.3 Pd(II)-catalyzed direct allylic acyloxylation

a- State of the art

The direct γ-allylic acetoxylation of methyl but-3-enoate has been recently reported by Szabò using PhI(OAc)$_2$ [136] or NaBO$_3$·H$_2$O[137] as terminal oxidants (Scheme 6.12). In both cases the reaction is expected to proceed through a Pd(II)/Pd(IV) catalytic cycle.
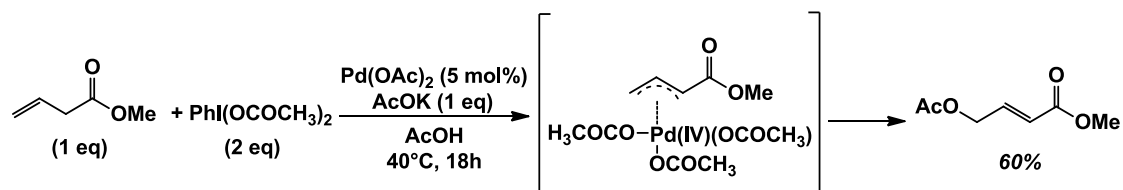
Scheme 6.12

Furthermore, Della Ca' *et al.* have developed the acetoxylation in γ position of heptadienoates by using MnO$_2$/BQ as oxidant system (Scheme 6.13).[138] In this case, the mechanism is expected to involve an acetoxypalladation path (Scheme 6.8, pathway II) rather than allylic C-H activation (Scheme 6.8. pathway I).
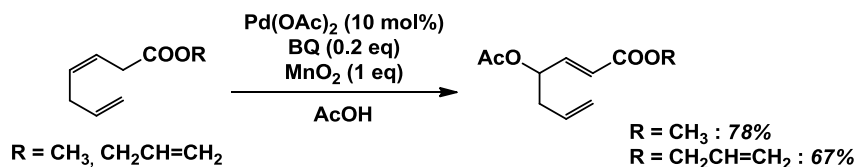
Scheme 6.13

Finally, Stahl investigated the allylic C-H acetoxylation of terminal olefins under aerobic conditions (Scheme 6.14).[139] In this case, the use of 4,5-diazafluorenone as an ancillary ligand for Pd(OAc)$_2$ is mandatory to form linear allylic acetoxylationproducts in good yields and selectivity under 1 atm O$_2$.
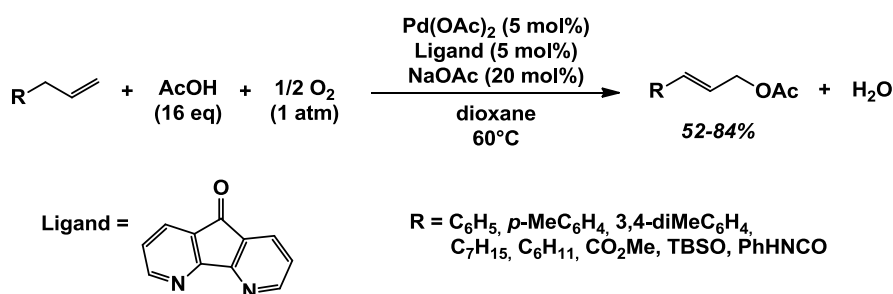
Scheme 6.14

b- Direct acyloxation of but-3-enamides

Taking inspiration from the protocols just described, we performed different tests on but-3-enamide **1a,** adopting the same or similar reaction conditions as those above described (Scheme 6.15). All the reactions led to allylic acetoxylation in γ position, with generation of the *E* configuration at the double bond, though in very low yields.
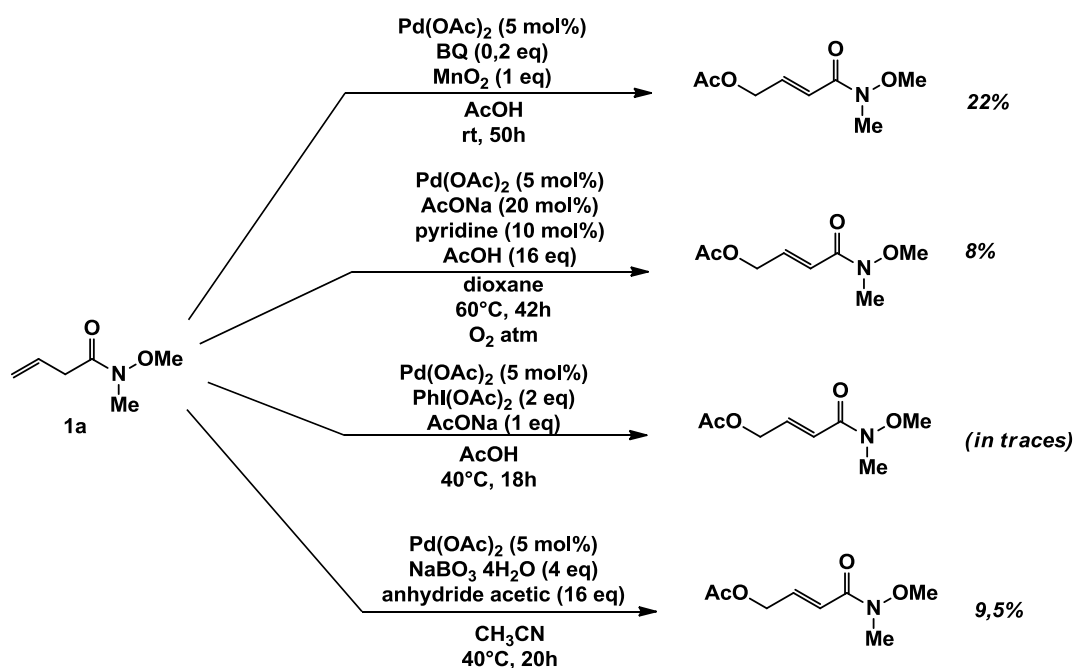
Scheme 6.15

The best result in this set of experiments was obtained with the conditions [Pd(OAc)$_2$ (5 mol%), BQ (0.2 equiv.), MnO$_2$, AcOH]. Accordingly, we continued our optimization by fine tuning of these reaction condition on **1a** (Table 6.2).

Table 6.2: screening the reaction conditions for the direct acetoxylation on **1a**

Entry	Pd(OAc)$_2$ (mol%)	BQ (eq)	MnO$_2$ (eq)	Other solvent	T° (°C)	Time (h)	Yield* (%)
1	5	0,2	1	-	rt	50	22
2	5	0,2	1	-	50	27	34
3	5	0,2	1	-	rt	100	23
4	10	0,2	1	-	rt	48	20
5	5	0,2	1	AcOH 0,6M	rt	48	24
6	5	0,2	2	-	rt	45	16
7	5	0,4	1	-	rt	48	28

8	5	0,2	1	AcOH/H$_2$O 1:1	rt	50	24
9	5	0,2	1	AcOH/DMSO 1:1	80	50	24
10	10	2	-	-	50	24	54
11	10 (+ 15%LL)**	2	-	-	50	24	40
12	10	2	-	-	50	48	23
13	10	2	-	AcOH 0,6M	50	24	41
14	5	2	-	-	80	7	16
15	5	2	-	-	80	22	32
16	10	2	-	AcOH/DMSO 1:1	50	24	35

* Isolated yield; ** LL = PhSO(CH$_2$)$_2$SOPh

We carried out the reaction optimization by modifying the following parameters: temperature (entries 1 and 2), time (entries 3 and 4), solvent (entry 5), ratio of oxidative system (BQ/MnO2) (entry 6) in various solvents and time (entries 8 and 9), nature of the oxidant (only BQ), (entries 10-16) with different amount of palladium-catalyst and solvents.

Good yield was obtained by using 10 mol% Pd(OAc)$_2$ and 2 equivalents of BQ, carrying out the reaction at 50°C (entry 10). No improvements were obtained extending reaction times (entries 12 and 13) or increasing the temperature (entries 14 and 15). Interestingly, the presence of a specific ligand was unnecessary for the success of the experiment (entry 11). As expected, starting material was recovered using substrate **1a'**, isomer of **1a** having the internal *E* double bond (Scheme 6.16).
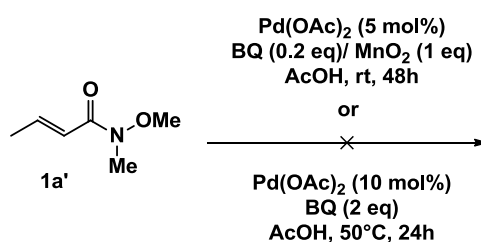
Scheme 6.16

A similar screening was then carried out on substrate **1b**. In this case, best results were obtained using a smaller amounts of palladium catalyst (5 mol%) %), 2 equivalents of BQ at 80°C (entry 6), which gave product **2b** in 80% yield (Table 6.3). The reaction, conducted at room temperature in the presence of couple BQ/MnO$_2$ as oxidizing system (entry 2), led to a low yield, while modest yields were obtained operating at 50°C (entries 1,3,4 and 5). Finally, the presence of the disulfoxyde ligand did not allow any improvement, as previously observed for the acetoxylation of **1a** (entry 3).

1b → 2b

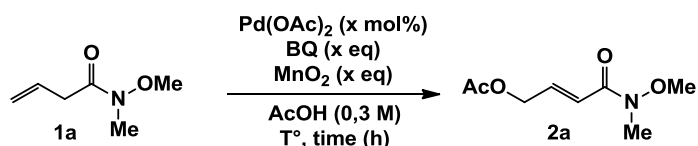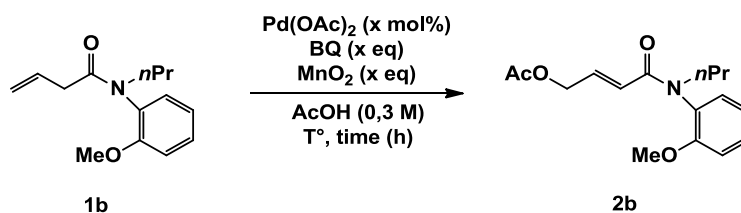**Table 6.3**: screening the reaction conditions for the direct acetoxylation of **1b**

Entry	Pd(OAc)$_2$ (mol%)	BQ (eq)	MnO$_2$ (eq)	Other solvent	T° (°C)	Time (h)	Yield* (%)
1	10	2	-	-	50	24	66
2	5	0,2	1	-	rt	50	28
3	10 (+15%LL)**	2	-	-	50	25	64
4	5	2	-	-	50	24	48
5	5	2	-	AcOH 0,6M	50	24	50
6	5	2	-	-	80	18	80

* Isolated yield; ** LL = PhSO(CH$_2$)$_2$SOPh

Finally, the acetoxylation reaction was carried out on substrates **1c** and **1e** as well as on the secondary amide **1d**, (Table 6.4). In the case of amide **1c**, despite further modifications of the reaction conditions, such as varying the amount of catalyst (entries 2 and 6), extending the reaction times (entries 2 and 4), decreasing or increasing the reaction temperature (entries 2 and 6), product **2c** was obtained in low yields (30%). The best conditions were Pd(OAc)$_2$ (10 mol%), BQ (0.4 equiv.), MnO$_2$ (1.0 equiv.) (entry 3).

In the case of the secondary amide **1d**, the acetoxylated product **2d** was obtained in 73% yield using the same experimental condition as employed for the formation of **2a** [10 mol% Pd(OAc)$_2$, 2 eq BQ in AcOH at 50°C] (entry 7). On the other hand, no reaction occurred using substrate **1e** (entry 8) (probably due to the coordination of palladium by the nitrogen atom of the pyridine ring). In all cases the conversion was incomplete.
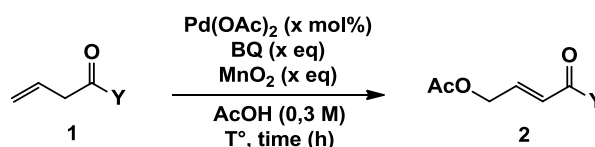
Table 6.4: direct acetoxylation reaction on substrate **1c**, **1d** and **1e**

Entry	Substrate	Pd(OAc)$_2$ (mol%)	BQ (eq)	MnO$_2$ (eq)	Other solvent	T° (°C)	Time (h)	Yield* (%)
1	1c	10	2	-	-	50	24	23
2	1c	5	0,2	1	-	rt	44	7
3	1c	10	0,4	1	-	50	24	29
4	1c	10	2	-	-	50	48	23
5	1c	10	2	-	AcOH/CH$_3$CN 1:1	50	24	26
6	1c	5	2	-	-	80	7	4
7	1d	10	2	-	-	50	24	73
8	1e	10	2	-	-	50	24	sm

* Isolated yield

In 2010, Le Bras reported the allylic acyloxylation of terminal alkenes in buffered acetate medium (Scheme 6.17).[140] The best results were obtained employing the catalytic system [Pd(OAc)$_2$ (10 mol%), LiOH·H$_2$O (2 equiv), BQ (2.0 equiv.), RCO$_2$H (20 equiv.)], which gave high regioselectivity and good stereoselectivity.
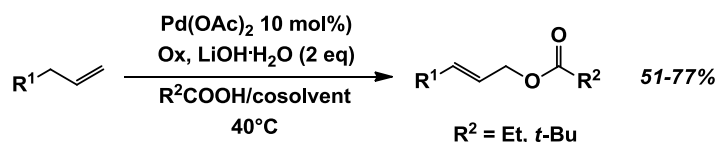
Scheme 6.17

We thus decided to apply the above experimental conditions to substrates **1a-e**, using *t*-BuCO$_2$H both as carboxylic acid partner and solvent and CH$_3$CN as co-solvent. The results are summarized in Table 6.5.
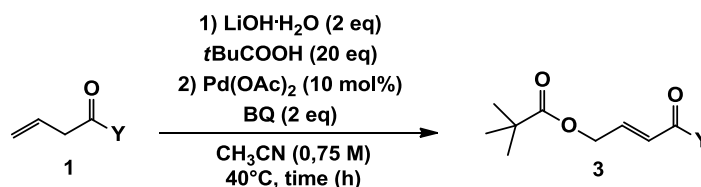
Table 6.5: direct acyloxylation of substrate **1**

Entry	Substrate	Time (h)	Yield (%)*
1	1a	26	48
2	1b	18	48
3	1c	22	15
4	1d	22	63
5	1e	24	sm

*Isolated yield

Unfortunately, this new protocol did not improve our previous results. Furthermore, in this case **1e** did not react at all (entry 5), whereas substrate **1c** gave a mixture of the desired product in very low yield (entry 3) in mixture with the disubstituted product.

Moderate yields (48%) were obtained in the allylic pivaloylation of substrates **1a** and **1b** (entries 1 and 2). Once again, the secondary amide **1d** appeared to be the best candidate for the γ-acyloxyation (entry 4).

At this stage of our study, with these preliminary results in hand, we next focused our attention to the second step, namely, the introduction of the nitrogen nucleophile from the acyloxylated products **2** or **3**.

6.3.4 Pd(0)-catalyzed allylic amination

Phthalimide was chosen as the nitrogen nucleophile to test this step. Interestingly, this nucleophile was found by Cook *et al*.[141] to attack, under H-bond control, the more substituted terminus of a transient η³-allylpalladium complex, affording selectively the branched allylated product (Scheme 6.18):
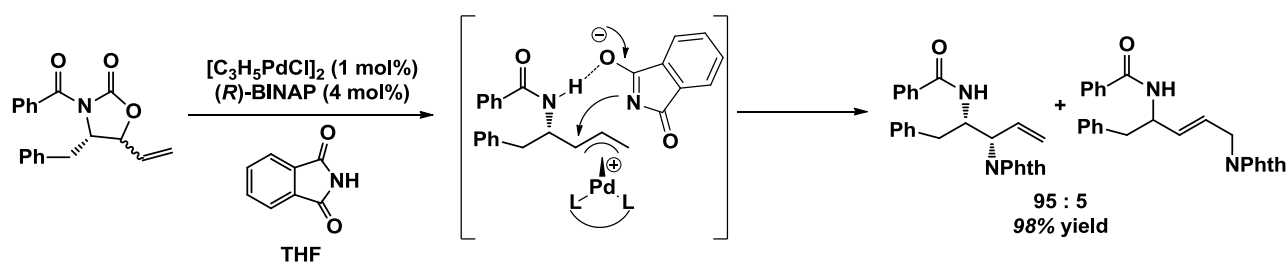
Scheme 6.18

The above study encouraged us to test phtalimide as the nucleophile in the Pd(0)-catalyzed aminations of our γ-acyloxyallyl amides **2** and **3**. In particular, we reasoned that the reaction between phthalimide and the secondary amide **1d** might have taken place abnormally at the α position, according to H-bond control (Scheme 6.19).
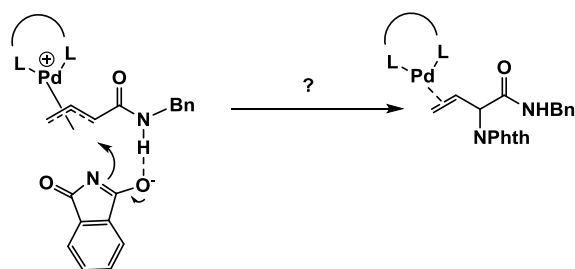
Scheme 6.19

Pd-catalyzed couplings between phthalimide and amides **2a-d**, **3a** and **3d** were carried out using $(C_3H_5PdCl)_2$ as the palladium source, BINAP as the ligand and NaH as base (Table 6.6).
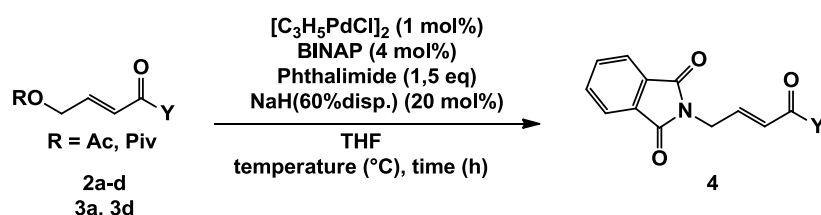
Table 6.6: Pd(0)-catalyzed allylic amination of substrate **2** and **3**

Entry	Substrate	Time (h)	T° (°C)	Yield (%)*
1	2a	24	rt	**4a**:**2a** 1:0.8
2	2a	19	reflux	72
3	2b	17	reflux	43
4	2c	20	reflux	**4c**:**2c** 1:0.75
5	2d	20	reflux	54
6	3a	23	reflux	18
7	3d	3	reflux	83

*Isolated yield

Substrate **2a** was first tested. Carrying out the reaction at room temperature, the desired product **4a** was obtained to some extent (entry 1). However, the conversion was incomplete and separation from starting material turned out to be impossible. Gratifyingly, raising the reaction temperature to reflux of THF improved the yield to 72% yield (entry 2). The same protocol was then applied to the other acetate substrates: for **2b** and **2d**, the corresponding aminated products were obtained in moderate yields (entries 3 and 5), while **2c** gave a mixture of the desired product and starting material (entry 4), which were impossible to separate.

The pivalates **3a** and **3d** led to contrasting results. While the tertiary amide **3a** afforded **4a** in a modest 18% yield (entry 6), the secondary pivalamide **3d** afforded the corresponding phthalate in only 3 hours in **4d** (83%) (entry 7). In any case, the observed reactivity was always at the terminal (γ) position.

Once more, best results were obtained using the secondary amide derivative **2d**, which was thus chosen as the model substrate to study the scope of this allylic amination.

Following the same protocol, reaction of **3d** with *N*-tosyl methyl carbamate as nucleophile gave the aminated product **5d** in 73% yield, while reaction of dimethyl malonate gave **6d** in 28% yield (Scheme 6.20). Again, the *E* configurated aminated products were the only isomers observed.
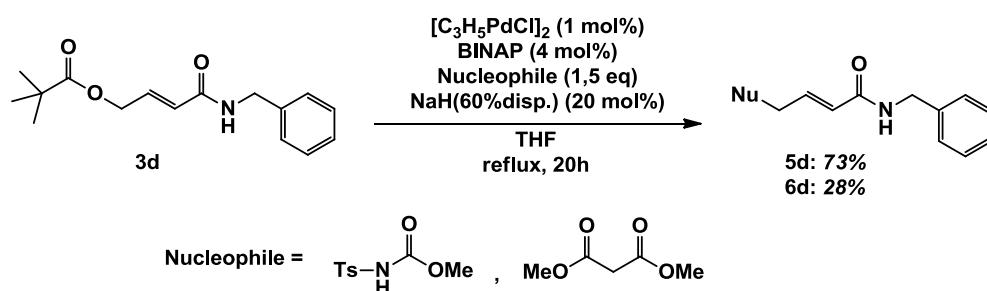
Scheme 6.20

With these promising results in hands, we settled to investigate in more detail the sequential Pd(II)/Pd(0) catalyzed allylic amination.

6.3.5 Sequential Pd(II)/Pd(0) amination

Having obtained satisfactory preliminary results for the oxidative Pd(II)-catalyzed allylic acylation of but-3-enamides, and for the isohypsic Pd(0) catalyzed amination of the resulting allylic esters, we were ready for the last phase of the project: merging of the two protocols in a single synthetic operation. However, such a fine-tuning appeared not trivial. Indeed, although the two protocols share the catalytic use of palladium, their merging implies matching of the acidic oxidizing conditions of the first step with the buffered isohypsic conditions of the second step. To overcome this problem, we decided to use Pd(OAc)$_2$ for both the steps, and a stoichiometric (or a slight sub-stoichiometric) amount of oxidant, so as to obtain a palladium (0) species at the end of the first step, ready to catalyze the latter step.

Furthermore, we decided to minimize the amount of carboxylic acid in the first step, and buffer the medium through the addition of a base, before addition of the nitrogen nucleophile.

We started optimizing the reaction conditions for the acyloxylation step, using **1d** as reference substrate, by varying the amounts of oxidant and carboxylic acid (Table 6.7). Best results were obtained using 1.0

equivalent of oxidant and 20 equivalent of pivalic acid (entry 2). Decreasing the amount of t-BuCO$_2$H from 20 to 10 equivalents brought about a slight decrease of the yield (entry 1), while a further decrease to 5 equivalents caused a serious yield drop (entries 3 and 5).

Conversely, use of sub-stoichiometric amounts of oxidant did not brought about significant yield erosion (entry 4).
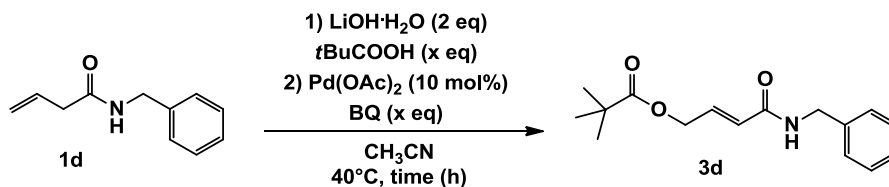
Table 6.7: screening conditions of pivaloylation reaction on substrate **1d**

Entry	BQ (eq)	Acid (eq)	[ ] solvent (M)	Time (h)	Yield (%)*
1	2	10	0.75	20	56
2	1	20	0.75	20	67
3	2	5	0.75	22	32
4	0.95	20	0.75	22	57
5	2	5	0.28	22	28

*Isolated yield

Not unexpectedly, attempts to employ basic conditions for the acetoxylation step met with failure (Table 6.8). In fact, in the case of **1a**, use of AcONa as base brought about only double bond isomerization to **1a'** (entry 1), while employ of LiOH·H$_2$O gave modest yields (entry 2), also in the case of **1d** (entry 3).
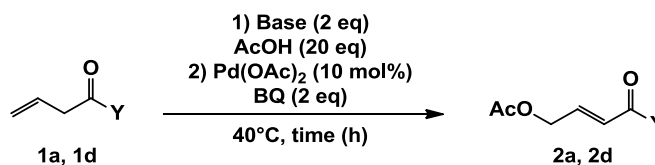
Table 6.8: acetoxylation in basic conditions

Entry	Substrate	Base (2 eq)	Co-Solvent	Time (h)	Yield (%)*
1	**1a**	AcONa	-	19	**1a'**
2	**1a**	LiOH·H$_2$O	-	24	39
3	**1d**	LiOH·H$_2$O	CH$_3$CN	24	26

*Isolated yield

Fine tuning of the real one-pot process was finally tackled. To this purpose, we selected pivaloylation of the secondary butenamide **1d** followed by phthalation, as these options gave the best results in each the individual steps (Table 6.9).
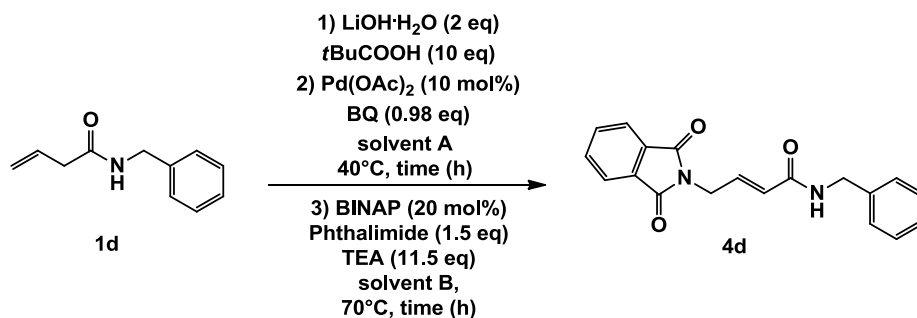
Table 6.9: sequential Pd(II)/Pd(0) amination

Entry	Solvent A	Solvent B	Time (I-II, h)	Yield (%)*
1[a]	-	THF	2-22	Only **3d** and **1d**
2[b]	CH₃CN	CH₃CN	6-20	Only **3d** and **1d**
3	CH₃CN	CH₃CN	7-16	41
4	CH₃CN	CH₃CN	18-24	40
5	CH₃CN (70°C)	CH₃CN	18-24	33
6[c]	CH₃CN	CH₃CN	24-24	30
7	THF	THF	20-3	30
8	-	THF	22-4	35
9	CH₃CN	THF	17-24	40

[a] The reaction was performed without BINAP and TEA; [b] the reaction was performed without TEA; [c] reaction performed with 1 mol% of [C₃H₅PdCl]₂.
* Isolated yield

The ligand and the base were required for the success of the reaction (entries 1 and 2). No improvement was detected by either extending the reaction time (entries 3 and 4), or by carrying out the reaction at higher temperature (entry 5), or by adding a new Pd(0) source in the second step (entry 6). Regarding the solvent employed in the reaction, the use of CH_3CN in both steps led to obtain **4d** in 40% yields (entries 3 and 4); THF decreased the overall yield, but accelerated the second step (entries 7 and 8). Employment of CH_3CN in the first step and THF in the second step afforded compound **4d** in 40% yield, in relatively long times (entry 9).

This optimization was continued in the laboratory by Daria Diamante during her PhD and the best

conditions are reported in Scheme 6.21.
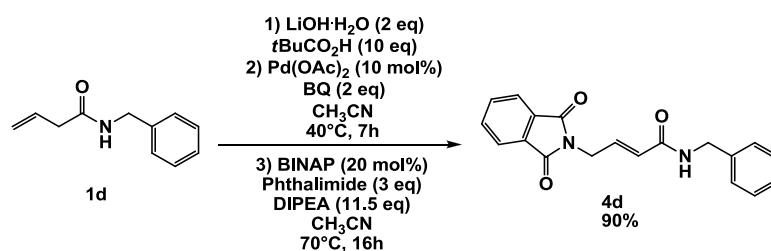
Scheme 6.21

6.4 Conclusions

In conclusion, we developed an original Pd-catalyzed dehydrogenative amination of but-3-enamides.
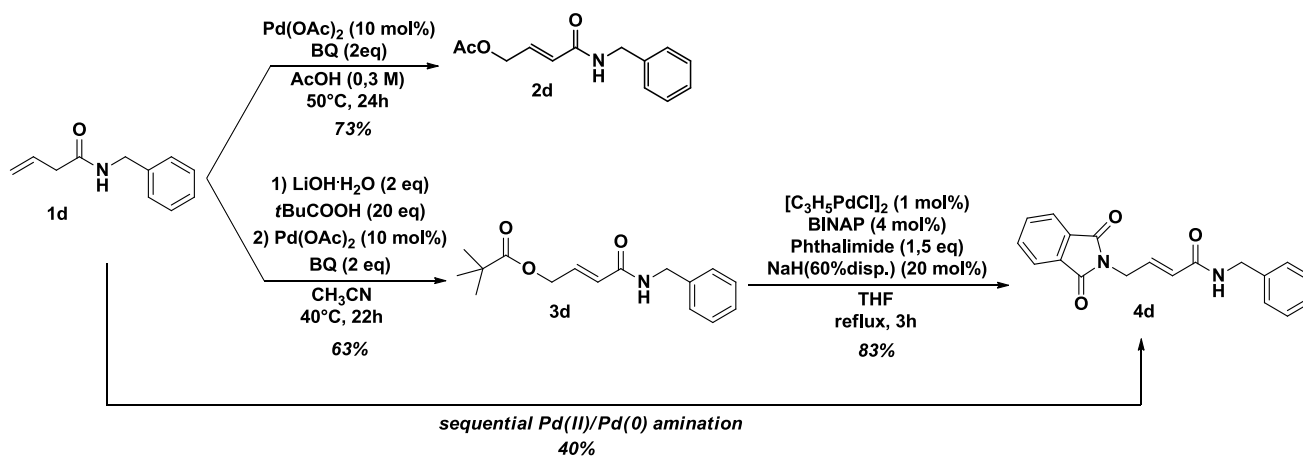
Scheme 6.22

This transformation is best accomplished via a first oxidative PdX_2 catalyzed allylic acetylation or pivaloylation of the secondary enamide **1d** to give the allyic acetate **2d** (73% y), or pivalate ester (63% y) **3d**, followed by the isohypsic Pd(0)-catalyzed phthalation of the pivalate to give the allylic phthalate **4d** (83% y) (Scheme 6.21). Extension to the amination of pivalate ester **3d** with methyl *N*-tosyl carbamate is also possible (73% y). In all the cases studied, total selectivity for the amination at the γ-position with formation of the *E*-configured product was observed. Finally, merging of the two Pd-catalyzed steps into a more convenient sequential one-pot procedure could be developed, although at expenses of some yield erosion (40% y).

6.5 *EXPERIMENTAL SECTION*

6.5.1 General information

Reagents and chemicals were purchased from commercial sources and used as received. IR spectra were recorded on a Bruker Tensor 27 (ATR diamond) spectrophotometer and only the strongest or the structurally most important peaks were listed. NMR ^{1}H, ^{13}C, spectra were recorded at room temperature on 400 and 100 MHz, respectively, using a Bruker AVANCE 400 spectrometer equipped with a BBFO probe. Chemical shifts are reported in ppm, using, for ^{1}H and ^{13}C of deuterated solvent, the solvent residual peak as internal standard references. Coupling constants (J) are reported in Hertz (Hz). Thin layer chromatographies (TLC) were performed on Merck silica gel 60 F 254 and revealed with a ultra-violet lamp (λ = 254 nm). Flash chromatography was conducted on silica Geduran® Si 60 Å (40 – 63 μm). High resolution mass spectrometry was performed on a Thermo Fisher Scientific LTQ Orbitrap (ESI). Melting points were measured using a SMP3 Stuart Scientific melting point apparatus.

6.5.2 Synthetic procedures

I. *Starting materials 1*

- *Substrate 1a: N-methoxy-N-methylbut-3-enamide*
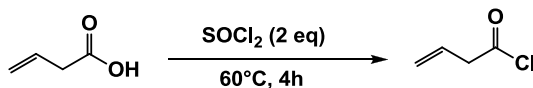
Thionyl chloride (2 equiv.) was added dropwise to the 3-butenoic acid (1 equiv.). The mixture was stirred for 4 hours at 60 °C, carefully evaporated and immediately used without purification.
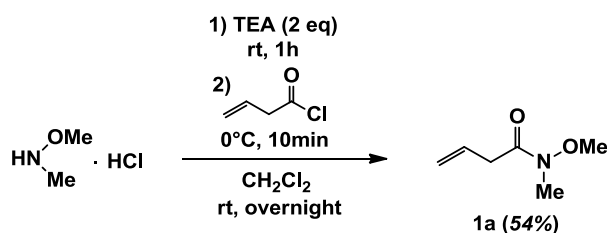
A mixture of N,O-dimethylhydroxylamine hydrochloride (1 equiv., 604 mg, 6.2 mmol) and triethylamine (2 equiv., 12.4 mmol, 1.72 mL) in dichloromethane (30 mL) was stirred for 2 hours at room temperature; then, at 0 °C, the but-3-enoyl chloride freshly prepared (1 equiv., 648 mg, 6.2 mmol) was added dropwise and the mixture was stirred for 10 minutes at 0 °C, then at rt overnight.

The mixture was hydrolyzed with a HCl 1N solution, then with a saturated aqueous NaHCO$_3$ solution and water. The organic layer was extracted and dried over MgSO$_4$, filtered and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography (eluent: AcOEt/CycloHexane 6:4) to afford the amide **1a** in 54% yield (430 mg, 3.33 mmol).

Analytical data:
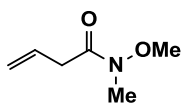
C$_6$H$_{11}$NO$_2$
M.W.: 129,0790

Pale yellow oil

^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.18 (s, 3H), 3.23 (d, 2H, *J* = 6.7 Hz), 3.69 (s, 3H), 5.15-5.16 (m, 1H), 5.18-5.19 (m, 1H), 5.92-6.02 (m, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 25.2, 37.2, 61.3, 118.1, 131.2, 172.4.

IR (cm^{-1}) υ = 2969, 1664, 1381, 1176, 1002 cm^{-1}.

HRMS (ESI) *m/z* calcd for C$_6$H$_{11}$NNaO$_2$ [M+Na]$^+$ 152.0687, found 152.0682.

- *Substrate 1b: N-(2-methoxyphenyl)-N-propylbut-3-enamide*

1b (70%)
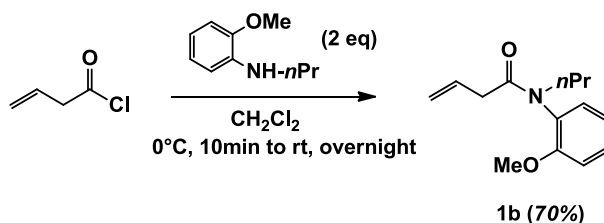
To a solution of 2-methoxy-*N*-propylaniline (2 equiv., 316 mg, 1.91 mmol) in dichloromethane (5 mL), at 0 °C, but-3-enoylchloride freshly prepared (1 equiv., 100 mg, 0.96 mmol) was added dropwise. The mixture was stirred for 10 minutes at 0 °C, then at rt overnight.

The mixture was hydrolyzed with a HCl 1N solution, then with a saturated aqueous $NaHCO_3$ and water. The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography (eluent: AcOEt/CycloHexane 2:8) to afford the amide **1b** in 70% yield (158 mg, 68.2 mmol).

Analytical data:

$C_{14}H_{19}NO_2$
M.W.: 233,1416
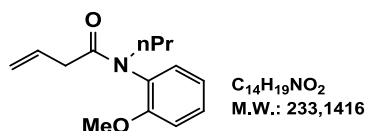
Brown oil

^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.87 (t, 3H, *J* = 7.4 Hz), 1.48 (q, 2H, *J* = 7.5 Hz), 2.77 (dd, 2H, *J* = 6.8, 1.2 Hz), 3.33-3.39 (m, 1H), 3.75-3.80 (m, 1H), 3.82 (s, 3H), 4.86 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.01 (dd, 1H, *J* = 10.2, 1.5 Hz), 5.86-5.93 (m, 1H), 6.96-6.98 (m, 2H), 7.11 (dd, 1H, *J* = 8.1, 1.7 Hz) 7.33 (td, 1H, *J* = 8.2, 1.6 Hz).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 11.5, 21.1, 39.2, 50.1, 55.5, 111.9, 117.2, 120.9, 129.5, 130.3, 131.1, 132.5, 155.6, 171.5.

IR (cm^{-1}) υ: 2962, 1652, 1246, 1044, 909, 751.

HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NNaO_2$ [M+Na]$^+$: 256.1313, found 256.1308.

- *Substrate 1c: 3-(But-3-enoyl)oxazolidin-2-one*
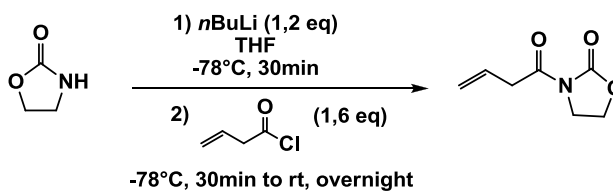
n-BuLi (1.25 M, 2.2 mL, 2.76 mmol) was added dropwise to a stirred solution of 2-oxazolidinone (1 equiv., 200 mg, 2.3 mmol) in THF (12 mL) at -78 °C, under Argon atmosphere. The mixture was stirred for 30

minutes, then but-3-enoylchloride freshly prepared (1.6 equiv., 384 mg, 3.7 mmol) was added at -78 °C. The mixture was stirred at this temperature for 30 minutes, then allowed to warm up to rt and stirred overnight. Gaulbert salt was added to the mixture (10 equiv., 7.410 g, 0.023 mmol) and stirred for 15 minutes, after the mixture was filtered and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography (eluent: AcOEt/CycloHexane 6:4) to afford the amide **1c** in 45% yield (161 mg, 1.04 mmol).

Analytical data:
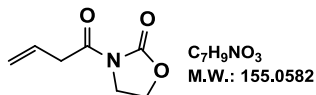
Yellow oil

^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.71 (dt, 2H, J = 9.0, 1.7 Hz), 4.02 (t, 2H, J = 11.1 Hz), 4.41 (t, 2H, J = 11.1 Hz), 5.17-5.19 (m, 1H), 5.21-5.24 (m, 1H), 5.90-6.04 (m, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 39.9, 42.6, 62.2, 119.3, 129.8, 153.6, 171.4.

IR (cm^{-1}) υ: 2923, 1766, 1694, 1641.

HRMS (ESI) *m/z* calcd for C$_7$H$_9$NNaO$_3$ [M+Na]$^+$: 178.0480, found 178.0475.

- ***Substrates 1d and 1e***

General procedure 1 for the synthesis
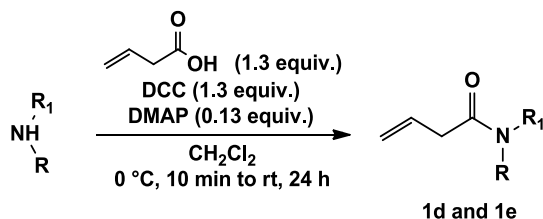
Under Argon atmosphere, at 0 °C, DCC (1.3 equiv.) was added to a stirred solution of corresponding amine (1.0 equiv.), DMAP (0.13 equiv.) and 3-butenoic acid (1.3 equiv.) in CH$_2$Cl$_2$ (0.2M). The reaction mixture was stirred for 10 minutes at 0 °C, then at rt for 24 hours.

The precipitate was filtered off and washed with CH$_2$Cl$_2$ (25 mL). Then the organic layer was hydrolyzed with saturated aqueous NaHCO$_3$, extracted and dried over MgSO$_4$ and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography to afford the corresponding amide **1**.

Analytical data:

_N_-Benzyl-3-butenamide (1d)

$C_{11}H_{13}NO$
M.W.: 175,0997
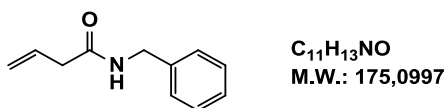
Following *general procedure 1* with benzylamine (1 equiv., 1.0 g, 9.3 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1d** in quantitative yield (1.9 g, 10.8 mmol).

White solid

^{1}H NMR (CDCl₃, 400 MHz): δ 3.09 (td, 2H, *J* = 1.3, 7.2 Hz), 4.48 (d, 2H, *J* = 5.7 Hz), 5.23-5.29 (m, 2H), 5.91-6.07 (m, 2H), 7.29-7.40 (m, 5H).

These spectroscopic data are in good agreement with those reported in the literature.[142]

_N_-methyl-_N_-(pyridin-2-yl)but-3-enamide (1e)

$C_{10}H_{12}N_2O$
M.W.: 176.0950
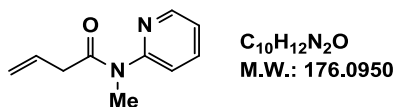
Following *general procedure 1* with 2-(methylamino)pyridine (1 equiv., 2.5 mmol, 0.26 mL). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CH₂Cl₂ 7:3) to afford **1e** in 54% yield (235 mg, 1.33 mmol).

Purple oil

^{1}H NMR (CDCl₃, 400 MHz): δ 3.11 (d, 2H, *J* = 6.6 Hz), 3.35 (s, 3H), 4.97 (d, 1H, *J* = 17.2 Hz), 5.06 (dd, 1H, *J* = 10.2, 1.04 Hz), 5.88-5.96 (m, 1H), 7.16-7.20 (m, 1H), 7.26-7.28 (m, 1H), 7.73 (td, 1H, *J* = 8.0, 1.9 Hz), 8.47 (dd, 1H, *J* = 4.7, 1.0 Hz).

^{13}C NMR (CDCl₃, 100 MHz): δ 35.6, 40.0, 117.9, 120.7, 122.0, 131.7, 138.3, 149.0, 156.1, 171.3.

IR (cm⁻¹) υ: 2951, 1658, 1585, 1363, 1135, 915, 786.

HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_2NaO$ [M+Na]⁺: 199.0847, found 199.0842.

II. *Acyloxylated compounds 2 and 3*

- *Acetoxylated compounds 2a, 2b, 2d*

General procedure 2:
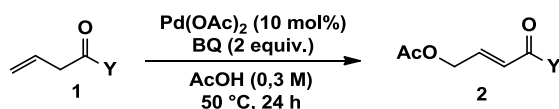
A mixture of the corresponding amide **1** (1 equiv.), Pd(OAc)$_2$ (10 mol%), BQ (2 equiv.) in AcOH (0.3 M) was stirred for 24 hours at 50 °C.

The reaction was hydrolyzed with brine, filtered and washed with Et$_2$O. The liquid phase was extracted with Et$_2$O, then the organic layer was washed with water, extracted, dried over MgSO$_4$ and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography (eluent: AcOEt/CycloHexane 4:6) to afford the corresponding acetoxylated compound **2**.

Analytical data:

(E)-4-(methoxy(methyl)amino)-4-oxobut-2-en-1-yl acetate (2a)

C$_8$H$_{13}$NO$_4$
M.W.: 187,0845
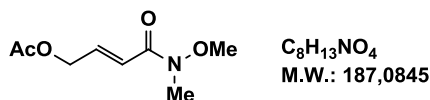
Following *general procedure 2* with amide **1a** (1 equiv., 118 mg, 0.91 mmol) to afford **2a** in 54% yield (93mg, 0.5mmol).

Brown oil

^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.11 (s, 3H), 3.25 (s, 3H), 3.70 (dd, 2H, J = 5.0, 1.7 Hz), 4.76 (dd, 2H, *J* = 5.0, 1.7 Hz), 6.60 (d, 1H, *J* = 15.5 Hz), 6.94 (dt, 1H, *J* = 15.5, 5.0 Hz).

^{13}C NMR (CDCl$_3$, 75 MHz): δ 20.9, 32.5, 61.9, 63.3, 120.3, 139.7, 166.0, 170.5.

IR (cm^{-1}) υ: 2939, 1739, 1668, 1636, 1377, 1220.

HRMS (ESI) *m/z* calcd for C$_8$H$_{13}$NNaO$_4$ [M+Na]$^+$: 210.0742, found 210.0737.

(E)-4-((2-methoxyphenyl)(propyl)amino)-4-oxobut-2-en-1-yl acetate (2b)

C$_{16}$H$_{21}$NO$_4$
M.W.: 291,1471
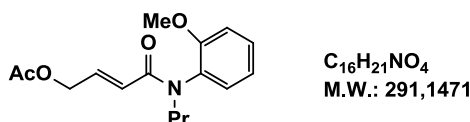
Following *general procedure 2* with amide **1b** (1 equiv., 60 mg, 0.26 mmol) to afford **2b** in 80% yield (61 mg, 0.21 mmol).

Brown oil

^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.88 (t, 3H, *J* = 7.4 Hz), 1.53 (q, 2H, *J* = 7.5 Hz), 1.93 (s, 3H), 3.44 (dt,

1H, *J* = 13.2, 7.5 Hz), 3.80 (s, 3H), 3.86 (dt, 1H, *J* = 13.3, 7.7 Hz), 4.56 (dd, 2H, *J* = 5.2, 1.8 Hz), 5.77 (d, 1H, *J* = 15.2 Hz), 6.78-6.85 (m, 1H), 6.97-6.99 (m, 2H), 7.10 (dd, 1H, *J* = 8.1, 1.7 Hz), 7.34 (td, 1H, *J* = 8.0, 1.8 Hz).

¹³C NMR (CDCl₃, 100 MHz): δ 11.5, 20.7, 21.1, 50.2, 55.6, 63.3, 112.1, 116.3, 120.9, 123.3, 129.6, 130.3, 137.4, 155.7, 165.6, 170.4.

IR (cm⁻¹) υ: 2963, 1744, 1669, 1631, 1216, 1024, 752.

HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NNaO_4$ [M+Na]⁺: 314.1368, found 314.1363.

(*E*)-4-(Benzylamino)-4-oxobut-2-en-1-yl acetate (2d)
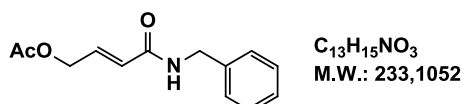
Following *general procedure 2* with **1d** (1 equiv., 105 mg, 0.6 mmol) to afford **2d** in 73% yield (102 mg, 0.44 mmol).

Brown solid, **mp:** 93-95 °C.

¹H NMR (DMSO-d⁶, 400 MHz): δ 2.07 (s, 3H), 4.33 (d, 2H, *J* = 5.9 Hz), 4.69 (dd, 2H, *J* = 4.7, 1.8 Hz), 6.13 (dt, 1H, *J* = 15.5, 1.8 Hz), 6.66 (dt, 1H, *J* = 15.5, 4.7 Hz), 7.22-7.34 (m, 5H), 8.55 (t, 1H, *J* = 5.6 Hz).

¹³C NMR (DMSO-d⁶, 100 MHz): δ 20.5, 42.1, 62.5, 124.8, 126.8, 127.3, 128.3, 136.2, 139.2, 164.1, 169.9.

IR (cm⁻¹) υ: 3230, 1732, 1671, 1619, 1223, 966, 732.

HRMS (ESI) *m/z* calcd for $C_{13}H_{15}NNaO_3$ [M+Na]⁺: 256.0950, found 256.0944.

- *Acetoxylated compound 2c: (E)-4-oxo-4-(2-oxooxazolidin-3-yl)but-2-en-1-yl acetate*
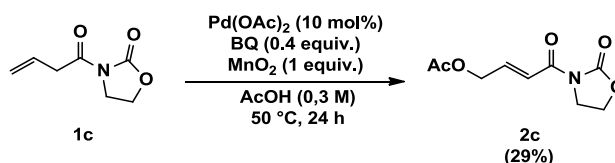
A mixture of the amide **1c** (1 equiv., 110 mg, 0.71 mmol), Pd(OAc)₂ (10 mol%, 16 mg, 0.071 mmol), BQ (0.4 equiv., 30 mg, 0.28 mmol) and MnO₂ (1 equiv., 62 mg, 0.71 mmol) in AcOH (3 mL) was stirred for 24 hours at 50 °C. The reaction was hydrolyzed with brine, filtered and washed with Et₂O. The liquid phase was extracted with Et₂O, then the organic layer was washed with water, extracted, dried over MgSO₄ and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography (eluent: AcOEt/CycloHexane 1:1) to afford the corresponding acetoxylated compound **2c** in 29% yield (44 mg, 0.21 mmol).

Analytical data:

AcO... C$_9$H$_{11}$NO$_5$
M.W.: 213,0637
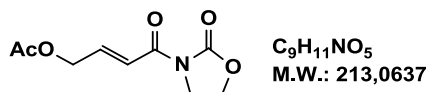
Yellow oil

^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.12 (s, 3H), 4.06 (t, 2H, *J* = 8.3 Hz), 4.42 (t, 2H, *J* = 8.7 Hz), 4.79 (dd, 2H, *J* = 4.6, 2.0 Hz), 7.09 (dt, 1H, *J* = 15.6, 4.6 Hz), 7.42 (dt, 1H, *J* = 15.5, 2.0 Hz).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 20.8, 42.7, 62.2, 63.0, 120.7, 143.1, 153.5, 164.5, 170.5.

IR (cm^{-1}) υ: 2945, 1767, 1730, 1689, 1645.

HRMS (ESI) *m/z* calcd for C$_9$H$_{11}$NNaO$_5$ [M+Na]$^+$: 236.0535, found 236.0529.

- *Pivaloxylated compounds 3a-3d*

General procedure 3:

A) LiOH.H$_2$O (2 equiv.)
tBuCOOH (10 equiv.)
B) Pd(OAc)$_2$ (10 mol%)
BQ (2 equiv.)
─────────────
CH$_3$CN
40°C, t (h)

A flask was charged with LiOH·H$_2$O (2 equiv.) and tBuCOOH (10 equiv.) and the mixture was heated at 40 °C for 10 minutes. Then BQ (2 equiv.), Pd(OAc)$_2$ (10 mol%) and CH$_3$CN (0.2 M) were added. The mixture was stirred for 15 minutes at rt, then the corresponding amide **1** (1 equiv.) was added. The mixture was stirred at 40°C until the completion of the reaction.

After cooling to rt, the mixture was filtered through a SiO$_2$ pad and washed with Et$_2$O (40 mL).

NaOH (2M) was added and the mixture was stirred for 15 minutes. The organic phase was hydrolyzed with H$_2$O, extracted with Et$_2$O, dried over MgSO$_4$, filtered and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography to afford the corresponding pivaloxylated product **3**.

Analytical data:

(*E*)-4-(methoxy(methyl)amino)-4-oxobut-2-en-1-yl pivalate (3a)

C$_{11}$H$_{19}$NO$_4$
M.W.: 229,1314
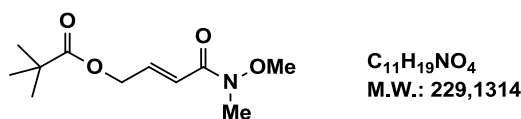
Following *general procedure 3* with amide **1a** (1 equiv., 60 mg, 0.46 mmol) for 26 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **3a** in 48% yield (51 mg, 0.22 mmol).

Yellow oil

¹H NMR (CDCl₃, 400 MHz): δ 1.22 (s, 9H), 3.23 (s, 3H), 3.68 (s, 3H), 4.74-4.75 (m, 2H), 6.58 (d, 1H, J = 15.6 Hz), 6.91-6.96 (m, 1H).

¹³C NMR (CDCl₃, 100 MHz): δ 27.3, 32.5, 39.0, 61.8, 63.1, 119.6, 140.2, 166.1, 177.8.

IR (cm⁻¹) υ: 2971, 1730, 1669, 1633, 1364.

HRMS (ESI) *m/z* calcd for $C_{11}H_{19}NNaO_4$ [M+Na]⁺: 252.1212, found 252.1206.

(*E*)-4-((2-methoxyphenyl)(propyl)amino)-4-oxobut-2-en-1-yl pivalate (3b)

$C_{19}H_{27}NO_4$
M.W.: 333,1940

Following *general procedure 3* with amide **1b** (1 equiv., 103 mg, 0.44 mmol) for 18 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 4:6) to afford **3b** in 48% yield (72 mg, 0.22 mmol).

Purple oil

¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, 3H, J = 7.5 Hz), 1.02 (s, 9H), 1.52 (q, 2H, J = 7.5 Hz), 3.39-3.46 (m, 1H), 3.79 (s, 3H), 3.81-3.87 (m, 1H), 4.58 (dd, 2H, J = 4.4, 1.9 Hz), 5.79 (dt, 1H, J = 15.3, 1.9 Hz), 6.83 (dt, 1H, J = 15.2, 4.3 Hz), 6.94-6.97 (m, 2H), 7.08-7.11 (m, 1H), 7.31 (td, 1H, J = 7.6, 1.7 Hz).

¹³C NMR (CDCl₃, 100 MHz): δ 11.5, 21.1, 27.2, 38.8, 50.1, 55.7, 62.9, 112.1, 120.9, 121.9, 129.5, 130.3, 130.7, 137.9, 155.7, 165.6, 177.7.

IR (cm⁻¹) υ: 2970, 1731, 1670, 1632, 1139, 1024, 751.

HRMS (ESI) *m/z* calcd for $C_{19}H_{27}NNaO_4$ [M+Na]⁺: 356.1838, found 356.1832.

(*E*)-4-oxo-4-(2-oxooxazolidin-3-yl)but-2-en-1-yl pivalate (3c)

$C_{12}H_{17}NO_5$
M.W.: 255,1107

Following *general procedure 3* with amide **1c** (1 equiv., 105 mg, 0.67 mmol) for 22 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 6:4) to afford **3c** in 15% yield (26 mg, 0.10 mmol).

Yellow oil

¹H NMR (CDCl₃, 400 MHz): δ 1.24 (s, 9H), 4.06 (t, 2H, J = 8.3 Hz), 4.42 (t, 2H, J = 8.3 Hz), 4.79 (dd, 2H, J = 4.2, 2.1 Hz), 7.11 (dt, 1H, J = 15.5, 4.2 Hz), 7.45 (dt, 1H, J = 15.5, 2.0 Hz).
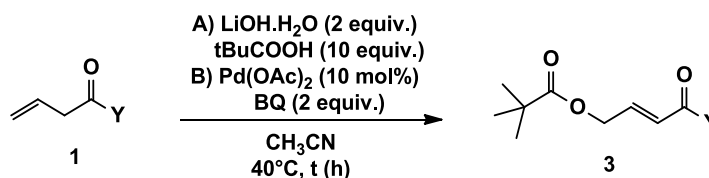
¹³C NMR (CDCl₃, 100 MHz): δ 27.3, 39.0, 62.2, 62.8, 120.0, 143.7, 153.5, 164.5, 178.0.

IR (cm⁻¹) υ: 2976, 1771, 1728, 1682, 1647.

HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NNaO_5$ [M+Na]⁺: 278.1004, found 278.0999.

(*E*)-4-(benzylamino)-4-oxobut-2-en-1-yl pivalate (3d)

$C_{16}H_{21}NO_3$
M.W.: 275,1521
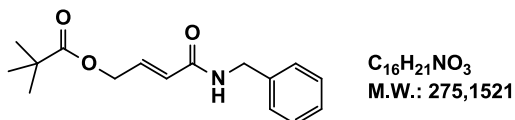
Following *general procedure 3* with **1d** (1 equiv., 300 mg, 1.70 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **3d** in 98% yield (458 mg, 1.67 mmol).

White solid, **mp:** 66-68 °C

¹H NMR (CDCl₃, 400 MHz): δ 1.23 (s, 9H), 4.50 (d, 2H, *J* = 5.7 Hz), 4.69 (dd, 2H, *J* = 4.7, 1.8 Hz), 6.02 (d, 1H, *J* = 15.4 Hz), 6.15 (br s, 1H), 6.84-6.90 (m, 1H), 7.26-7.35 (m, 5H).

¹³C NMR (CDCl₃, 100 MHz): δ 27.3, 38.9, 43.8, 62.9, 124.3, 127.7, 128.0, 128.8, 137.9, 138.1, 165.0, 178.0.

IR (cm⁻¹) υ: 3247, 2968, 1727, 1678, 1629, 1278, 1159.

HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NNaO_3$ [M+Na]⁺: 298.1419, found 298.1414.

III. *Aminated products*

- *Compounds obtained from acyloxylated products*

General procedure 4:
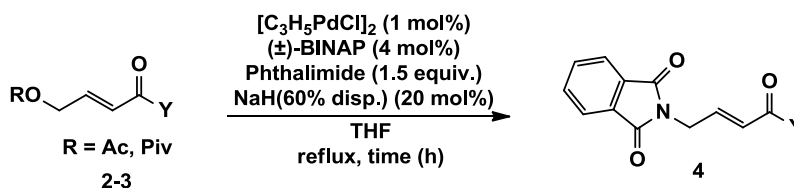
The flask was charged with the corresponding substrate **2** or **3** (1 equiv.), [C₃H₅PdCl]₂ (1 mol%), (±)-BINAP (4 mol%), Phthalimide (1.5 equiv.), NaH (60% dispersion in mineral oil) and THF (1 mL) and the mixture was stirred at reflux for the time required to complete the reaction.

The solution was filtered through a small plug of silica gel, washed with AcOEt and concentrated at reduced pressure.

The crude product was purified by silica gel column chromatography to afford the corresponding aminated compound **4**.

Analytical data:

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-methoxy-*N*-methylbut-2-enamide (4a)

$C_{14}H_{14}N_2O_4$
M.W.: 274,0954
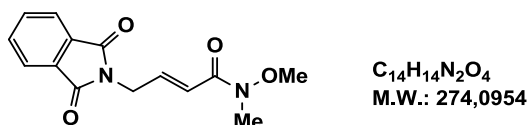
Following *general procedure 4* with the acetoxylated compound **2a** (1 equiv., 100 mg, 0.53 mmol) for 19 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4a** in 72% yield (104 mg, 0.37 mmol).
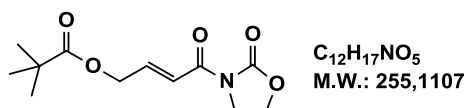
Following *general procedure 4* with the pivaloxylated compound **3a** (1 equiv., 51 mg, 0.22 mmol) for 23 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4a** in 18% yield (11 mg, 0.040 mmol).

Yellow solid, **mp:** 139-140 °C

^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.24 (s, 3H), 3.67 (s, 3H), 4.47 (d, 2H, *J* = 4.7 Hz), 6.60 (d, 1H, *J* = 15.4 Hz), 6.88 (dt, 1H, *J* = 15.4, 5.9 Hz), 7.71-7.76 (m, 2H), 7.84-7.89 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 32.3, 38.8, 62.0, 121.7, 123.6, 132.2, 134.3, 139.1, 167.8.

IR (cm^{-1}) υ: 2973, 1768, 1710, 1664, 1628, 1355.

HRMS (ESI) *m/z* calcd for $C_{14}H_{14}N_2NaO_4$ [M+Na]$^+$: 297.0851, found 297.0846.

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(2-methoxyphenyl)-*N*-propylbut-2-enamide (4b)

$C_{22}H_{22}N_2O_4$
M.W.: 378.1580

Following *general procedure 4* with the acetoxylated compound **2b** (1 equiv., 88 mg, 0.30 mmol) for 17 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 4:6) to afford **4b** in 54% yield (63 mg, 0.17 mmol).

Brown solid, **mp:** 108-110 °C

^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.84 (t, 3H, *J* = 7.4 Hz), 1.45 (q, 2H, *J* = 7.5 Hz), 3.39-3.46 (m, 1H), 3.72-3.80 (m, 4H), 4.23 (dd, 2H, *J* = 5.7, 1.6 Hz), 5.67 (dt, 1H, *J* = 15.2, 1.6 Hz), 6.72 (dt, 1H, *J* = 15.2, 5.7 Hz), 6.81-6.85 (m, 2H), 7.01-7.03 (m, 1H), 7.15 (td, 1H, *J* = 8.1, 1.7 Hz), 7.68-7.70 (m, 2H), 7.76-7.78 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 11.4, 21.0, 38.6, 50.1, 55.5, 111.8, 120.7, 123.3, 124.2, 129.3, 130.1, 130.4, 132.0, 134.1, 136.4, 155.6, 165.5, 167.5.

IR (cm^{-1}) υ: 2971, 1767, 1711, 1670, 1640, 1384, 1021, 747.

HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_2NaO_4$ [M+Na]$^+$: 401.1477, found 401.1472.

(*E*)-*N*-benzyl-4-(1,3-dioxoisoindolin-2-yl)but-2-enamide (4d)

C$_{19}$H$_{16}$N$_2$O$_3$
M.W.: 320,1161
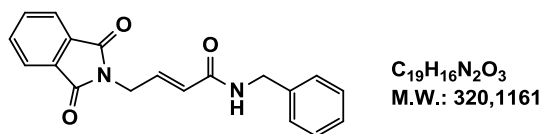
Following *general procedure 4* with the acetoxylated compound **2d** (1 equiv., 100 mg, 0.43 mmol) for 20 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4d** in 54% yield (75 mg, 0.23 mmol).

Following *general procedure 4* with the pivaloxylated compound **3d** (1 equiv., 100 mg, 0.36 mmol) for 3 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4d** in 83% yield (98 mg, 0.3 mmol).

White solid, **mp:** 184-185 °C

^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 4.28 (d, 2H, J = 5.9 Hz), 4.33 Hz (dd, 2H, *J* = 4.6, 1.9 Hz), 5.96 (dt, 1H, *J* = 15.5, 1.8 Hz), 6.68 (dt, 1H, *J* = 15.4, 4.6 Hz), 7.20-7.22 (m, 3H), 7.27-7.29 (m, 2H), 7.85-7-92 (m, 4H), 8.39 (t, 1H, *J* = 5.7 Hz).

^{13}C NMR (DMSO-d$_6$, 100 MHz) δ 38.0, 42.1, 123.2, 124.4, 126.8, 127.4, 128.3, 131.6, 134.5, 136.3, 139.1, 164.0, 167.4.

IR (cm^{-1}) υ = 3282, 1771, 1701, 1629, 977, 720.

HRMS (ESI) *m/z* calcd for C$_{19}$H$_{16}$N$_2$NaO$_3$ [M+Na]$^+$ 343.1059, found 343.1053.

- **General procedure for the introduction of others nucleophiles on compound 3d**

General procedure 5
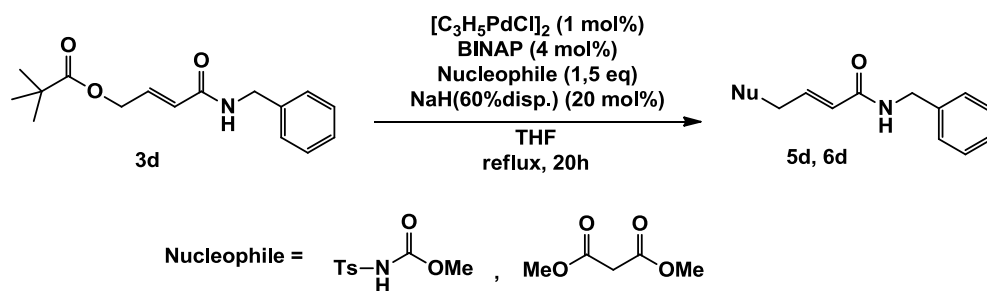
The flask was charged with substrate **3d** (1 equiv.), [C$_3$H$_5$PdCl]$_2$ (1 mol%), (±)-BINAP (4 mol%), nucleophile (methyl tosylcarbamate, dimethyl malonate) (1.5 equiv.), NaH (60% dispersion in mineral oil) (20 mol%) and THF (0.2M) and the mixture was stirred at reflux for 20h.

The solution was filtered through a small plug of silica gel, washed with AcOEt and concentrated at reduced pressure.

Flash chromatography (AcOEt/CycloHexane) led to the compounds **5d, 6d**.

Analytical data:

(*E*)-methyl (4-(benzylamino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (5d)
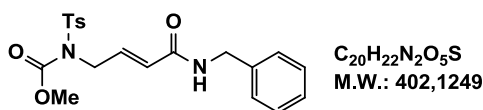
$C_{20}H_{22}N_2O_5S$
M.W.: 402,1249

Following *general procedure 5* with the pivaloxylated compound **3d** (1 equiv., 100 mg, 0.36 mmol) and methyl tosylcarbamate (1.5 equiv., 217 mg, 0.54 mmol) for 20 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **5d** in 73% yield (105 mg, 0.26 mmol).


White solid, **mp** 145-146°C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.41 (s, 3H), 3.64 (s, 3H), 4.34 (d, 2H, *J* = 5.9 Hz), 4.53 (dd, 2H, *J* = 5.2, 1.5 Hz), 6.12 (dt, 1H, *J* = 15.4, 1.5 Hz), 6.64 (dt, 1H, *J* = 15.4, 5.2 Hz), 7.23-7.28 (m ,3H), 7.32-7.35 (m, 2H), 7.42 (d, 2H, *J* = 8.0 Hz), 8.64 (t, 1H, *J* = 5.9 Hz).

^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.0, 42.2, 47.4, 54.1, 125.7, 126.8, 127.4, 128.0, 129.6, 135.8, 136.9, 139.3, 144.8, 151.9, 164.0.

IR (cm^{-1}) υ = 3317, 1737, 1673, 1634, 1440, 1165, 981, 700.

HRMS (ESI) calcd for $C_{20}H_{22}N_2NaO_5S$ [M+Na]$^+$ 425.1147, found 425.1142.

(*E*)-dimethyl 2-(4-(benzylamino)-4-oxobut-2-en-1-yl)malonate (6d):
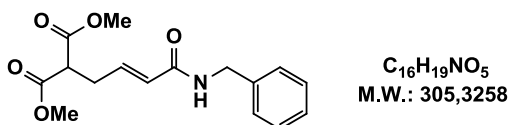
$C_{16}H_{19}NO_5$
M.W.: 305,3258

Following *general procedure 5* with the pivaloxylated compound **3d** (1 equiv., 100 mg, 0.36 mmol) and dimethyl malonate (1.5 equiv., 165 mg, 0.54 mmol) for 20 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 4:6) to afford **6d** in 28% yield (31 mg, 0.10 mmol).

White solid, **mp** 77-78°C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.63 (td, 2H, *J* = 7.3, 1.2 Hz), 3.66 (s, 6H), 3.74 (t, 1H, *J* = 7.4 Hz), 4.31 (d, 1H, *J* = 5.9 Hz), 5.99 (d, 1H, *J* = 15.4 Hz), 6.57 (dt, 1H, *J* = 15.2, 7.1 Hz), 7.23-7.25 (m, 3H), 7.29-7.33 (m, 2H), 8.46 (t, 1H, *J* = 5.8 Hz).

^{13}C NMR (DMSO-d_6, 100 MHz) δ 30.5, 42.1, 49.9, 52.4, 126.5, 126.8, 127.3, 128.2, 138.0, 139.4, 164.3, 168.3.

IR (cm^{-1}) υ = 3284, 2952, 1729, 1667, 1628, 1543, 982, 1014, 746.

HRMS (ESI) calcd for $C_{16}H_{19}NNaO_5$ [M+Na]$^+$ 328.1161, found 328.1155.

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