DEVELOPMENT OF A NEW CLASS OF ATROPISOMERS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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To my family
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<td>Ar</td>
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<tr>
<td>Ax</td>
<td>Axial</td>
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<tr>
<td>B$_2$(cat)$_2$</td>
<td>Dicatechol-diborane</td>
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<td>BINAP</td>
<td>2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl</td>
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<td>1,1'-Bi-2-naphthol</td>
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<td>Bn</td>
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<td>tert-Butylcarbonyl</td>
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<td>Tf</td>
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<tr>
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<td>Tetrahydrofuran</td>
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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

DEVELOPMENT OF A NEW CLASS OF ATROPISOMERS

By

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Chair: Aaron Aponick
Major: Chemistry

The design of new chiral ligands is on the cutting edge of organic synthesis. In particular, atropisomeric ligands have been demonstrated to be very successful in asymmetric catalysis; however, the majority of axially chiral biaryl ligands such as BINAP are comprised of six-membered aromatic rings. The presence of five-membered heteroaromatics in chiral biaryl compounds are rare due to larger bond angles and, in consequence, smaller barriers to rotations. Chiral biaryls with five-membered rings have not been explored in asymmetric catalysis, but should offer significant advantages. In this context, creative new atropisomeric ligand scaffolds with smaller ring sizes should advance the field.

In this dissertation, a novel strategy towards the design of chiral ligands is described, which allows the synthesis of atropisomeric ligands containing a five membered ring in the chiral biaryl backbone. At the outset, we aimed to design a new system in which the barrier to rotation of a biaryl bond is increased due to the decrease of the ground state energy of enantioconformers. In general, the presence of sterically demanding groups ortho to the atropisomeric axis are employed to increase the barrier to rotation, but to the best of our knowledge the simple concept of ground state stabilization reported herein has not been explored. Initial studies were aimed at determining the feasibility of this strategy and simple model compounds were designed to
undergo intramolecular π-stacking. The strategy was then applied in the creation of a new axially chiral P,N-ligand comprised of a five-membered imidazole ring in the biaryl backbone. This ligand was prepared as a single enantiomer and evidence of π-stacking interactions was observed in solution and in the solid state. After developing a method to isolate significant amounts of this P,N-ligand as a single enantiomer, it was necessary to evaluate its performance in enantioselective catalysis. It was found that in the A₃-coupling reaction, our ligand furnished the products in 24h at 0 °C in high yields and enantioselectivities over a broad range of substrates, including alkyl and aryl aldehydes. The method overcomes the limitations in scope associated with QUINAP, the benchmark ligand for this reaction. Moreover, copper-catalyzed acetylide addition to pyridinium ions or Michael acceptors were explored and gave good initial results. The ligand could also be employed in palladium-catalyzed allylic alkylation reaction to give the products in high ee. Research in this area is ongoing in our group and this dissertation documents the results obtained during the past five years.
CHAPTER 1
INTRODUCTION

The present dissertation will cover from fundamental aspects of atropisomers to the application of an axially chiral P,N-ligand for asymmetric catalysis. In Chapter 1, a general introduction to the field will be made with emphasis on biaryl atropisomers which are particularly important for the work presented in chapters 2, 3 and 4.

1.1 Definition of Atropisomerism

The word “atropisomer” is derived from the Greek language in which “a” means “non” and “trop” means “turn”. IUPAC defines atropisomers as: “A subclass of conformers which can be isolated as separate chemical species and which arise from restricted rotation about a single bond. e.g. ortho-substituted biphenyl, 1,1,2,2-tetra-tert-butylethane”. As represented in Figure 1-1, the interconversion between the conformers of a tetra-ortho-substituted biphenyl must pass through a high energy coplanar conformation 1-2. Due to severe steric interactions between the ortho-substituents, this interconversion is not facile.

Figure 1-1. Atropisomerism in biphenyl 1-1 and axial chirality in biphenyl 1-3

In a similar system, 1-3, with two different pairs of ortho-substituents the same phenomenon is observed. In this case the conformers are not superimposable mirror images thus
leading to axial chirality in this biaryl system. Atropisomerism is an important topic, due to the occurrence of axial chirality in natural products, drug discovery, and catalysis.

Although the term “atropisomer” was first used by Kunn in 1933 the phenomenon was reported in 1922 by Kristie. In his study, 6,6’-dinitro-2,2’-diphenic acid 1-6 was resolved by fractional recrystallization using brucine 1-7 and the conformers 1-8 and 1-9 isolated after recrystallization were shown to have opposite optical rotations (Figure 1-2). Since then, the chirality of biaryl systems has been widely studied and applied in different areas.

Figure 1-2. First report of biaryl atropisomers

The occurrence of biaryl atropisomers in nature has been well documented. Axially chiral natural products can appear in either simple or complex structures (Figure 1-3). Vancomycin 1-10 is an important example due to its complex molecular architecture and antibiotic activity. This sophisticated glycopeptide contains numerous stereogenic centers including a chiral biaryl unit. Pharmaceutical companies have also been exploring this type of chirality in drug discovery. Recently, medicinal chemists at Pfizer reported that PH-797804 1-11 presents higher inhibiting activity against p38α kinase than its mirror image structure. Asides from biologically active compounds, axial chirality has been widely utilized in catalysis. Biaryl ligands such as BINOL and BINAP are classified as privileged chiral catalysts due to their efficiency in asymmetric reactions.
An important aspect regarding atropisomers is that the barrier to rotation about a single bond can vary significantly depending on the chosen molecule. Three examples are shown in Figure 1-4.

For instance, biphenyl 1-14 has a very low barrier to rotation which has been calculated to be ~2 kcal/mol in the gas phase. The barrier to rotation of 1,1'-binaphthyl 1-16 was experimentally determined to be 23.5 kcal/mol and it has a half-life ($t_{1/2}$) of 14.5 min at 50 °C. Interestingly, biaryl 1-16 could be spontaneously resolved from its melt to generate optically
active enantiomers 1-16 or 1-17. In the chiral auxiliary 1,1'-bi-2-naphthol (BINOL) the enhanced steric effects about the biaryl bond leads to a very high barrier to rotation of ~38 kcal/mol (measured at 220 °C in diphenyl ether). Due to this high barrier, enantiomerically pure BINOL is optically stable at 100 °C for 24 hours in dioxane-water. The analysis of these three examples begs the question: how high does the barrier to rotation of a molecule have to be in order to define it as an atropisomer? In 1983, an arbitrary but useful definition was made by Oki: atropisomers are molecules in which an isolated conformer has a half-life $t_{1/2}$ of at least 1000 seconds (17 minutes) at a specified temperature. At 25 °C, this corresponds to a ~22 kcal/mol barrier to rotation, therefore, biphenyl 1-14 is not considered an atropisomer. By definition binaphthyl 1-16 (half-life $t_{1/2}$ is 14.5 minutes) is not considered an atropisomer at 50 °C. BINOL 1-12 has a very high barrier to rotation and is defined as an atropisomer up to at least 100 °C since it is thermally stable at this temperature. It is important to mention that, beyond the arbitrary definition, the racemization rate of axially chiral ligands or catalysts will be crucial when considering their use in asymmetric catalysis. For practical purposes, a useful chiral ligand or catalyst must be configurationally stable under the reaction conditions in which it is applied.

1.2 Resolution of Chiral Atropisomers

Enantiomerically pure atropisomers can be obtained from resolution of racemates using chiral HPLC or resolving agents. The resolution of racemic BINOL rac-1-12 was performed on a multi-gram scale using $N$-benzylcinchonidinium chloride 1-19 as a resolving agent (Figure 1-5). Chiral salt 1-19 selectively forms a complex with (R)-BINOL to form the insoluble salt 1-20 and enantiomerically pure (S)-BINOL remains in solution. After work-up 1-20 is converted to (R)-BINOL in high enantiomeric excess.
Another attractive approach to obtain enantiomerically pure atropisomers is the asymmetric synthesis since all the starting materials can be converted into a single enantiomer. A classic example is the “lactone concept” developed by Bringmann and applied in the synthesis of many axially chiral natural products. It involves a dynamic kinetic resolution process where a configurationally unstable lactone is opened in a diastereoselective fashion affording optically active biaryls. For example, the biaryl lactone conformers 1-21a and 1-21b are stereochemically labile and, when exposed to the chiral oxazaborolidine-borane reagent 1-22, conformer 1-21b reacts much faster affording product 1-23 in 81% yield and 96% ee (Figure 1-6). After recrystallization, 1-23 is obtained in >99% ee and converted to (+)-Knipholone 1-24 in several steps.

With the impressive development of metal-catalyzed cross-couplings in the past years, the enantioselective synthesis of biaryl atropisomers seems to be a very convenient approach (Figure 1-7). There are many reports on this type of strategy but the substrate scope and
stereoselectivity are still limited. As previously discussed, *ortho*-substituents are necessary for configurational stability of chiral biaryls. However, *ortho*-substituents also raise the energy of the reaction intermediates and, to overcome these effects, high temperatures are usually required to obtain reasonable yields in these reactions. These “forcing” conditions can affect the atropselectivity of the reaction resulting in low enantiomeric excesses.

Figure 1-7. General cross-coupling towards congested biaryls

A successful example of catalytic atropselective cross-coupling was developed by Buchwald (Figure 1-8). The palladium-catalyzed Suzuki-coupling between phenylboronic acid 1-28 and aryl bromides 1-29 provided enantioenriched biaryls in up to 98% yield and 92% ee. Interestingly, the chiral ligand applied was (S)-KenPhos 1-31, a C$_1$-symmetric axially chiral P,N-ligand. A drawback of this method is that it requires the *ortho*-phosphite substituted 1-29 to obtain high enantiomeric excesses, leading to limited scope.

Figure 1-8. Buchwald’s atropselective Suzuki-coupling

In 2014, a very efficient Suzuki-Miyaura coupling was developed and applied during the first total syntheses of korupensamines A and B$^{31}$ (Figure 1-9). Boronic acid 1-32 and arylbromide 1-33 were subjected to optimized conditions employing catalytic amounts of bis-
phosphine ligand 1-34 and Pd(OAc)$_2$ at 35 °C affording biaryl 1-35 in 96% yield and 93% ee. After a few additional steps, synthesis of korupensamine A 1-36 was accomplished. The synthesis of korupensamine B was performed through the same route employing ligand ent-1-34 in the cross-coupling reaction.

Figure 1-9. Stereoselective syntheses of korupensamines A and B

1.3 Heteroaromatic Biaryl Atropisomers

The majority of the axially chiral biaryls are comprised of six-membered naphthalene or benzenoid rings. In fact, they are the most abundant in natural and synthetic systems. However, there are many important examples in which a heterocycle is present in the chirality axis, such as in the Pfizer drug PH-797804$^8$ 1-11 (Figure 1-3). Changing from an all-carbon aromatic ring to a nitrogen heteroaromatic can significantly affect the properties of a molecule. This can be exemplified by the interannular distance of C-C = 1.48 Å in biphenyls, N-C = 1.40 Å in N-phenylazoles$^{34}$ and N-N = 1.36 Å in N,N-linked biazoles.$^{35}$ It is intuitive that shorter distances in the interannular bond will enhance the steric crowding thus the barrier to rotation. However, the size of the rings will also be decisive. The geometrical distinctions between six and five-
membered rings will affect the distances between the interacting groups of an atropisomer and its restricted rotation. As illustrated in Figure 1-10, the larger bond angles between the substituents in a five membered ring will result in a less restricted biaryl bond. As a result, the vast majority of chiral biaryl atropisomers are comprised of six-membered rings whereas five-membered rings are less common.

![Figure 1-10. Geometrical distinctions between six and five-membered rings in a biaryl](image)

Examples of optically active natural products containing five-membered heteroaromatic are usually highly substituted around the axis to overcome the “loss” in steric from the smaller ring. As presented below, they are often dimers of naturally occurring indole or carbazole heteroaromatics. Naturally occurring polybrominated indoles *1-41* and *1-42* have been isolated from Australian algae (Figure 1-11).^36^

![Figure 1-11. Naturally occurring polybrominated biindoles *1-41* and *1-42*](image)

While C-C linked biindole *1-41* did not present optical rotation (probably due to fast racemization as a consequence of the 5,5-ring connection), biindole *1-42* presented a high optical rotation ([α]_20^D_ = +71° (c 1.00) in CHCl₃), suggesting a higher barrier to rotation.
Bringmann’s work on murrastifoline F, an N-C linked bicarbazole natural product, required the development of an oxidative C-N coupling (Figure 1-12). The dimerization of murrayafoline A employing Pb(OAc)$_4$ gave racemic murrastifoline F in 60% yield. Resolution by chiral HPLC was performed in order to determine the absolute configuration of the alkaloid. In 2012, Dixiamycins A and B were discovered as the first examples of atropisomerism of naturally occurring N–N coupled atropdiastereomers. Recently, Baran and co-workers accomplished the first total synthesis of Dixiamycin B through a new N-N coupling. The dimerization of known xiamycin A involved a diastereoselective electrochemical oxidative coupling using a carbon anode and furnished the natural product in 28% yield.

Figure 1-12. Synthesis of murrastifoline F and dixiamycin B
1.4 Overview of Dissertation

This present dissertation covers the synthesis and applications of biaryls for use in asymmetric catalysis. As described in Chapter 1, five-membered biaryl atropisomers are rare and we aim to develop a new family of chiral ligands incorporating this ring size. This task required the development of a new strategy to increase the barrier to rotation of biaryl molecules.

In Chapter 2, this new approach to atropisomers will be described in a fundamental fashion. The strategy involves intramolecular aromatic interactions to stabilize the chiral ground state conformation of biaryls. Model compounds containing moieties designed for intramolecular \( \pi \)-stacking interactions were synthesized and analyzed by variable temperature NMR in order to evaluate the feasibility of the proposed strategy.

In Chapter 3 the design and synthesis of a new axially chiral ligand incorporating the strategy described in Chapter 2 will be presented. This new P,N-ligand was prepared as a single enantiomer through a novel two-step deracemization process which will be described in detail.

In Chapter 4, an overview of enantioselective reactions catalyzed by axially chiral P,N-ligands will be provided. Testing of the new P,N-ligand in different asymmetric transformations will be described and compared to known ligands from the literature. In particular, a full methodological study was performed in the so called A\(^3\)-coupling reaction in which our new P,N-ligand excelled.
CHAPTER 2
A NEW APPROACH TO ATROPISOMERISM

2.1 Introduction to the Designed Model

The design of new chiral ligands is on the cutting edge of organic synthesis. In particular, atropisomeric ligands have been shown to be very successful in asymmetric catalysis. However, the majority of axially chiral biaryl ligands are comprised of six-membered aromatic rings (Figure 2-1). In this context, creative new atropisomeric ligand scaffolds should advance the field and one way this could be accomplished is by using other ring sizes.

Figure 2-1. Examples of successful biaryl ligands comprised of six-membered rings

When coordinated to a metal, these bidentate ligands have two important properties: the dihedral angle $\theta$ and the bite angle $\phi$. As an example, the dihedral angle $\theta$ and the bite angle $\phi$ in QUINAP/rhodium complex 2-6 are graphically represented in Figure 2-2. QUINAP performs extremely well in the asymmetric hydroboration of arylalkenes and it is believed that these angles in their optimal position are associated with this success (this topic will be discussed in more detail in chapters 3 and 4). In order to change the properties of QUINAP, Brown and co-workers attempted to modify the dihedral and bite angles by substituting the naphthalene ring to a five-membered indole heteroaromatic. This ring contraction would generate a new ligand 2-8 which could open the “chiral pocket” of the catalyst in hopes of accommodating larger substrates in enantioselective reactions. Unfortunately 2-8 is not configurationally stable (probably due to reduce steric congestion around the biaryl bond) and biaryl ligands of this type have not been explored in asymmetric catalysis. In addition to the changes in the dihedral angle $\theta$ and bite
angle $\phi$ there are other advantages on employing electron-rich five-membered heteroaromatics in biaryl ligands. Their syntheses are well-known, which reduces the difficulty in their preparation and exploration of analogues for fine tuning.48,49

Figure 2-2. Dihedral angle $\theta$ and bite angle $\phi$ on QUINAP/rhodium complex 2-6 and indole-based P,N-ligand 2-8

In regards to the problem of conformational stability described for ligand 2-8, a fundamental question arose: how can the ring sizes of a chiral biaryl be contracted without losing their configurationally stability? Is there any strategy other than steric obstruction of rotation that can be used to increase the barrier to rotation? As described in Chapter 1, the usual strategy to increase the barrier to rotation in biaryls involves the employment of larger groups ortho to the chiral axis, which can be graphically represented as going from a to b in Figure 2-3. In contrast, we sought to introduce a new strategy in which the barrier to rotation of a biaryl bond is increased due to the decrease of the ground state energy of chiral conformers. Graphically, this could be described as going from a to c in Figure 2-3. Surprisingly the simple concept of ground state stabilization presented herein has not been explored in the context of atropisomerism.
Fundamentally, the proposed approach could be explored with any type of intramolecular interaction (e.g., π-stacking interactions, π-cation interactions, hydrogen bonding interactions etc.). The proposed model system is a biaryl structure comprised of three aromatic units A, B, and C designed to π-stack intramolecularly (Figure 2-4). The presence of a heteroaromatic ring B allows easy functionalization or structure modification for the synthesis of chiral ligands or catalysts. Before this application, it was necessary to study model systems in order to test the feasibility of this intramolecular interaction. As represented in Figure 2-4, the proposed structure will be in equilibrium between a π-stacked conformation 2-9 and a conjugated coplanar conformation 2-10. Our hypothesis is that π-stacking interactions will be the main factor governing the energy minima of this system rendering 2-9 to be the lowest energy conformation.

In addition, this system is designed for the easy calculation of the barrier to rotation using variable temperature NMR. The methylene protons in the chiral conformation 2-9 are diastereotopic allowing for differentiation between H^a and H^b on the NMR time scale (Figure 2-5). On the other hand, other conformation such as 2-10 would display H^a and H^b as a singlet.
since they are enantiotopic. Also, this method does not require the isolation of enantiomerically pure samples or chiral probes to measure the racemization rates and/or barriers to rotation of the compounds. As long as the compound has diagnostic peaks that coalesce below the NMR temperature limits, the barrier to rotation can be measured. This would allow us to compare different model compounds and quickly evaluate our hypothesis.

Figure 2-5. Diastereotopic protons H^a and H^b in the chiral stacked conformation 2-9

Despite the fact that intramolecular π-stacking interactions have been widely studied,\textsuperscript{51,52} the system proposed here remains unexplored. Due to the importance of this non-covalent interaction in our system, a brief introduction on the topic will be given herein.

### 2.2. General Background on Aromatic Interactions

Intra- and intermolecular interactions involving aromatic units play an important role in the properties of not only biological but also chemical systems (Figure 2-6).\textsuperscript{51,52} In organic transformations, these interactions often explain stereoselectivity in reaction outcomes.\textsuperscript{53,54} For instance, Yamada’s work\textsuperscript{55} on the nucleophilic addition of malonate to the pre-organized pyridinium ion 2-12 involved the design of an intramolecular cation-π interaction to give product 2-13 in excellent regio- and diastereoselectivities. The biologically relevance of many compounds are also rationalized with structure/activity studies involving aromatic interactions. For example, in the binding mode 2-14 of anti-Alzheimer drug E20202 to the enzyme acetylcholinesterase\textsuperscript{56,57} aromatic rings are π-stacking in three different sites, demonstrating the diversity of this interaction.
In general, the interaction between two benzene rings can adopt three configurations: parallel displaced, T-shaped edge-to-face, and eclipsed-face-to-face (Figure 2-7).\textsuperscript{51,52} The strength of the interaction will vary depending on many factors such as substituents on the aromatic ring and nature of the solvent.

There are different theoretical and experimental models designed to study the interactions between aromatic rings. In a broad sense, the theories are divided into either London dispersions or polar electrostatic interactions and there is still a debate as to which is dominant in the overall energetics of these interactions.\textsuperscript{51,52} Regardless of the nature of the interaction, there are many models that demonstrate their existence and those were very valuable to the development of our...
project. In this context, we were interested in a strong stacking energy and the analysis of known models directed us to the arene-perfluoroarene interactions that we used in the end (vide infra).

Perfluoroaromatics are well known to bind strongly to other arenes and this behavior has been explored in many areas such as supramolecular chemistry and catalysis.\textsuperscript{51,52} The strength of this interaction is well illustrated by formation of a solid when benzene and hexafluorobenzene are combined (Figure 2-8). These two compounds are liquids in their pure forms but a 1:1 mixture of benzene and hexafluorobenzene forms a solid with a melting point of 23.7 °C.\textsuperscript{58a} X-ray crystallography showed that the crystals are constituted of alternating molecules of benzene and hexafluorobenzene. Studies on this type of interaction reveals that the inverted quadrupole moment of 2-19 (+32 x 10\textsuperscript{-40} C m\textsuperscript{2}) when compared to 2-18 (-29 x 10\textsuperscript{-40} C m\textsuperscript{2}) is essential for the strong binding.\textsuperscript{59}

![Figure 2-8. Properties of benzene, hexafluorobenzene, and their dimer](image)

Tsuzuki and co-workers performed theoretical studies on the system and determined that the arrangement of the interaction can be parallel-displaced, face-to-face, T-shaped and inverse T-shaped (Figure 2-9).\textsuperscript{60} Among them, the first case is predicted to be the strongest with an energetic stabilization of 5.38 kcal/mol. Their studies concluded that dispersion interaction is predominant in this system, although electrostatic interaction also contributes to the attraction.
Figure 2-9. Geometries and calculated interaction energies of the hexafluorobenzene-benzene dimers (the reported distances are the interplanar distance for 2-20 and intercentroid distances for 2-21, 2-22, and 2-23, as indicated)

Experimental models were also explored to study perfluorinated aromatic rings. Cozzi and Siegel have studied the 1,8-diarylnaphthalene system 2-23 illustrated below (Figure 2-10). In this work, the effects of a variety of substituents on the phenyl groups on the face-to-face π-stacking interactions was studied. For example, increasing the number of fluorine atoms on the phenyl ring enhances the barrier to rotation due to stronger intramolecular π-stacking. It was observed that for each fluorine atom added, the barrier to rotation increased by approximately 0.5 kcal/mol.

Figure 2-10. Cozzi’s (left) and Gung’s (right) models to study intramolecular aromatic interactions

More recently, Gung and co-workers designed another model which, in contrast to the former, the intramolecular π-stacking occurs in a parallel-displaced arrangement (Figure 2-10).
Their studies involve the equilibrium between a folded syn 2-24 and unfolded anti 2-25 conformation, being the π-stacking syn 2-24 favored.

This strong interaction was also useful in the macrocyclization depicted in Figure 2-11. The pentafluorobenzyl moiety in 2-26 shields one side of the aromatic ring forcing the olefins to cyclize through a ring-closing metathesis reaction. The absence of the pentafluoro moiety in the substrate resulted in no reaction with the recovery of starting material and undesired oligomers.

Figure 2-11. Pentafluorophenyl-phenyl interaction role in ring-closing methathesis

2.3 Synthesis and NMR Data for Model Compounds

Based on these precedents, we decided to prepare compounds 2-10 and 2-31 hoping that the latter would undergo a strong intramolecular interaction favoring conformation 2-32 (Figure 2-12). The easy analysis of the methylene protons H° and H° by 1H NMR in each molecule would quickly give insight if the equilibrium below favors the stacked conformation 2-32.

Figure 2-12. Using π-stacking to stabilize the ground state energy of the chiral conformation
The syntheses of 2-10 and 2-32 began with a Suzuki cross-coupling between 1-bromonaphthalene 2-33 and N-Boc-pyrrole-2-boronic acid 2-34 to give 2-aryl pyrrole 2-35 in 59% over two steps after deprotection (Figure 2-13). Benzylation using benzyl bromide gave 2-10 in 84% yield. Employing pentafluorobenzylbromide, compound 2-32 was readily prepared in 57% yield.

\[
\begin{align*}
\text{Br} & \quad \text{N} \quad \text{Br} \\
\text{2-33} & \quad \text{Boc} \quad \text{Br} \\
\text{2-34} & \quad \text{2-35} \\
\text{NaH, DMF, 84%} & \quad \text{NaH, DMF, 57%}
\end{align*}
\]

Figure 2-13. Synthesis of compounds 2-10 and 2-32

To our delight, it was found by \(^1\)H NMR that the methylene group of 2-10 showed a broad singlet while 2-32 exhibited an AB system (Figure 2-14, 2-10 and 2-32 \(^1\)H NMR in CDCl\(_3\)). This behavior could be explained by the fact that, in the perfluorinated molecule, the intramolecular interaction restricts rotation about the biaryl bond due to intramolecular stacking interactions and, by consequence, the methylene protons are diastereotopic on the \(^1\)H NMR time scale. With this in mind, we decided to measure the barriers to rotation of 2-10 and 2-32 using the coalescence method.

As shown in Figure 2-14, the coalescence method requires \(^1\)H NMR analysis of 2-10 and 2-32 at different temperatures. The diagram in Figure 2-14 shows the \(^1\)H NMR (expanded in the
methylene peak region) for compounds 2-10 and 2-32 at different temperatures. As expected, the AB system observed for the methylene peak of 2-32 gradually coalesced to a broad singlet at a higher temperature. On the other hand, the broad singlet observed for 2-10 at room temperature gradually separated into an AB system when the sample was cooled to -15 °C. The coalescence temperature $T_c$ is the lowest temperature where there is no minimum between the two coalescing peaks of the AB system. Careful analysis of the spectra provided a coalescence temperature of 9 °C and 57 °C for 2-10 and 2-32, respectively.

![Diagram of 1H NMR Spectra of 2-10 and 2-32 at different temperatures]

Figure 2-14. $^1$H NMR Spectra of 2-10 and 2-32 at different temperatures

Although the coalescence temperatures observed demonstrate a higher barrier to rotation in the biaryl bond of compound 2-32, calculations are needed to obtain the actual free energy of activation $\Delta G^\ddagger$ for interconversion of $H^a$ and $H^b$ between the two sites. As an example, compound 2-32 will be used to demonstrate how these energy values can be obtained. First, a $^1$H
NMR analysis has to be performed at a temperature where no change in the peak shape is observed (low enough that the AB pattern is constant at this temperature and below). For compound 2-32 the $^1$H NMR spectrum at 10 °C was used (Figure 2-15). The exchange rate constant $k_c$ is given by equation 1 derived for AB systems and employs $J_{AB}$ (coupling constant in each site of the AB system) and $\delta \nu$ (chemical shift between the two sites).$^{21,50}$ For compound 2-32, the exchange rate constant was calculated to be 145 s$^{-1}$. The free energy of activation $\Delta G^\ddagger$ at the coalescence temperature ($T_c = 57 °C = 330 K$) is calculated using the Eyring equation (eq. 2). Employing $k_c$ and $T_c$ in equation 2, the free activation energy $\Delta G^\ddagger$ at the coalescence temperature for compound 2-32 is found to be 16.1 kcal/mol. It is important to mention that there is a minimum error associated with these experiments. Raban and co-workers$^{67}$ studied the error on these types of approximations and it was found that even if error of 100% in the exchange rates would be observed, this would only translate to an error of 0.4 kcal/mol in the free energy of activation. In other words, this simple method allows for an useful determination of the barrier to rotation in these biaryl compounds.

![Figure 2-15. Calculation of $\Delta G^\ddagger$ employing $k_c$ and $T_c$](image-url)

The rate constant is obtained using the expression:

$$k_c = n/2^{1/2} \times (\delta \nu^2 + 6J_{AB}^2)^{1/2} \text{ [eq. 1]}$$

$k_c = 145$ s$^{-1}$

The free energy of activation $\Delta G^\ddagger$ at $T_c$ is given by the Eyring equation:

$$\Delta G^\ddagger = R \times T_c \times \ln(k_b T_c/k_b) \text{ [eq. 2]}$$

Where: $R$ = gas constant

$k_b$ = Boltzmann's constant,

$h$ = Planck's constant,

$T_c$ = coalescence temperature

Using $T_c = 57 °C = 330 K$ and $k_c = 145$ s$^{-1}$

$$\Delta G^\ddagger_{\text{at } T_c} = 16.1 \text{ kcal/mol}$$
By analogy, using the coalescence temperature for biaryl 2-10 we determined the activation energy as 13.7 kcal/mol. The activation energies of compounds 2-10 and 2-32 are shown in Figure 2-16, along with the coalescence temperature and solvent employed in the analysis.

Figure 2-16. Free energy of activation $\Delta G^\ddagger$ of 2-10 and 2-32 at the coalescence temperature $T_{pc}$.

These results verified that there is a higher barrier to rotation in compound 2-32. Comparing the calculated energies required for bond rotation in compounds 2-10 and 2-32 gives a $\Delta \Delta G^\ddagger$ of 2.4 kcal/mol for compound 2-32. By analogy to the previously described models, this energy can be attributed to intramolecular $\pi$-stacking interactions$^{66b}$ and this value is in agreement with other $\pi$-stacking energies involving pentafluoroaromatic moieties.$^{51,52}$

In addition, compound 2-10 is an oil and compound 2-32 is a white solid. This provided the opportunity to grow good quality single crystals, and to use X-ray diffraction to obtain a crystal structure of compound 2-32 (Figure 2-17). What seems to be involved is an arene-arene interaction in the parallel-displaced arrangement. The two arenes are parallel to each other with the center of one arene (benzyl) on top of the edge of the other. The dihedral angle that defines the planes of the A- and B-rings is $88^\circ$ and the A- and C-rings are $\pi$-stacked with an interplanar distance of 3.26 Å. Since the two stacked aromatic rings are not perfectly in parallel, 3.26 Å is this distance between the averaged planes of each of the rings. Interestingly, this is closer than the interplanar distance of 3.4 Å between $C_6H_6$ and $C_6F_6$ in the well-known co-crystal.$^{58b}$ In the
packing of the structure there is also intermolecular π-stacking interactions between alternating naphthalenes and pentafluorobenzene rings.

Figure 2-17. Single crystal X-Ray analysis of 2-32

The synthetic versatility of our model system enabled the systematic study of the influence of substituents on rings A, B or C (Figure 2-18). This was important to understand how electronic and steric factors affect the system. Initially, substitution on the naphthalene ring C was studied with compounds 2-36 and 2-37.

Figure 2-18. General modification on the model system and compounds 2-36 and 2-37 substituted on the naphthalene

The synthetic routes to prepare 2-36 and 2-37 are analogous to the previous compounds. To prepare 2-36, the hydroxyl group on 2-38 was converted to a triflate in 85% yield. Next, a Suzuki coupling between 2-39 and 2-34 followed by deprotection gave 2-40 in 26% yield over two steps. The low yield obtained in this two-step process is probably due to the instability of boronic acid 2-34 leading to low conversion in the Suzuki cross-coupling. To complete the
synthesis, the alkylation of 2-40 furnished 2-36. This compound was prepared with the intention of adding an electron donating group (-OMe) in a position away from the axis, in order to combine an electron-rich naphthalene ring and an electron-poor pentafluorobenzyl group. Based on the X-ray structure of 2-32, the substitution at 5-position of the naphthalene would increase the electron density to provide a more electron-rich ring where the π-stacking takes place. Unfortunately, the barrier to rotation in 2-36 was very similar (ΔG‡ = 16.3 kcal/mol and Tc = 61 °C) to compound 2-32 suggesting that the pentafluorobenzyl moiety dominates the interaction regardless of the nature of the naphthalene ring. It is important to note that Gung and co-workers also observed the same trend when studying π-stacking interactions involving strongly electron deficient aromatic rings.\textsuperscript{62}

![Chemical diagram]

Figure 2-19. Synthesis and analysis of 2-36

The methoxy group was also placed on compound 2-42 by a similar route using from bromide 2-41.\textsuperscript{69} Benzylation afforded compound 2-37 containing a methoxy group ortho to the biaryl bond, which presented a very high barrier to rotation. As previously stated, the presence of a bulky group close to the axis would increase the restriction on the biaryl bond due to more severe steric interactions. In this case, the variable temperature NMR required the use of a solvent with a higher boiling point and 1,1,2,2-tetrachloroethane-d\textsubscript{2} (C\textsubscript{2}D\textsubscript{2}Cl\textsubscript{4}, BP = 145-146 °C) was the solvent of choice. \textsuperscript{1}H NMR analysis in C\textsubscript{2}D\textsubscript{2}Cl\textsubscript{4} at 120 °C showed an AB system and the
barrier could not be determined since that temperature was above the upper limit of the equipment.

![Chemical reaction](image1)

Figure 2-20. Synthesis and analysis of 2-37

Having successfully synthesized and studied pyrrole derivatives we proceeded to investigate other heteroaromatic analogues. Among the different heterocycles that could be explored, we chose to analyze indole derivatives 2-46 and 2-47 (Figure 2-21). Compound 2-45 was readily prepared through a Fischer indole synthesis according to a literature procedure. Benzylations of 2-45 gave 2-46 and 2-47 in very good yields.

![Chemical reaction](image2)

Figure 2-21. Synthesis and analysis of compounds 2-46 and 2-47

Unexpectedly, the barrier to rotation for the indole pair (2-46 and 2-47) increased considerably in comparison to the corresponding pyrrole structures 2-10 and 2-32. The changes were from 13.7 to 15.3 kcal/mol for the non-fluorinated pair and from 16.7 to 17.3 kcal/mol for the fluorinated pair. These data show that the nature of the heterocyclic ring B affects the barrier to rotation of these biaryl compounds. After careful analysis, two explanations for this result (or a combination of both) emerged. Firstly, the geometries of these heteroaromatics were studied.
and we were encouraged to compare the X-ray structure of our pyrrole 2-32 to a similar indole structure 2-48 from the literature.\textsuperscript{71} As shown in Figure 2-22, a slightly larger N-C-C bond angle and a shorter biaryl bond is observed for the indole compound. These subtle factors could be leading to a larger barrier to rotation on indolic compounds.

![Figure 2-22. Comparison between pyrrole and indole X-ray structures](image)

Additionally, the “buttressing” effect should also be considered.\textsuperscript{72} This effect is observed in biaryls when a meta-substituent is present in a biaryl structure. For instance, rotation in tetraiodobiphenyl 2-50 (\(\Delta G^\ddagger = 30.1\) kcal/mol at 25 °C) is more difficult than in diidoanalogue 2-49 (\(\Delta G^\ddagger = 23.4\) kcal/mol at 25 °C) by a significant energy amount (Figure 2-23).\textsuperscript{73}

![Figure 2-23. Example of a “buttressing” effect](image)

By analogy, the presence of an extra benzenoid ring on the indole (when compared to pyrrole) could be “buttressing” the benzyl group towards the naphthalene ring resulting in a higher barrier to rotation in the biaryl bond (Figure 2-24).

![Figure 2-24. Suggested rationale for the higher barrier to rotation observed](image)
To further investigate this rationale we turned our attention into a pyrrole analogue in which the \( \pi \)-system would be the same but 5-position of the pyrrole would be substituted with a methyl group (Scheme 6). To this end, diketone 2-51\(^{74} \) was submitted to standard Paal-Knorr conditions\(^ {75} \) to give the desired compounds 2-52 and 2-53 in 74 and 51% yields, respectively. The observed barriers to rotation were increased in comparison to 2-10 and 2-32 (13.7 and 16.1 kcal/mol, respectively) suggesting that a “buttressing” effect might be involved and in this case the extra methyl group could be “buttressing” the benzyl groups causing the barrier to increase.

![Figure 2-25. Synthesis and barriers to rotation of compounds 2-52 and 2-53](image)

In Figure 2-26, the graph summarizes the data of the three pairs of compounds. Interestingly, the introduction of the methyl group to the pyrrole ring increases the barrier to rotation in 0.8 kcal/mol (13.7 to 14.5 kcal/mol) in the non-fluorinated compounds whereas the fluorinated analogues increases in only 0.4 kcal/mol (16.1 to 16.5 kcal/mol). This could also be explained by a greater \( \pi \)-stacking between the pentafluorobenzyl group and the naphthalene diminishing the “buttressing” effect. Another observation is that the \( \Delta \Delta G^\ddagger \) in the indolic (2-46 and 2-47) and 5-methylsubstituted (2-52 and 2-53) pairs were found to be 2.0 kcal/mol which is slightly smaller than in the pyrrole analogues but still a significant stabilization energy.
Furthermore, three additional indolic derivatives 2-54, 2-55, and 2-56, containing different benzyl groups, were easily prepared from 2-45. As presented in Figure 2-27, no significant difference in the biaryl bond rotation was observed for any of the compounds. Even 2-54 containing a fluorine in the para position presented similar energy barrier which indicates that perfluorinated analogues results in higher stabilization. Also, either an electron rich para-methoxyphenyl or a heterocyclic pyridine ring did not resulted in significant energy differences when compared to non-fluorinated indole 2-47.

Figure 2-26. Comparison between pyrrole and indole biaryls

Having identified the highest barrier to rotation for compound 2-46 containing a pentafluorobenzyl ring C and an indole ring B, we decided to investigate an isoquinolinic analogue 2-57 (Figure 2-28). This compound is a potential precursor for atropisomeric ligands or
catalysts with an indole 3-position available for functionalization along with a co-ordinating nitrogen. In the next Chapter studies towards P,N-ligand 2-59 will be presented.

Figure 2-28. Potential functionalization of isoquinolinic compound 2-57

The preparation of 2-57 begins with a Fischer indole synthesis\(^7^6\) employing ketone 2-60 and phenylhydrazine to give 2-61 in 75% yield (Figure 2-29). Subsequent pentafluorobenzylolation furnished 2-57. Unfortunately, the isoquinoline derivative 2-57 presented a very low barrier to rotation, probably due to minimized steric demand on the nitrogen. When 2-57 was cooled down to 0 °C in CDCl\(_3\) the methylene peak still appeared as a sharp singlet and its barrier to rotation was not determined. In order to restore a reasonably high barrier to rotation, a palladium catalyzed C-H functionalization\(^7^7\) was performed giving acetate 2-62 in 68% yield. VT-NMR studies on this 3-substituted indole gave a higher barrier of 15.4kcal/mol although still too low to attempt the isolation of an optically active atropisomer. Studies on the functionalization of 2-57 are ongoing in the laboratory with the goal of the synthesis of an N-oxide such as 2-58 (Figure 2-29) which can be a potential chiral organocatalyst for asymmetric synthesis.

Figure 2-29. Synthesis of 2-57 and C-H functionalization to 2-62
2.4 Outcome

In summary, a new concept to increase the barrier to rotation in atropisomers was
demonstrated. A variety of compounds were synthesized with different rings A, B and C and it
was shown that when ring C is perfluorinated a stabilization of 2.0 - 2.4 kcal/mol is observed. It
was also found that rings A and B can affect the barrier to rotation depending on their steric
and/or electronic properties. The absolute $\Delta G^\ddagger$ values ranged from 13.7 to 17.3 kcal/mol. It is
important to remind that, by definition, an atropisomer presents at least a barrier of ~22 kcal/mol,
which means that steric will usually be the main component for the occurrence of the
phenomena. However, a “small” stabilization can possibly be relevant depending on the
magnitude of the barrier to rotation. Indeed the next Chapters will show that a stabilization of ~2
kcal/mol can be crucial when developing new ligands for asymmetric catalysis. We believe that
these studies provide a new strategy when desiring to increase the barrier to rotation in biaryl
atropisomers. This concept can also be expanded to other non-covalent interactions or even
covalent bonds. Studies along these lines are underway in our laboratory.
Chapter 3 will describe the work on the design and preparation of P,N-ligand 3-1 (Figure 3-1). Part of this work was published in the Journal of the American Chemical Society: Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. J. Am. Chem. Soc., 2013, 135, 14548–14551. Initially, how we became interested in this area will be presented, which was sparked by our desire to apply the studies from Chapter 2 for the creation of a new family of P,N-ligands. Then, an overview of the methods used to resolve axially chiral P,N-ligands will be required to explain our approach to the preparation of optically active 3-2. It involved a novel two-step deracemization approach which allows conversion of the racemic ligand 3-1 into a single enantiomer, 3-2.

Figure 3-1. New imidazole-based chiral biaryl P,N-ligand

3.1 Axially Chiral P,N-ligands

In the early 1990s, Brown and co-workers started their work on the development of previously unexplored axially chiral P,N-ligands. Aware of the success of chiral bidentate C_2-symmetric ligands, they became interested to prepare a BINAP parent ligand in which one phosphine would be substituted with a basic nitrogen atom (Figure 3-2). The targeted C_1-symmetric ligand would have structure 3-4 containing an isoquinoline ring, and this is the reason for the chosen name for this ligand: QUINAP.
Interestingly, it was revealed by the Brown group that the initial goal was to apply these novel P,N-ligands in cross-coupling reactions but we will see that things did not go this way.\textsuperscript{80a} In a first attempt, difficulties were encountered in preparing QUINAP 3-4 and a similar P,N-ligand 3-5 was prepared (Figure 3-2). Unfortunately, 3-5 was stereochemically labile precluding any application in asymmetric catalysis.\textsuperscript{80a}

Next, Brown and co-workers prepared and resolved QUINAP 3-4 which was considered, since the beginning, the best heterocyclic analogue of BINAP 3-3. The synthesis was accomplished employing a Suzuki cross-coupling between 3-6 and 3-7 to build the biaryl moiety in 3-8 (Figure 3-3). Methoxy deprotection and triflation gave the substrate 3-9 for a C-P coupling. A nickel-catalyzed coupling followed by reduction of the phosphine oxide gave QUINAP 3-4.\textsuperscript{80b} The resolution of QUINAP involved the use of a chiral palladium complex.
which will be discussed in detail in Section 3.3.1. Alternatively, nickel-catalyzed C-P coupling of Ph₂PH gave QUINAP 3-4 in a single step from the triflate 3-9, but this method was developed several years later.³¹

With enantiomerically pure QUINAP in hand, they explored two asymmetric reactions: palladium-catalyzed allylic alkylation⁸² and rhodium-catalyzed hydroboration of styrenes.⁴⁵,⁴⁶ The success achieved in these two reactions opened a new avenue in ligand design and reaction discovery that has been continuously going until these days.⁸³

The first application of (S)-QUINAP 3-12 was in the palladium-catalyzed asymmetric allylic alkylation between 3-13 and 3-14 (Figure 3-4). After some optimization, they were able to obtain product 3-15 in 98% enantiomeric excess overcoming previous results with C₂-symmetric ligands, such as BINAP.⁴⁵,⁴⁶ Although this result was excellent, at about the same time, three groups independently reported⁸⁴,⁸⁵,⁸⁶ the preparation of PHOX type ligands 3-16 which proved to be an even better P,N-ligand for this type of reaction. In light of this, the exploration of QUINAP on allylic alkylation was not substantially explored.

Figure 3-4. Palladium-catalyzed allylic alkylation employing (S)-QUINAP 3-12

On the other hand, QUINAP stands out as one of the best ligands for the asymmetric rhodium-catalyzed hydroboration of styrenes.⁴⁵,⁴⁶ The rhodium-catalyzed hydroboration/oxidation of arylalkenes delivers the Markovnikov product allowing for an enantioselective reaction. The reaction requires a cationic source of rhodium (usually [Rh(COD)₂]BF₄) and catecholborane, followed by an oxidation step. A comparison between (R)-
QUINAP 3-11 and (R)-BINAP\textsuperscript{87} 3-17 is displayed in Figure 3-5, illustrating that in general QUINAP yields better enantioselectivities. For styrene 3-18 the better performance of QUINAP is impressive giving high selectivities at ambient temperature (95% ee versus 57% ee with BINAP). With substituted styrene 3-19 the superiority is even more significant. The use of QUINAP furnishes the product 3-21 in 95% ee at room temperature whereas with BINAP it requires a very low temperature to give only 42% ee.

![Figure 3-5. Comparison between (R)-QUINAP and (R)-BINAP in the asymmetric Rh-catalyzed hydroboration of styrenes](image)

To interpret these results, Brown analyzed the X-ray crystal structures of BINAP and QUINAP in metal complexed environments (Figure 3-5, the metal is palladium in both structures). The proposed rationale postulates that the less sterically demanding isoquinoline ring allows more sterically demanding substrates to undergo the reaction in high enantioselectivities.\textsuperscript{26} In other words, switching from BINAP to QUINAP, a 6-membered chelate is formed (instead of 7-membered) and the “chiral pocket” is able to accommodate larger substrates. It is important to mention that this is probably only one of the factors involved since
there are other differences that could be postulated, such as the electronic properties of the bidentate ligands (P,P versus P,N-ligands).

These were the earliest examples in which QUINAP excelled. Nowadays, QUINAP is part of a class of chiral ligands which are referred as “axially chiral P,N-ligands”. The success of these ligands in asymmetric metal-catalyzed reactions will be summarized in Chapter 4.

3.2 Design of a Biaryl P,N-Ligand Containing a Five-Membered Heteroaromatic

Since its first appearance, a variety of QUINAP type ligands have been synthesized and explored in asymmetric catalysis. Among them, an “indole” version of QUINAP 3-23 (discussed in Chapter 2) has been studied by Brown and co-workers. In this report it was stated that: “variation of the ring size either of the isoquinoline (e.g. modifying to a benzpyrazole) or of the naphthalene (e.g. modifying to an indole) should permit some appraisal of the effects on reactivity and selectivity of varying the bite angle.” These variations are presented in Figure 3-6.

Figure 3-6. Five-membered QUINAP analogues proposed by Brown

As described in Chapters 3 and 4, the isolation of these biaryl structures as a single enantiomer could be difficult because of the less sterically demanding five-membered ring. Although the benzpyrazole analogue 3-22 was never synthesized, the “indole QUINAP” 3-23 was prepared and its resolution attempted. Unfortunately, this system is stereochemically labile precluding application in asymmetric catalysis. Such type of C₁-symmetric axially chiral P,N-
ligands (containing a biaryl system with a 5- and 6-membered rings) have not been explored in asymmetric catalysis. Recently, a few examples of achiral biaryl P,N-ligands, such as 3-24 and 3-25, were reported proving their importance in catalysis. Their application in cross-coupling reactions have attracted many research groups. On the other hand, there is only one example of an axially chiral P,N-ligand comprised of a five-membered ring: BIMNAP 3-26. Although 3-26 was prepared and resolved there are no reports of its use in asymmetric catalysis. The fact that no other examples of such type of P,N-ligands exist is probably related to the challenges of preparing configurationally stable biaryls with smaller ring sizes.

Figure 3-7. Achiral and chiral biaryl P,N-ligand containing five-membered rings

In this context, we were encouraged to approach this issue applying our strategy to five-membered biaryl atropisomers described in Chapter 2. By analogy to the structures proposed by Brown, P,N-ligands 3-1 and 3-28 were envisioned. Based on our studies on model compounds, we hypothesized that an extra stabilization by π-stacking interactions could increase the barrier to rotation of these biaryls and allow for the isolation of conformationally stable ligands (Figure 3-8).
As described in Chapter 2, the dihedral angle $\theta$ and bite angle $\phi$ of ligands when coordinated to a metal play an important role in their performance in catalytic reactions. In a recent review,\textsuperscript{44} Guiry and Brown collected all X-ray crystal structures of P,N-ligands chelated to a metal and analyzed their properties. Although single crystal X-ray analysis might not be the most appropriate representation of the catalyst in solution, they suggested that the analysis of many structures can provide good trends on the performance of a type of ligand in a specific reaction. For instance, axially chiral P,N-ligands in chelate complexes exhibit a rigid backbone with dihedral angles between $\sim55$ and $\sim75^\circ$ while, for example, PHOX type P,N-ligands are more flexible and this property ranges from $\sim20$ to $\sim55^\circ$.\textsuperscript{44}

In Figure 3-9, there are hypothetical rhodium complexes of the targeted P,N-ligand structures 3-29 and 3-30. Taking QUINAP/rhodium\textsuperscript{45} complex 3-31 as a reference, it is evident that changing the size of a ring in the biaryl moiety will affect the geometries of the complexes. In addition, the electronic properties of the coordinating sites will be different. In P,N-ligand 3-28, the phosphine will be linked to the 3-position of an indole ring enhancing the electron density at the phosphorus (when compared to QUINAP). Along the same lines, in the imidazole-based P,N-ligand 3-1 there is a more electron-rich heteroaromatic than the isoquinoline ring of QUINAP 3-4. 

Figure 3-8. Proposed P,N-ligands using our new approach to atropisomers
These conformational and electronic modifications would allow for a new family of chiral ligands that were unexplored in asymmetric catalysis before. For these reasons, we were encouraged to plan the syntheses of 3-1 and 3-28 (Figure 3-10). For synthesis of the indole analogue 3-28, it seemed apparent to employ intermediate 3-36 which is readily available from a Fischer indole synthesis between ketone 3-35 and phenylhydrazine 3-34 (this reaction was shown in Chapter 2). Benzylation and phosphination would provide P,N-ligand 3-28. Synthesis of biaryl 3-1 would employ a one-pot imidazole synthesis using diketone 3-37, aldehyde 3-38 and ammonia. Benzylation and nickel-catalyzed P-C coupling delivers P,N-ligand 3-1. An advantage of incorporating five-membered aromatic heterocycles such as imidazole into these new ligands is the well-known array of methods to prepare these type of rings. The biaryl core structure of the ligands are constructed in the first step of their synthesis which are well established methods and can be performed on a large scale.
Figure 3-10. Retrosynthetic analysis of P,N-ligands 3-1 and 3-28

The attempted synthesis of P,N-ligand 3-28 began with a bromination at 3-position of indole 3-40 using N-bromosuccinimide in 84% yield (Figure 3-11). Next, the phosphine synthesis was planned through a lithiation of bromoindole 3-41 with n-butyllithium followed by the addition of chlorodiphenylphosphine, but this reaction was not successful. In the analysis of the crude reaction mixture the reduced compound 3-40 and decomposition products were observed.

Figure 3-11. Attempted synthesis of P,N-ligand 3-28.

In parallel, the synthesis of 3-1 was also explored. The preparation of racemic 3-1 was achieved in several straightforward steps starting with 2-hydroxy-1-naphthaldehyde 3-38, whereby the requisite heterocycle was readily introduced (Figure 3-12). In the event,
condensation of 3-38 with benzil 3-37 and ammonium acetate as a source of ammonia furnished 3-39 in 80% yield. This reaction is very efficient and can be done on a deca-gram scale. The free alcohol was then protected as the TBS ether in 78% yield, and the resulting imidazole was alkylated with pentafluorobenzyl bromide to yield 3-42. The benzylation step required an unusually low temperature of -78 °C otherwise the reaction was not consistent and desilylated products were often observed. The alcohol was then easily deprotected and converted to the triflate 3-44 using reagent 3-43 in 95% yield over two steps.

Figure 3-12. Synthesis of triflate 3-44.

Next, we explored the nickel-catalyzed C-P coupling needed for the formation of 3-1. The most prevalent methods to convert a triflate to a phosphine are listed in Figure 3-13. The first method (Method A), developed by Merck, uses Ni(dppe)Cl₂, diphenylphosphine and DABCO. Chemists at Monsanto developed a similar method (Method B) employing Ni(dppe)Cl₂ and Zn/PPh₂Cl. These two methods were used in the synthesis of BINAP 3-3 and related phosphines. Although P,N-ligands, such as QUINAP 3-4, were also prepared by methods A and B, our attempts to convert 3-44 to 3-1 were not successful. Kwong and co-workers reported the same results when trying to prepare pyphos 3-48, a pyridine-base P,N-ligand from triflate 3-47. They suspected that the more coordinating pyridine nitrogen could be chelating to nickel causing a retarding effect in the phosphination reaction. To overcome that, a new catalyst
system was developed (Method C) employing a monodentate triphenylphosphine ligand and they were able to isolate pyphos $3\text{-}48$ in 41\% yield.

![Diagram showing reaction pathways for Methods A, B, and C](image)

Figure 3-13. Methods to convert a triflate $3\text{-}45$ to an arylphosphine $3\text{-}46$

The imidazole nitrogen of triflate $3\text{-}44$ could cause the same retarding effect and when we employed the method C on a small scale the desired phosphine $3\text{-}1$ was isolated in similar yield (30-40 \%). This reaction employs a relatively inexpensive source of nickel catalyst Ni(PPh$_3$)$_2$Cl$_2$ and activated zinc. After optimization, it was found that large scale reactions would provide the desired phosphine in 60\% yield after two days (Figure 3-14). A procedure starting with \textasciitilde{}6g of triflate $3\text{-}44$ provided \textasciitilde{}4g of P,N-ligand $3\text{-}1$ after column chromatography and this procedure was repeated several times. A drawback of the method is the utilization of 0.5 equivalents of the nickel catalyst and efforts are being made to optimize this coupling reaction.

![Diagram showing synthesis of racemic P,N-ligand $3\text{-}1$](image)

Figure 3-14. Synthesis of racemic P,N-ligand $3\text{-}1$
In these reactions, full conversion of the triflate is observed and the desired product is formed along with phosphine oxide 3-49 and reduced product 3-50. The yields of these byproducts vary from 10-20% each. Fortunately, phosphine oxide 3-49 can be reduced back to 3-1 using HSiCl₃ in 77% yield (Figure 3-15).

Figure 3-15. Reduction of phosphine oxide 3-49.

Racemic P,N-ligand 3-1 is a very non-polar compound and its crystallization was challenging. After exposing many solvent systems, it was found that 3-1 crystallizes from acetonitrile at room temperature over the course of several hours. An X-ray structure of 3-1 was obtained and it is shown in Figure 3-16. Importantly, the expected π-stacking interactions were observed in the solid state.

Figure 3-16. X-ray structure of racemic P,N-ligand 3-1.

Interestingly, the coordinating atoms of the free ligand are pointing in opposite directions and this will be different when coordinated to a metal. The dihedral angle of the biaryl bond is 84.9°. In contrast to the pyrrolic structure 3-17 discussed in Chapter 2, there is no intermolecular π-stacking and the crystals contain alternating enantiomers in the packing (Figure 3-17).
Figure 3-17. Comparison between the packing of 3-1 and 3-17

3.3 Resolution of Axially Chiral P,N-Ligands

At this point, P,N-ligand 3-1 was prepared as a racemate, but whether or not the compound was configurationally stable needed to be determined. In other words, it needed to be determined if this compound could be chiral and therefore potentially useful for asymmetric catalysis. In order to evaluate this the resolution of 3-1 needed to be performed. In this section, the usual methods to resolve atropisomeric P,N-ligands will be presented. There are four different approaches: 1) use of chiral palladium complexes as auxiliaries; 2) installation of a second chiral center in order to separate diastereomers of the P,N-ligand; 3) separation by preparative chiral HPLC; 4) enantioselective synthesis. Finally, the method developed to deracemize our new P,N-ligand, in contrast to a traditional resolution, will be described.

3.3.1 Chiral Palladium Complexes

The use of chiral metal complexes to resolve ligands for asymmetric catalysis has been known for decades. In the case of axially chiral P,N-ligands, there are many examples in which a chiral palladacycle was used. The most common palladacycles are shown in Figure 3-18.
Their preparation involves an Eschweiler–Clarke methylation of commercially available chiral amines followed by cyclopalladation with Na$_2$PdCl$_4$ and triethylamine to form the C-Pd bond.$^{100}$

Figure 3-18. Common palladacycle used to resolve P,N-ligands

The general three-step resolution process is depicted in Figure 3-19. It involves the complexation of the racemic P,N-ligand 3-54 with, for example, palladacycle 3-52 to give a 1:1 mixture of diastereomers which are easily differentiated by NMR. Then, diastereomers are separated by fractional recrystallization or column chromatograph. A pure diastereomer 3-55 or 3-56 is decomplexed using a stronger ligand (usually dppe) to deliver the free, optically active, P,N-ligands 3-57 or 3-58, respectively.

Figure 3-19. General scheme on the use of chiral palladium complexes to resolve P,N-ligands
It is important to describe a few important drawbacks to the method. Firstly, it requires one equivalent of palladium and another equivalent of an expensive chiral amine 3-50. Besides the price, the separation of diastereomers formed after complexation with the chiral ligand are known to be very tedious. Nevertheless, this method has proven to be efficient for many axially chiral P,N-ligands. In fact, it is quite amazing how well this method works across a broad range of ligands.

The method described above is used for resolution of QUINAP 3-4. QUINAP 3-4 is synthesized as a racemate and this requires resolution since the molecule contains only the axis of chirality. In the first appearance of QUINAP 3-4 Brown stated: “Several attempts were made to resolve the racemic phosphine…a series of experiments were carried out with tartaric acid and related compounds, but in no case was there any evidence for the selective formation of a single diastereomeric salt.” Although QUINAP type P,N-ligands contain a basic site at the nitrogen heterocycle, no reports on its protonation with a chiral acid exists in the context of ligand resolution.

After many attempts to resolve QUINAP, it was found that chiral palladium complex dimer 3-52 was the most successful. Initially, Brown and co-workers prepared an equimolar mixture of diastereomers and separated them by fractional crystallization (Figure 3-20). In this case, one of the diastereomers 3-59 crystallized from chloroform leaving the diastereomer 3-60 in solution. After decomplexation of 3-59 with ethylenebis(diphenylphosphine) 3-61, a stronger bidentate ligand, it was obtained enantiomerically pure (S)-QUINAP 3-12 in 88% yield for this step and an overall yield of 41%. It is important to mention that this process was not possible with Pd-complex 3-51. When 3-51 was mixed with racemic QUINAP 3-4 a diastereomeric mixture was observed but the fractional crystallization was unsuccessful.
Figure 3-20. First generation resolution of QUINAP 3-4

After optimization, they found that mixing 3-52 with QUINAP 3-4 in a 1:4 ratio a single diastereomer would be predominantly formed along with optically active free ligand 3-11 after heating the mixture in acetone for 2h. Upon cooling this solution, diastereomer 3-59 precipitates and optically active (R)-QUINAP 3-11 remains in solution. Ten years after the first synthesis of QUINAP 3-4, Brown and co-workers reported a resolution of ~40g of QUINAP employing this strategy (Figure 3-21).

Figure 3-21. Second generation resolution of QUINAP 3-4
Careful analysis of this process showed that it initially generates a 1:1 mixture of diastereomers and one equivalent of racemic free ligand 3-4. When a 1:1 mixture of 3-59 and 3-60 in dichloromethane was allowed to stand at room temperature it was observed, after 24h, the formation a single diastereomer 3-59. This is possible through an extensive number of complexation/decomplexation events in which the most stable diastereomer 3-59 becomes predominant over the time. This was a very significant improvement because employing this method requires only half of an equivalent of palladium and avoids the fractional crystallization step.

After the discovery of QUINAP, a few groups prepared similar type P,N-ligands containing different nitrogen heterocycles and/or carbon backbones (Figure 3-22). Guiry and co-workers developed a related class of ligands called Quinazolinap 3-63. Kwong and co-workers developed pyphos 3-48 containing a pyridine heterocyclic ring. All these P,N-ligands were resolved using chiral palladium complexes.

Figure 3-22. QUINAP type ligands that were resolved with chiral palladacycles

The success of QUINAP in many enantioselective reactions encouraged many research groups to develop better syntheses and resolution methods for this ligand. An improvement in the synthesis strategy would provide an entry to different analogues of QUINAP, which are rare. In addition, the development of new methods to resolve QUINAP would avoid the use of chiral
palladium complex in the resolution of this type of ligand. In the following Sections it will be described alternative methods to prepare optically active P,N-ligands.

3.3.2. Separation by Chiral HPLC

Kwong et al. explored pyphos 3-48,\textsuperscript{103} a pyridine analogue of QUINAP. The report included the fractional recrystallization of a mixture of palladium complexes diastereomers, as described for QUINAP, and racemic 3-48 was achieved with success. As an alternative, they also investigated separation of pyphos 3-48 using preparative chiral HPLC which ultimately proved to be unsuccessful. To overcome that, an oxidation to the more polar phosphine oxide 3-63 was performed and they were able to separate the enantiomers by HPLC (Figure 3-23). The drawback of this process is that optically active phosphine oxides 3-64 or 3-66 have to be converted back to the phosphine requiring two extra steps for this type of resolution. Additionally, although the barrier to rotation of these ligands are relatively low, they did not observe racemization of the optically active pyphos 3-48 under the harsh reaction conditions for reduction of the oxide.

![Figure 3-23. Use of chiral HPLC for the resolution of pyphos 3-48](Image)

3.3.3. Separation of Diastereomers: the PINAP Case

Carreira and co-workers identified (S)-QUINAP 3-12 as the best ligand for the copper catalyzed alkynylations of Meldrum’s acid alkylidenes\textsuperscript{104,105} (This topic will be discussed in Chapter 4). Although the enantiomeric excess was only 42%, that was the best result among 25
ligands tested in the reaction. It is known that structural modification on QUINAP is not well explored so the improvement of the enantioselectivity of this reaction required the development of a new family of ligands. Along with this, Carreira group decided to adopt a different strategy to obtain the optically active P,N-ligand. Instead of using a chiral palladium complex, they designed a ligand that would incorporate a chiral center allowing for the separation of diastereomers. The chiral center would be away from the axis as in the diastereomeric structures 3-72 and 3-73 (Figure 3-24). This new family of ligands was named PINAP (PhthaloRineAP phthalene in analogy to QUINAP). A 1:1 diastereomeric mixture of triflate 3-71 was prepared in three steps from 3-68, 2-naphthol 3-69 and enantiopure alcohol or amine 3-70. A nickel-catalyzed C-P coupling gives the P,N-ligand as a 1:1 mixture of diastereomers of 3-72 and 3-73. The diastereomers can be separated by chromatography on silica gel or fractional crystallization. This method was an important contribution since it avoids the use of chiral palladium complexes and it allows the synthesis of analogues by the use of other chiral groups (other chiral alcohols or amines were employed instead of 3-70).

Figure 3-24. Synthesis of PINAP type ligands

3.3.4. Asymmetric Synthesis of QUINAP

Knochel and co-workers took a different approach to the synthesis of QUINAP (Figure 3-25). They separated diastereomeric sulfoxide intermediates 3-76 and 3-77 and then converted them, after separation via column chromatography, to enantiopure QUINAP in 4 additional
steps.\textsuperscript{106} They considered this protocol comparable to the conventional preparation in terms of yields, time and effort.

Figure 3-25. Knochel’s approach to (R)-QUINAP 3-11 using chiral sulfoxides

In a related report, Clayden and co-workers\textsuperscript{107} studied the equilibration of the same atropdiastereomeric sulfoxides 3-78 and 3-79 and, upon heating, it was observed a predominant formation of 3-79 (Figure 3-26). They were able to isolate 3-79 in 77\% yield. Sulfoxide 3-79 is an intermediate in Knochel’s QUINAP synthesis and this characterized a dynamic thermodynamic route to QUINAP.

Figure 3-26. Clayden’s approach to (R)-QUINAP 3-11 using chiral sulfoxides

More recently, in 2013, Stoltz and Virgil reported a very relevant advance in the field.\textsuperscript{108} The synthesis of optically active QUINAP was performed employing a kinetic resolution (KR) and dynamic kinetic resolution (DKR). This work represents the state of the art for the synthesis of QUINAP and will be briefly described here. The dynamic behavior of QUINAP and its precursors in a cross coupling between Ar-X (X = Br, OTf, OSs) and diphenylphoshine were
analyzed. In Figure 3-27, the main possibilities are depicted. Employing a palladium catalyzed coupling, the presence of an optically active chiral ligand would generate diastereomeric intermediates 3-81/3-83.

For instance, an atroposelective oxidative addition with a chiral palladium catalyst could favor the formation of either aryl-Pd 3-81 or 3-83 and, ideally, the final product would be (R) or (S)-QUINAP in 50% yield. This would require conditions in which the aryl-Pd intermediate and QUINAP do not rotate about the axis of chirality. After extensive optimization, this KR was achieved employing ligand 3-85 at 70 °C in dioxane giving (S)-QUINAP 3-12 in 45% yield and 99.5% ee (Figure 3-28). The remaining bromide 3-84 was recovered in 44% yield and 99.7% ee.

Figure 3-28. Kinetic resolution of bromide 3-74.
During the course of their work, they also explored a more elegant DKR in which a single enantiomer of QUINAP would be obtained in higher than 50% yield (hypothetically in 100% yield). After an extensive optimization of different chiral ligands, it was found that this DKR was possible (Figure 3-29). Now utilizing a triflate 3-9 and Josiphos type ligand 3-89 at 80 °C in dioxane the Stoltz group was able to convert all the starting material to enantioenriched product (90% ee).

![Chemical structure diagram]

Figure 3-29. Dynamic kinetic resolution of triflate 3-9

Under these reaction conditions both enantiomers of triflate 3-9 (3-86 and 3-87) undergo oxidative addition to give palladium intermediates 3-83 and 3-81. As represented in Figure 3-29, the key for the success of this process was to find reaction conditions in which the equilibration between diastereomeric intermediates 3-83 and 3-81 was facile favoring 3-81 which undergoes reductive elimination giving optically active 3-12 as the major product.
3.4 Deracemization of the New Chiral Imidazole-Based P,N-ligand

With our imidazole-based P,N-ligand 3-1 in hand, our next task was to obtain the ligand as a single enantiomer. At this point we did not have any evidence that ligand 3-1 was configurationally stable. The only evidence in this regard was the fact that it shows an AB pattern for the benzylic protons in the $^1$H NMR spectrum of 3-1, indicating that they are diastereotopic on the NMR time scale, however, according to our studies from Chapter 2, this information does not translate to a configurationally stable chiral compound. As expected, the AB system of this compound did not coalesce up to 120°C and this method could not be used. Actually, if coalescence occurred at that temperature or lower, the barrier to rotation would not be considerably high enough to result in a useful atropisomer for asymmetric catalysis.

Then we turned our attention to the reaction of 3-1 with palladium complex 3-51. For that, P,N-ligand 3-1 and 3-51 were dissolved in deuterated methanol in an NMR tube and analyzed. The result was satisfying since we observed the formation of two diastereomers 3-90 and 3-91 in a 1:1 ratio (Figure 3-30).

An unsatisfactory result could have been something similar to what was observed with achiral “indole QUINAP” 3-23 (Figure 3-31). The reaction between 3-23 and palladium complex 3-52 led to a single diastereomer 3-92 at room temperature. This indicates that under these reaction conditions, the biaryl bond was stereochemically labile. Upon treatment with dppe 3-61, an optically inactive ligand was recovered confirming that 3-23 is achiral.
Our next step was to attempt the fractional crystalization of the diastereomeric mixture 3-90/3-91. Many attempts using different solvent systems did not lead to a selective crystallization. Next, use of the analogous palladium complex 3-52 was attempted. As expected, upon treatment of 3-1 with complex 3-52 at room temperature, a 1:1 mixture of diastereomers was formed (Figure 3-32). Unfortunately, only one diastereomer selectively crystallized but in very poor yields and the conditions were not reproducible. The selective formation of a single diastereomer described for the resolution of QUINAP 3-4 (Figure 3-21) employing four equivalents of ligand to palladium complex (2 equivalent of ligand in relation to palladium atoms) was also attempted but the same trend was observed. This method seemed to work better, since we could get the pure diastereomer 3-93 in satisfactory yields of 30-40%.

Figure 3-32. Preliminary results on the resolution of 3-1 with palladacycle 3-52
Over the course of the optimization of this process, it was realized that during the recrystallization procedures the ratio of diastereomers would slightly change. This observation was made when conditions higher than ambient temperatures were employed and begged the question of the energy to interconversion between the diastereomers. Brown’s indole 3-23 readily gives one diastereomer when treated with chiral palladium complex 3-92 at room temperature (Figure 3-31), but QUINAP complexes 3-59/3-60 do not interconvert even at relatively higher temperatures (Figure 3-21). It seemed possible that in terms of activation energy for rotation about the biaryl bond, complexes 3-93/3-94 could be somewhere in between complexes 3-92 and 3-59/3-60. In other words, these data suggests a simple question: what would happen if we submit our diastereomeric complexes 3-93/3-94 to a higher temperature? Would both complexes be converted to a single diastereomer like Brown’s indole 3-92 did at room temperature? To probe this, a 1:1 mixture of diastereomers 3-93/3-94 in deuterated acetone was heated at 60 °C in an NMR tube. To our delight, after 24h a single diastereomer was observed as judged by $^1$H and $^{31}$P NMR (Figure 3-33).

![Interconversion of 3-94 to 3-93 under thermodynamic conditions](image)

To evaluate the practicality of this process, the experiment was performed on a larger scale by mixing racemic phosphine 3-1 with palladium complex 3-52 and KPF$_6$ in acetone. After refluxing the mixture for 24 hours the solution was filtered off, the solvent removed, and a single diastereomer was observed in the NMR of the crude reaction mixture. A single recrystallization gives the pure diastereomer 3-93 as a yellow solid in 81% yield (Figure 3-34).
In Figure 3-35, the $^1$H NMR of the 1:1 mixture of diastereomers 3-93 and 3-94 formed at room temperature is shown and the single diastereomer 3-93 after heating in acetone for 24h.

With a single diastereomer in hand, it was likely that one enantiomer of the ligand 3-2 would be isolated after decomplexation. Many research groups working in this area assume that after the decomplexation event the free ligand is obtained in >99% ee. This is likely because most of the ligands have such a high barrier that they will not racemize. Since the biaryl axis of complexes 3-93/3-94 was converted to a single diastereomer 3-93 it could be possible that
under the decomplexation conditions it could partially epimerize back. So a careful analysis of
the enantiomeric excess of free ligand 3-2 was needed after decomplexation.

The most accurate method of analysis to determine the enantiomeric excess of 3-2 would
be using a HPLC with a chiral column. However, all attempts to separate the racemic ligand 3-1
by HPLC were unsuccessful. As previously described for pyphos,\textsuperscript{103} oxidation of 3-1 to
phosphine oxide 3-96 was encouraged in hopes to obtain a more polar material and a better
separation by HPLC. This oxidation could be performed in quantitative yields using hydrogen
peroxide in dichloromethane and was usually in an analytical fashion (1-5 mg of material). As
expected, the racemic phosphine oxide 3-96 exhibits very good baseline separation using the
CHIRALPAK® 1A chiral column on the HPLC. The conditions employed are displayed in
Figure 3-36. Although this procedure was not as easy as the direct analysis of 3-1, it allowed for
the precise determination of the ee of phosphine 3-2. For all ligand ee’s describe herein, it will be
implicit that the enantiomeric excess was determined by this method.

![Figure 3-36. Oxidation of 3-1 and analysis of the oxide 3-96 by HPLC](image)

As previously described, the decomplexation is performed using one equivalent of dppe
3-61, a stronger bidentate biphosphine. The experiment was run at room temperature in
dichloromethane and 3-2 was recovered in high yield after column chromatograph. This
procedure was repeated a few times and the enantiomeric excesses determined using the method
described in Figure 3-36. Interestingly, the enantiomeric excess of 3-2 would range from 88 to 92% among different experiments.

Figure 3-37. Decomplexation of 3-93 at room temperature

State of the art ligands for asymmetric catalysis require a single enantiomer of the chiral ligand, so clearly this procedure needed improvement. However, many important experiments were able to be performed with these enantioenriched samples: 1) several enantioselective reactions were evaluated with optically active ligand 3-2 in order to decide if there was promise that this ligand would work well and whether it was worthwhile to continue working on it. Fortunately, very promising results were obtained with ~90% ee ligand and will be discussed in detail in Chapter 4; 2) ligand 3-2 was stored in the refrigerator for a period of time and analyzed for loss of the enantiomeric excess after months. It was found that the ligand does not racemize and this is essential when developing a ligand for enantioselective catalysis.

In light of that, our attention turned to improving the enantiomeric excess of the free ligand 3-2. Three possible reasons for this relatively low enantiomeric excess were envisioned:

1. The free ligand 3-2 is racemizing at some point after the decomplexation. This hypothesis was ruled out since it was found that it is configurationally stable for months with no loss of optical purity at the temperature of the experiment.

2. There is ~4-6% of the minor diastereomer (3-94) present in the starting material samples of 3-93. This possibility was very unlikely since there was a single peak in the $^{31}$P.

3. The axial chirality is being slightly scrambled during the decomplexation or oxidation step.
The third possibility seemed most likely since it is known that a 1:1 mixture of diastereomers 3-93/3-94 equilibrates to a single diastereomer 3-93. This dynamic behavior of the system could be allowing the formation of a small amount of 3-94 during the decomplexation. Also, bisphosphine 3-61 could be coordinating to the palladium complex in a random fashion releasing the undesired phosphine 3-95 to a small extent. In order to avoid this, different temperatures were explored for the decomplexation (Figure 3-38). A decomplexation at 0 °C was performed and no improvement was observed neither in terms of yield nor enantiomeric excess. Next, we attempted an experiment at very low temperature (-78 °C) but there was no reaction due to low solubility of 3-61 in dichloromethane. Finally, it was found that adding 3-61 as a solid to a solution of 3-93 at -78 °C and quickly transferring the mixture to 0 °C ice bath would release the ligand in 98% enantiomeric excess after one hour.

Figure 3-38. Optimization of the decomplexation step

The HPLC chromatograms of the corresponding oxides 3-96 (racemic) and 3-97 (98% ee) are represented in Figure 3-39. This procedure was repeated many times and has also been repeated by other PhD students in our group proving to be a reliable protocol. Usually, the decomplexation reaction gives about 100 mg of 3-2 in a single experiment.
Figure 3-39. HPLC chromatograms of 3-96 (racemic) and 3-97 (98% ee)

It is important to mention that the decomplexation using 3-61 at room temperature has been the standard procedure in the resolution process of many P,N-ligands\textsuperscript{99,101} and usually it is assumed that the ligand is enantiomerically pure based on the NMR of the single diastereomer prior to decomplexation. However, for ligands presenting relatively low barrier to rotations about the chiral axis, the decomplexation step can compromise the entire effort spent to obtain a single diastereomer of the palladium complex. In our case, this was avoided by checking the enantiomeric excess of the final ligand 3-2 through derivatization to its oxide 3-96.

### 3.5 Determination of the Absolute Stereochemistry of the P,N-Ligand

The absolute stereochemistry of P,N-ligand 3-2 was determined by X-ray crystallography of palladium complex 3-99 (Figure 3-40). 3-99 is the enantiomer of 3-92 and was prepared using palladium complex 3-53 under the same conditions as in Figure 3-38. The single crystal was obtained by vapor diffusion of diethyl ether into a concentrated solution of 3-99 in dichloromethane. Since we know the stereochemistry at the benzylic position to be (S) we can define unambiguously that in 3-99 the P,N-ligand is (R). And, by analogy, the configuration in ligand 3-2 is (S) obtained from 3-93.
Figure 3-40. X-ray crystal structure of 3-99 (hexafluorophosphate counter anion and hydrogens are omitted for clarity)

It is important to mention that in the solid state, the pentafluorobenzyl group is pointed away from the naphthalene ring. Indeed, the fluorinated aromatic ring is π-stacking with the phenyl ring at 5-position of the imidazole. A possible explanation for this is that the small dihedral angle of 54.3° observed in the biaryl moiety is required to bind to the metal. Consequently, it positions the pentafluorophenyl too close to the naphthalene and this results in repulsive interactions. In other words, rotation decreases the dihedral angle preventing the π-stacking interaction observed in the free phosphine 3-1. In the case of the free ligand 3-1 (dihedral angle: 84.9°), without metal binding, there is no need for such a small dihedral angle and the π-stacking interaction occurs with the naphthalene ring. The fact that this interaction is not with the naphthalene ring in the complex does not compromise the objectives of the project for a few reasons. Firstly, in the free ligand these interactions are happening as expected and this is probably contributing to the barrier to rotation (this topic will be discussed in Section 3.7). In addition, it will be shown in Chapter 4 that using different metals (copper, for example) π-stacking can indeed occur with the naphthalene ring.
Figure 3-41. Comparison between X-ray crystal structures of 3-99 and 3-100 (The pictures present only the core of the structures)

For a point of comparison with QUINAP 3-4, the X-ray crystal structure of palladium complex 3-100 was analyzed. Both structures (3-99 and 3-100) are displayed in Figure 3-41 and they have the same stereochemistry in all respects. The dihedral angles $\theta$ and bite angles $\phi$ are listed for both structures. Although the bite angle $\phi$ is slightly smaller in 3-99, the dihedral angle $\theta$ is significantly smaller (>10° difference) probably due to the smaller five-membered imidazole ring. The metal environments with either P,N-ligands are shown. The chiral auxiliaries and counter anions were removed for clarity. The selected views demonstrate that a significant difference in the steric profile of the complexes is present at the nitrogen binding site. It appears that the phenyl rings of the imidazole generate a bulky chiral environment at this area.

3.6 Rationalization of the Two-Step Deracemization

With regards to the two-step deracemization process, it can be viewed as a dynamic thermodynamic resolution. A general energy diagram can be drawn to illustrate the two-step process (Figure 3-42).
Figure 3-42. Energy and reaction diagram for the two-step deracemization process

The racemic mixture of ligand 3-1 is represented by L_S and L_R in Figure 3-42.

Complexation of 3-1 with the chiral palladium complex 3-52 at room temperature gives an equimolar mixture of 3-93 and 3-94. At this point, 3-93 and 3-94 are equimolar and have different energies, they are diastereomers. The decomplexation of this mixture using dppe 3-61 provides a racemic mixture of ligand 3-1. In order to obtain optically active 3-2, a fractional crystallization can, in principle, be performed to separate 3-93 and 3-94 and decomplexation of 3-92 provides 3-2. However, as previously discussed this did not provide satisfactory results. On the other hand, exposure of the mixture to acetone at 60 °C causes equilibration and the less stable diastereomer 3-94 converts to the most stable diastereomer 3-93. Fortunately, under
thermodynamic conditions, the final material contains essentially a single diastereomer 3-93 and decomplexation gives enantioenriched 3-2 (L_S).

In order to understand the difference in stability between the two diastereomers 3-99 and 3-101, the isolation of crystals for X-ray analysis of the unobserved and presumably less stable diastereomer 3-101 was attempted but this proved to be difficult. As an alternative, X-ray quality crystals of the equimolar mixture of diastereomers 3-99/3-101 were obtained (prepared as in Figure 3-32) and the structure solved.

![Figure 3-43. X-Ray crystal structure of 3-99/3-101 (hydrogen atoms are omitted)](image)

The X-ray structure of the crystals revealed a 1:1 packing of the two diastereomers (Figure 3-43). This structure was useful because a conformational analysis of each diastereomer became possible and insight into the favored and disfavored interactions on each structure was gained.

The structures of each diastereomer are depicted separately in Figure 3-44. The most relevant difference between the two structures is the conformation of the highlighted five-membered ring. In the more stable isomer 3-99 it has adopted a stable “envelope” conformation whereas it is flattened in 3-101 suggesting a more strained system. It is believed that this difference is directly associated with the relative stereochemistry of each diastereomer which
will be discussed in the next paragraphs.

Figure 3-44. Conformational analysis of 3-59 and 3-60

Another important feature of this deracemization is that the naphthalene ring from 3-52 is required for the feasibility of this process. A control experiment employing palladium complex 3-51 was performed and a 1:1 mixture of diastereomers is obtained under the same conditions described before (Figure 3-45).

Figure 3-45. Attempt of deracemization with 3-51

A very similar trend was observed by Brown while studying the diastereomeric palladium complexes 3-100/3-102 and 3-102/3-104 formed from QUINAP 3-4 (Figure 3-46). He suggests that the presence of an extra benzene ring in 3-100/3-102 is important and a more strained system results. Consequently, a greater difference in energy for the pair of diastereomers is observed making the fractional crystallization more facile in this naphthyl-Pd system. In the
case of 3-103/3-104, the methyl group on the benzylic position has more degrees of freedom diminishing the energy difference between the diastereomers. Indeed, when Brown and co-workers tried to fractionally crystallize 3-103/3-104 a quasiracemate was formed in which each diastereomer would adopt very similar conformations. On the other hand, for 3-100 and 3-102 the benzylic methyl groups are “locked” since it interacts with the peri H of the naphthalene resulting in a more strained system and a greater energy difference between diastereomers. These results are consistent with our observations when trying to deracemize palladium complexes 3-90 and 3-91.

Figure 3-46. Palladium complexes 3-100/3-102 and 3-102/3-104

Studies on the importance of the counter-anion hexafluorophosphate was also performed. Interestingly, the inclusion of KPF$_6$ is vital to the success of the deracemization reaction, as two non-interconverting diastereomers are observed in the absence of this additive. Control experiments were performed to study this issue, and an equal mixture of two diastereomers 3-105/3-106 was formed when KPF$_6$ was omitted but under otherwise identical reaction conditions. Additionally, recomplexation of 3-2 in the absence of KPF$_6$ results in a single diastereomer 3-105 that does not revert to the same 1:1 mixture of diastereomers upon heating.
The different behavior of the palladium complexes **3-105/3-106** in the absence of hexafluorophosphate suggests that a cationic palladium is needed for the epimerization process to occur. As discussed previously, careful analysis of the X-ray structure of palladium complex **3-99** shows that the pentafluorobenzyl group rotated in order to π-stack with a phenyl group at 5-position of the imidazole. As described in Chapter 2, this directly affects the barrier to rotation around the biaryl bond. In other words, if the π-stacking is not occurring on the naphthalene ring, a reduced barrier to rotation might be expected. Actually, if the chloride is acting as a ligand instead of the imidazole nitrogen, as in **3-107**, the barrier to rotation around the biaryl bond would be expected to be higher (Figure 3-48). Therefore, switching to a less coordinating PF₆⁻ counteranion decreases the electron density on the palladium, forcing the nitrogen to coordinate in a bidentate fashion and the energy barrier for rotation about the biaryl bond decreases. The results shown in Figure 3-47 are consistent with this explanation.

Figure 3-48. Suggested conformational changes for neutral and cationic complexes
There are reports of P,N-ligand in the literature in which the square-planar palladium complex has a chloride coordinated instead of the nitrogen of the heterocycle (Figure 3-49).

![Figure 3-49. Monodentate P,N-ligands in complexes 3-108 and 3-109](image)

Palladium complexes 3-108\textsuperscript{112} and 3-109\textsuperscript{113} were isolated by other groups and the structures confirmed by X-ray crystallography. Interestingly, in both cases there is a sterically demanding group next to the potentially coordinating nitrogen which could be one of the factors favoring the coordination of the chloride instead. In 3-107, there is also a phenyl group adjacent to the imidazole nitrogen and an analogy can be drawn with 3-108 and 3-109.

![Figure 3-50. Suggested pathway for the deracemization process](image)

A suggested pathway for the deracemization process is illustrated in Figure 3-50. The complexation of racemic ligand 3-1 with chiral palladium complex 3-53 generates two diastereomers 3-107/3-110. In the presence of KPF\textsubscript{6}, the nitrogen coordinates to palladium and...
the pentafluorobenzyl group π-stacks on the phenyl group on the other side of the biaryl axis thereby lowering its barrier to rotation. Consequently, the less stable diastereomer 3-101 then converts to the observed diastereomer 3-99 by rotating about the biaryl bond.

3.7 Evidence of π-Stacking in Solution

Evidence of π-stacking was obtained early on when X-ray analysis of racemic P,N-ligand 3-2 was performed. In the solid state, the pentafluorophenyl ring is π-stacking with the naphthalene ring in a parallel displaced fashion. Besides this data, further evidence of the π-stacking interactions in solution was needed. As described in Chapter 2, model systems employed to study π-stacking interactions are well known.51,52 Usually, the feasibility of an intramolecular π-stacking interaction is studied by modifying one of the aromatic rings in a model system and analyzing the impact on the barrier to rotation.

![Figure 3-51. Fluorinated and non-fluorinated P,N-ligands 3-1 and 3-111](image)

In our case, a direct comparison of the barrier to rotation about the biaryl bonds in fluorinated 3-1 and 3-111, a non-fluorinated analogue, would be appropriate (Figure 3-51). Based on our studies described in Chapter 2, compound 3-111 would not have the same level of π-stacking ability as 3-1. The presence of an AB system for the methylene protons of both compounds suggested the use of VT-NMR to calculate the rotational barriers but, as mentioned before, the AB systems of both compounds did not coalesce up to 120 °C.

Since the coalescence method was not appropriate to determine barriers above approximately 25 kcal/mol, a different approach was needed. Compound 3-2 was obtained in
98% enantiomeric excess, therefore kinetic studies on the racemization of this compound would give the barrier to rotation. To make the desired comparison, the preparation of optically active 3-111 was essential and this compound was prepared by a similar route (Figure 3-52). Although the synthesis of racemic 3-111 occurred as expected, the two step deracemization process presented a different behavior. The equilibration event employing palladium complex 3-52 was feasible at room temperature, suggesting a lower barrier for the biaryl bond of 3-114. The reaction of 3-52 and 3-111 in the presence of KPF$_6$ gave 3-114 as a single diastereomer in 58% yield after 24h. Treatment of 3-114 with 3-61 at -78 to 0 °C released optically active 3-115 in 88% yield, however, the ee of 3-115 was observed to be only 52%. This is probably due to a more facile epimerization during the decomplexation event.

Figure 3-52. Synthesis and deracemization of 3-111

The enantiomeric excess was determined analogously to 3-2 by oxidation of 3-111 using hydrogen peroxide in dichloromethane (Figure 3-53).
Figure 3-53. Determination of the enantiomeric excess of 3-115

The HPLC chromatograms for the phosphine oxides 3-116 (racemic) and 3-117 (optically active) are presented in Figure 3-54.

Figure 3-54. Chromatograms of 3-111 and 3-117

With optically active 3-2 and 3-115 in hand, the racemization studies were performed (Figure 3-55). To make the right comparisons both compounds were submitted to the same conditions employing dichloroethane (DCE) as a solvent. Solutions (2 mM) of 3-2 (98% ee) or 3-115 (52% ee) in DCE were heated in a 75 °C oil bath. The enantiomeric ratio was measured by chiral HPLC (after oxidation of aliquots containing the phosphines to the corresponding oxides). The decay in enantiomeric excess of 3-2 and 3-115 over time are shown in the graphs below (Figures 3-56 and 3-57).
Figure 3-55. Racemization of optically active phosphines 3-2 and 3-115

Figure 3-56. Plot of the ee (%) versus time for the racemization 3-2

Figure 3-57. Plot of the ee (%) versus time for the racemization 3-115
Figure 3-58. Plot of $-\ln([M]_t-[M]_{eq})/([M]_0-[M]_{eq})$ versus time at 75 °C for 3-2

Figure 3-59. Plot of $-\ln([M]_t-[M]_{eq})/([M]_0-[M]_{eq})$ versus time at 75 °C for 3-115

A plot of $-\ln([M]_t-[M]_{eq})/([M]_0-[M]_{eq})$ versus time, according to the equation described by Müller,\textsuperscript{114} resulted in the graphs shown in Figures 3-58 and 3-59. Where $[M]_t$ is the enantiomeric ratio at a certain time and $[M]_{eq} = 0.5$. Using the slope of these lines and the Eyring
equation, the free activation energy ($\Delta G^\ddagger_T$) and the half-lives ($t_{1/2}$) for compounds 3-2 and 3-115 were determined (Figure 3-60). It was found that 3-115 has a half-life of 22 min at 75 °C in DCE, whereas 3-2 has a half-life of 8.70 h. The absolute free activation energies to rotation were calculated to be: 28.37 and 26.18 kcal/mol for compounds 3-2 and 3-115, respectively. This corresponds to $\Delta \Delta G^\ddagger (75 \degree C) = 2.2$ kcal/mol, a value that is within the range of previously reported values for $\pi$-stacking,\textsuperscript{51,52} and demonstrates that the electronic perturbation by simple inclusion of the fluorine atoms significantly increases the barrier to rotation of these biaryls.

\[
\ln \left( \frac{[M]_0 - [M]_{\text{eq}}}{[M]_0 - [M]_{\text{eq}}} \right) = \frac{-2kT}{R} \ln(k_0)(k) \\
t_{1/2} = \ln2/2k \\
\Delta G^\ddagger_T = RT \ln\left(\frac{k_0}{k}\right)(k) \\
\Delta G_{75^\degree C}^\ddagger = 28.4 \text{ kcal/mol} \\
t_{1/2} = 8.70 \text{ hours} \\
\Delta G_{75^\degree C}^\ddagger = 26.2 \text{ kcal/mol} \\
t_{1/2} = 0.37 \text{ hours}
\]

Figure 3-60. Determination of the barriers to rotation of 3-2 and 3-115 at 75 °C

3.8 Summary and Conclusions

In summary, the design and preparation of an imidazole-based chiral biaryl P,N-ligand 3-2 was accomplished. The presence of the pentafluorobenzyl moiety enhances the barrier to rotation of the P,N-ligand allowing it to be useful for asymmetric catalysis. The method to obtain optically active 3-2 appears as the first example of a deracemization process to obtain enantiomerically pure axially chiral P,N-ligands. The main drawback of this method is the use of one equivalent of palladium and efforts are being made towards the exploration of other metals and chiral auxiliaries for the deracemization. However, with a reliable protocol for obtaining this ligand as single enantiomer, the evaluation of 3-2 in different enantioselective reactions was
possible. Chapter 4 will describe the importance of P,N-ligands in metal-catalyzed asymmetric transformations and show the performance of 3-2 in these reactions.
CHAPTER 4
APPLICATIONS OF THE NEW P,N-LIGAND IN ASYMMETRIC TRANSFORMATIONS

The success of P,N ligands in asymmetric catalysis has been reported in several reviews.\textsuperscript{101,115,116} The most recent update, published in 2014 by Carroll and Guiry,\textsuperscript{83} shows how these type of ligands are continuing to be developed. Very recently, an interesting Perspective article appeared in the Journal of Organic Chemistry covering exclusively axially chiral P,N-ligands.\textsuperscript{117} Although P,N ligands have been known for decades, the number of axially chiral structures with this moiety is relatively small. Unfortunately, the present state of asymmetric catalysis does not allow predictions into the performance of a new ligand in a reaction. The incorporation of a five-membered heterocycle in the chiral axis might offer advantages. This motivated us to evaluate \textbf{4-1} in known and new transformations. As an obvious strategy, reactions in which QUINAP performs well were selected to be tested first.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ligands.png}
\caption{Axially Chiral P,N-ligands \textbf{4-1} and QUINAP \textbf{4-2}}
\end{figure}

It is important to mention that the extensive efforts for the preparation of a single ligand described in Chapter 3 was motivated by early data obtained in the application of \textbf{4-1} in asymmetric transformations. These preliminary data are presented herein. In addition, a full methodological study of the copper-catalyzed A\textsuperscript{3}-coupling employing \textbf{4-1} will be given.

\subsection{4.1. P,N-ligands in Asymmetric Catalysis}

New chiral ligands for asymmetric catalysis are reported very frequently and the number of ligands that catalyze specific reactions in high enantiomeric excess are extensive. However, the number of ligands that catalyze a number of diverse reactions are limited.\textsuperscript{15} These ligand...
scaffolds were coined by Jacobsen as “privileged structures” due to their ability to induce chirality in various transformations. Later, a book named “Privileged Chiral Ligands and Catalysts” divided these structures in eleven chapters, in which each chapter covers a privileged scaffold. The top row of Figure 4-2 shows three examples: bisoxazoline 4-3, BINAP 4-4 and Josiphos 4-5 type structures. These structures were selected to illustrate the three types of chirality discussed by Cahn, Prelog, and Ingold: central, axial, and planar chirality.

Figure 4-2. Privileged ligand structures (top) and P,N ligands (bottom)

In general, the current state-of-the-art for the development of new chiral ligands relies upon modification of a previous family of ligands. In this context, the first P,N-ligands were inspired by P,P or N,N ligands. The success of the latter ligands encouraged many chemists to switch a phosphorus to a nitrogen and vice-versa. Interestingly, the most successful P,N-ligands were derived from privileged structures (Figure 4-2). Indeed, PHOX type ligands 4-6 were designed as an extension of bisoxazolines 4-3 and now are also considered privileged. PHOX ligands appear frequently in metal-catalyzed asymmetric reactions and this topic will be revisited in Section 4.3.5. As stated in the previous chapters, axially chiral QUINAP 4-2 was inspired by
the success of BINAP 4-4. JOSIPHOS type P,N-ligands are exemplified by pyrazole-based ligands 4-7, but there can be other nitrogen donors. This is an important class of ligands that was suggested based on JOSIPHOS 4-5, but they will not be covered in detail.

In Figure 4-3, a general P,N-ligand structure is illustrated. The main distinction of a P,N-ligand, if compared to a N,N or P,P, is the presence of two chemically different binding sites. When coordinated to a metal, the soft phosphorus atom has \( \pi \)-acceptor and \( \sigma \)-donor properties whereas the hard nitrogen acts primarily as a \( \sigma \)-donor. This allows for very subtle tuning of the electronics at the metal center by changing the nature of the substituents at phosphorus and nitrogen atoms. In the majority of P,N-ligands, the phosphorus atom is part of a triaryl phosphine but alkyl groups also exist. On the other hand, the nitrogen donor appears in many different functionalities, such as amines, imines, heterocycles, etc. The nitrogen donor atoms of axially chiral P,N-ligands are usually \( sp^2 \) hybridized nitrogens such as in 4-1 and 4-2.

![Figure 4-3. General P,N-ligand structure and properties](image)

Togni’s work on the pyrazole-based ferrocenyl ligands 4-7 is a representative example of how tuning the electronics of a P,N-ligand can be effective (Figure 4-4). While studying the rhodium-catalyzed asymmetric hydroboration/oxidation of styrene 4-8, it was found that the combination of an electron-poor phosphine (\( Ar = 3,5-(CF_3)_2Ph \)) and an electron-rich pyrazole ring (\( R = CH_3 \)) in ligand 4-13 would deliver sec-alcohol 4-9 in 98.5% ee. Switching or changing the electronic properties of the P,N ligand would result in a poor enantiomeric excess (See results with 4-10, 4-11, and 4-12).
4.2. Asymmetric Reactions Catalyzed by Axially Chiral P,N-ligands

The aim of this section is to present the main asymmetric transformations in which axially chiral P,N-ligands stand out. After the seminal reports by Brown on the discovery of QUINAP, many groups developed new asymmetric reactions employing QUINAP and/or new axially chiral P,N-ligands.\textsuperscript{83,101} The most important examples of ligand variations are presented in Figure 4-5.

Guiry and co-workers developed a new family of ligands \textsuperscript{4-15},\textsuperscript{102,113} named Quinazolinap, comprised of a quinazoline heterocycle in the biaryl backbone. The advantage of these ligands is the possibility for variation at 2-position of the nitrogen heterocycle allowing for tuning of the electronic and steric factors on this side of the structure. Pyphos \textsuperscript{4-16,96,103} discussed in Chapter 3 (Section 3.3.2), is a pyridine analogue of QUINAP that was developed by
Kwong. PINAP ligands 4-17\textsuperscript{104,105} were developed by Carreira and co-workers during the course of their studies on alkynylation reactions. The main advantage of PINAP is the introduction of a chiral center to facilitate resolution (Section 3.3.3). Additionally, access to other PINAP analogues is facile. There are many reactions in which axially chiral P,N-ligands were employed with success. A few examples will be described to show the highlights of each reaction and it should be noted that this is not a comprehensive review on the field.

4.2.1. Rhodium-Catalyzed Hydroboration of Arylalkenes

As described previously, axially chiral P,N-ligands appear to be the best ligand choice for the rhodium-catalyzed hydroboration of arylalkenes, furnishing the sec-alcohols 4-19 in extremely high enantioselectivity for a wide range of substrates. The success of P,N-ligands from Figure 4-5 in this reaction is summarized and the results from each ligand is presented below (Figure 4-6). The chirality on the axis of the ligand correlates to the configuration of the product so that (\(S\))\textsubscript{ax} gives (\(S\)) sec-alcohol and (\(R\))\textsubscript{ax} gives (\(R\))-sec-alcohol in all cases.

![Figure 4-6. Examples of sec-alcohols 4-19 obtained through rhodium-catalyzed enantioselective hydroboration](image-url)
4.2.2. Rhodium-Catalyzed Diboration of Alkenes

In 2003, Morken and co-workers developed the first asymmetric diboration of alkenes employing rhodium catalyst 4-29 and dicatehol-diborane 4-30. In their studies, QUINAP 4-2 was shown to be a superior ligand in comparison to BINAP 4-4. For instance, in the reaction with \textit{trans}-alkene 4-28, a \textit{syn}-addition product is observed and retained through the oxidation to give the \textit{syn}-diol 4-32 in high ee (Figure 4-7).

![Diboration reaction](image.png)

Figure 4-7. Diboration of \textit{trans}-alkene 4-28 with B\textsubscript{2}(cat)\textsubscript{2}

4.2.3. 1,3-Dipolar Cycloadditions

Although 1,3-Dipolar Cycloadditions have been extensively explored, the development of asymmetric variants of this reaction is an ongoing process. Schreiber’s work on the development of a silver-catalyzed reaction between azomethine ylides and electron-poor alkenes revealed QUINAP as the best ligand. The reactions were carried out at -20 °C in THF to give the tetrasubstituted pyrrolidines in good yields and good enantioselectivities. As an example, the cycloaddition between iminoester 4-34 and \textit{tert}-butyl acrylate 4-33 yielded the cyclic product 4-35 as a single diastereomer in 84% ee and 97% yield (Figure 4-8). Reisman and co-workers extended this type of reaction to a double cycloaddition process. The first [3 + 2] cycloaddition is analogous to Schreiber’s, giving the pyrrolidine intermediate 4-37. In the same pot, a reaction between 4-37 and cinnamaldehyde 4-38 generates an iminium salt which can equilibrate to a new azomethine. Reaction between the new ylide and alkene 4-36 gives the
bicyclic product 4-39 in 90% ee and 74% yield. It is important to mention that the second step does not require the silver/QUINAP catalyst, giving the product in a diastereoccontrolled manner.

Figure 4-8. Examples of silver-catalyzed [3 + 2] cycloadditions

**4.2.4. Copper-Catalyzed Alkynylation of Iminium Ions**

The three-component reaction between an aldehyde 4-40, an amine 4-41 and a terminal alkyne 4-42 gives a propargylic amine 4-43 in one-pot in a very efficient manner (Figure 4-9). This reaction is the so-called A³-coupling and can be catalyzed by different metals with copper, gold, and silver complexes being the most prevalent.¹²⁴,¹²⁵ In general, this transformation tolerates aliphatic and aromatic aldehydes, primary and secondary amines and a variety of alkynes (Figure 4-9). The reaction is a very efficient way to access propargylic amines from simple substrates generating water as only byproduct.

Figure 4-9. General scheme for the A³-coupling reaction
In 2003, Knochel and co-workers reported the first enantioselective copper-catalyzed A³-coupling reaction. The method employed a QUINAP/CuBr catalytic system providing enantioenriched propargylic amines 4-44 (Figure 4-10).

![Chemical diagram](image)

**Figure 4-10. First examples of an enantioselective A³-coupling**

In general the reaction times were extremely long varying from 2-6 days. In a full report of their studies, a broad range of substrates were explored. Secondary aldehydes, such as cyclohexanecarboxaldehyde 4-45, furnished the propargylamines in excellent enantioselectivity. On the other hand, the lower reactivity of aromatic aldehydes had an impact on the yield and enantioselectivity of these reactions. For instance, the A³-coupling of aldehyde 4-49, phenylacetylene 4-50 and diallylamine 4-51 gave propargylamine 4-52 in 43% yield and 63% ee after five days. This specific reaction was explored with P,N-ligand 4-1 and will be discussed in more detail further in this chapter.

Although the elegant reaction developed by Knochel was the first example of an asymmetric A³-coupling, important drawbacks emerged. For instance, the reaction only worked with dibenzyl- or diallylamines generating propargylic tertiary alkyl amines that are difficult to
deprotect. The selective amine deprotection of dibenzylamine products is not possible without reduction of the alkyne and the diallylamine cleavage requires the use of excess of palladium catalysts (eight equivalents).\textsuperscript{128}

In view of this, Carreira and co-workers developed an alternative in which 4-piperidone 4-54 was used as the amine component and (R,R)-PINAP 4-55/CuBr as a catalyst to deliver propargylic amines in high yields and enantioselectivities (Figure 4-11).\textsuperscript{128} Using a polymer-supported scavenger the amine products, such as 4-56, were deprotected through a double-retro-Michael addition, with concurrent desilylation, to give the amine hydrochloride 4-57 as a single enantiomer.

![Figure 4-11](image_url)

Figure 4-11. Asymmetric A\textsuperscript{3}-coupling using piperidone 4-54

The potential application of these reactions was demonstrated early on by Knochel on the synthesis of (S)-coniine.\textsuperscript{127} Recently, Ma and co-workers used the method as an entry to disubstituted allenes (Figure 4-12).\textsuperscript{129} The two-step process generates the propargylic amines using (R,R)-PINAP 4-55/CuBr and, after filtration of the copper catalyst, the reaction mixture is treated with half an equivalent of ZnI\textsubscript{2} and NaI to provide enantioenriched allenes 4-60 in a
stereospecific fashion.

Figure 4-12. A³-coupling reaction as an entry to enantioenriched allenes

Another contribution to the field came from Schreiber’s group. The addition of acetylides to isolated dihydroisoquinoline iminium ions was explored. In this case, with the (S)-QUINAP 4-2/CuBr cyclic propargylic amines were obtained in good yields and enantioselectivities. The iminium salts were prepared and submitted to the reaction conditions to give the cyclic tertiary amines in excellent yields and enantiomeric excesses. The efficiency of the procedure is exemplified in a concise synthesis of the neuroactive alkaloid homolaudanosine 4-64 (Figure 4-13).

Figure 4-13. Concise synthesis of homolaudanosine 4-64

4.2.5. Copper-Catalyzed Acetylide Addition to Michael Acceptors

Carreira’s work on the alkynylation of Meldrum’s acid derivatives is a great combination of ligand design and reaction discovery. The reaction employed phenylacetylene 4-50 and alkylidene 4-65 to give product 4-66 (Figure 4-14). The reaction was performed in a biphasic medium between water and phenylacetylene 4-50. Also, although a source of copper(II) is initially added to the flask, this reaction is catalyzed by an in situ generated copper(I) species. This is easily done by mixing Cu(OAc)₂ with (+)-sodium ascorbate which acts as a reducing
agent. At the outset, they tested ~25 commercially available chiral ligands which would ligate copper and induce chirality in the reaction. Among them, QUINAP gave the best enantioselectivity of 42% although this is not high enough to have any practical synthetic utility (Figure 4-14).

Figure 4-14. Conjugate addition to Meldrum’s acid derivatives employing QUINAP 4-2

QUINAP derivatives for optimization were scarce and Carreira and co-workers proposed the design of a new family of ligands, which would allow the synthesis of analogues. The idea behind the design of PINAP ligands was previously discussed (Section 3.3.3). With approximately 10-15 PINAP analogues in hand, extensive optimization studies were conducted, to achieve a high enantiomeric excess for product 4-66.

Figure 4-15. Optimized conditions for the copper-catalyzed acetylide addition to Meldrum’s acid derivatives
As shown in Figure 4-15, the highest yields and enantioselectivities were obtained with PINAP ligand 4-68, (94% yield, 95% ee). Interestingly, the atropdiastereomer 4-69 gave low yield and enantioselectivity.\textsuperscript{131} As a consequence, besides the axial chirality, the other chiral center present in the ligand proved to be influential on the stereoselectivity outcome of the reactions.

4.2.6. Miscellaneous Nickel-Catalyzed Reactions

There are two very recent examples in which QUINAP was the preferred ligand in nickel-catalyzed reactions. The first involves an annulation reaction between heterocycle 4-70 and allene 4-71 to furnish sulfonamide 4-72 in 87% yield and 96% ee (Figure 4-16).\textsuperscript{132} The proposed pathway of this novel reaction involved a nitrogen extrusion of 4-70 with concurrent oxidative addition of nickel(0). An insertion at the central carbon of the allene followed by a reductive elimination provides 4-72. The product could be manipulated to β-methylphenethylamine 4-73 with high diastereoselectivity.

Another example, published in 2013, is a nickel-catalyzed [2 + 2 + 2] cycloaddition to furnish enantioenriched helicenes.\textsuperscript{133} For instance, when trialkyne 4-77 was treated with (R)-QUINAP/Ni(COD)\textsubscript{2} catalyst, product 4-79 was obtained in 80% yield and 85% ee.
Figure 4-17. Nickel-catalyzed enantioselective synthesis of helicenes

### 4.3. Enantioselective Reactions with Imidazole-Based P,N-ligand

Although QUINAP and analogues are not considered “privileged” structures, the number of different reactions catalyzed by the metal complexes of these ligands is impressive. As mentioned before, with enantioenriched P,N-ligand 4-1 in hand, a few of these enantioselective transformations were tested. Preliminary experiments on the rhodium-catalyzed hydroboration/oxidation were not successful due to regioselectivity issues and attention was directed to copper- and palladium-catalyzed reactions. Our work focused mainly on copper-catalyzed acetylide additions which perform exceedingly well with ligand 4-1. In addition, preliminary results on the acetylide addition to pyridinium ions and alkylidene of Meldrum’s Acid derivatives are presented. The palladium-catalyzed asymmetric allylic alkylation was investigated for a direct comparison with QUINAP and will be discussed at the end of this chapter.

#### 4.3.1. A³-Coupling Reaction Employing Imidazole-Based P,N-ligand

As described in Chapter 3 during the optimization of the ligand synthesis we obtained samples of ent-4-1 in 87-92% enantiomeric excess. Early data was obtained on the copper-catalyzed A³-coupling reactions employing enantioenriched P,N-ligand ent-4-1 (87% ee). For a direct comparison with QUINAP, the alkynylation of in situ generated iminium ions between aromatic aldehydes, phenylacetylene 4-50 and diallylamine 4-51 were evaluated (Figure 4-18). The desired propargylic amines were obtained in excellent yields and good enantioselectivities.
It is worth mentioning that Knochel encountered difficulties when employing QUINAP for these exact reactions.\textsuperscript{126,127} Although aliphatic aldehydes performed very well, aromatic aldehydes proved to be more challenging in terms of yields and enantioselectivities.

![Figure 4-18. Copper-catalyzed three component reaction](image)

In addition, as depicted in Figure 4-18, our reaction times were much shorter giving good to excellent yields for benzaldehyde 4-80, p-methoxybenzaldehyde 4-81, and p-trifluoromethanebenzaldehyde 4-49 in only 24 hours. Furthermore, using the 87\% ee ligand ent-4-1, the enantioselectivities were higher than those observed when QUINAP was employed as a single enantiomer (\textgreater 99\% ee). In particular, electron-poor aldehyde 4-49 gave only 43\% yield and 63\% ee with QUINAP ent-4-2 after five days\textsuperscript{126} whereas with imidazole-based ligand ent-4-1 (87\% ee ligand) the yield was 94\% and a respectable ee of 73\% after 1 day.

As pointed out, three main improvements were observed when employing ligand ent-4-1 instead of QUINAP ent-4-2 in the copper-catalyzed A\textsuperscript{3}-coupling: 1) shorter reaction times; 2) higher yields; 3) higher enantioselectivities for aromatic aldehydes. These results encouraged us to explore the reaction in more detail with a close eye on reactivity and stereoselectivity.

Knochel reported that reactions catalyzed by a CuBr/QUINAP complex took between 1-6 days for completion.\textsuperscript{126,127} As an example, when employing butyraldehyde 4-84, TMS-acetylene
and dibenzylamine 4-47 at room temperature the product was obtained in 88% yield after 5 days. With racemic ligand rac-4-1, a much shorter reaction time of 1 day was observed, furnishing the product in 97% yield. In order to explore the reactivity of our catalytic system, the same experiment was performed at 0 °C and the product was found in 92% yield. These results were encouraging since reactions at lower temperatures often provide better selectivities.

Figure 4-19. A³-coupling employing racemic ligand rac-4-1

With this motivation, we expended every effort to obtain 4-1 as a single enantiomer (Chapter 3). With this ligand in hand (98% ee), efforts were directed towards the enantioselectivity of the reaction with different substrates. As can be seen in Table 4-1, the reactions were highly enantioselective over a range of aldehydes. As might be expected, with aliphatic aldehydes α-substitution increases selectivity (e.g., entries 2 vs 4). It is also noteworthy that, using 4-1, these conditions work well for aromatic aldehydes, which are the most challenging substrates for the reaction. Remarkably, the presence of electron donating or -withdrawing groups has little effect on selectivity (entries 5–9), nor does the reaction temperature. When 4-49 was allowed to react at 0 °C, the reaction was very slow, yielding 4-97 in only 15% after 4 days, but in 95% ee (entry 8). Increasing the temperature to 22 °C restored the reactivity to an acceptable level (70% yield after 24 h) and had little effect on the ee (92% ee, entry 9). In comparison, the previous best yield obtained with this electron-deficient aldehyde was 43% after 4 days to obtain the product in 63% ee.
Due to the very low polarity of the products, a deprotection of the silyl group was needed in order to separate the enantiomers in the HPLC. That was done using a methanolic KOH solution which readily provided the desilylated products in quantitative yields (Figure 4-20).
Products 4-92 and 4-96 did not require this procedure since they were readily separable by HPLC.

Figure 4-20. Desilylation of propargylamines 4-86

Carreira and co-workers have also developed modified conditions to employ amine 4-54, which can be readily deprotected. With these conditions, using the PINAP ligand, it was reported that aromatic aldehydes do not provide satisfactory results. In contrast, ligand 4-1 enables the use of both aliphatic and aromatic aldehydes with high enantioselectivity (Figure 4-21).

Figure 4-21. Alkyne addition with 4-54

These results lead to the conclusion that 4-1 is the best ligand for the enantioselective $\text{A}^3$-coupling to date, displaying the highest levels of reactivity and selectivity over the broadest range of substrates. More importantly, these results demonstrate the potential of the new design element exemplified by 4-1.

4.3.2. Mechanistic Aspects of the Copper-Catalyzed $\text{A}^3$-Coupling Reaction

The mechanism of the copper-catalyzed $\text{A}^3$-coupling reaction is not fully understood to date. A tentative mechanism for the racemic version of the reaction is depicted in Figure 4-22. The coordination of the copper species to the triple bond of 4-42 enhances the acidity of the
terminal proton favoring the formation of copper acetylide species. Coordination of the metal to the terminal alkyne is important due to the absence of a strong base in the reaction medium (4-41 and 4-43 are not strong enough to deprotonate a terminal alkyne). The nucleophilic attack of the copper acetylide to an \textit{in situ} formed iminium ion furnishes the propargylamine products 4-43 and regenerates the catalyst.

![Chemical reaction diagram]

Figure 4-22. Tentative mechanism for the A$^3$-coupling

Preliminary aspects of the mechanism for the enantioselective A$^3$-coupling reaction were discussed by Knochel.$^{126,127}$ In his seminal report employing QUINAP, the mechanism was proposed based on two observations: a dimeric X-ray structure of [CuBr\((R)$-QUINAP\)]$_2$ 4-95$^{135}$ (Figure 4-23) and a strong positive non-linear effect on the reaction (Figure 4-24).

The dimeric structure of [CuBr\((R)$-QUINAP\)]$_2$ complex 4-95 has a distorted planar four-membered Cu$_2$(μ-Br)$_2$ ring. Although there are P-Cu bonds, the distances between copper and nitrogen are longer than usual, resulting in a weak Cu-N bond and a distorted tetrahedral geometry in both copper atoms.
Mechanistic studies by Knochel and co-workers shows a strong positive nonlinear effect (Figure 4-24). For instance, employing 10% ee QUINAP, propargylic amine 4-97 was obtained in 68% ee. This suggests that diastereomeric dimers are formed in solution and the heterochiral \([\text{Cu}_2\text{Br}_2\{(\text{R})/\text{(S)}-\text{QUINAP}\}\}_2\] complex reacts much more slowly than the homochiral \([\text{CuBr}\{(\text{R})-\text{QUINAP}\}\}_2\] complex.

Figure 4-23. X-ray structure of 4-95

Figure 4-24. Non-linear effect observed on the A³-coupling employing QUINAP
Based on these observations, a mechanism involving a dimeric complex 4-98 was proposed. The first step would be the activation of the alkyne $\pi$-system by the copper complex resulting in a $\pi$-complex 4-99. Aminal 4-100 generated by a reaction between the secondary amine 4-41 and aldehyde 4-40 would form an adduct with 4-99 resulting in 4-101. Deprotonation of the alkyne, followed by water elimination, would form complex 4-102 between an iminium ion and copper acetylide. Nucleophilic attack on the prochiral face of the iminium ion by the chiral copper acetylide complex leads to the product 4-44 and regenerates the catalyst 4-98. In this last event, in which the chiral center is formed, one diastereomeric transition state is favored leading to a high enantiomeric excess.

Figure 4-25. Tentative mechanism for the enantioselective copper-catalyzed A$^3$-coupling reaction

In order to obtain insight into the mechanism of the reaction with ligand 4-1, X-ray crystal structure analysis of rac-4-2/CuBr complex was desired. For this, different solutions of rac-4-1 and CuBr were dissolved in several solvent mixtures and recrystallization attempted. After optimization, white crystals were formed by the vapor diffusion of diethyl ether into a
yellow solution of \textit{rac}-4-2/CuBr in toluene/dichloromethane as solvent system. The optimized recrystallization conditions were employed with enantiopure ligand 4-1 to the formation of enantiomerically pure homochiral complex \( \text{[CuBr\{(S)-4-1\}]_2} \) \textbf{4-103}. Analysis of the X-ray crystal structure revealed that the connectivity of the dimeric heterochiral complex \( \text{[CuBr\{(S)-4-1\}]_2} \) \textbf{4-103} greatly differed from that of the QUINAP analogue \textbf{4-95}. The two P,N-ligands in \textbf{4-103} are clearly different because one of them is bidentate and the other is monodentate. Interestingly, the bidentate P,N-ligand is coordinated to two different copper atoms that are bridged with a bromine atom, forming an eight-membered ring (Figure 4-26). The formation of this large ring allows for an enlarged dihedral angle of 89.9° in the biaryl moiety. Consequently, the intramolecular \( \pi \)-stacking interaction between the pentafluorobenzyl moiety and naphthalene is feasible because they are not forced too close together. The monodentate P,N-ligand is also stacking and the dihedral angle is 78.4°.

![Diagram of 4-103](image)

**Figure 4-26.** X-ray crystal structure and analysis of \textbf{4-103}

A similar behavior was observed in Guiry’s Quinazolinap/CuCl structure \textbf{4-104} \textsuperscript{137} (Figure 4-27) in which the P,N-ligands are monodentate forming a chlorine-bridged dimeric structure. In
contrast to Knochel’s QUINAP/CuBr structure 4-95, in this case the copper atoms are purely trigonal planar.

Figure 4-27. X-ray crystal structure 4-104

By analogy to complexes 4-95 and 4-104, an analogous structure 4-105 was hypothesized (Figure 4-28). The final connectivity obtained in the crystal structure of 4-103 could come from the coordination of an imidazole nitrogen of 4-105 to copper and displacement of a bromine atom as shown below. This is a reasonable pathway to explain how this specific structure is formed and could be supported by the fact that imidazole nitrogens are more basic/nucleophilic than isoquinoines\textsuperscript{135} or quinazolines\textsuperscript{137}

Figure 4-28. Proposed formation of complex 4-103

With the X-ray structure of 4-103 solved, attention was given to a possible mechanism of the A\textsuperscript{3}-coupling reaction employing 4-1. Since the crystal structure of 4-103 is dimeric, as in QUINAP/CuBr structure 4-95, the same mechanism suggested by Knochel could be proposed. However, results from Figure 4-18, in which ligand \textit{ent-4-1} was used in 87\% ee, suggests that
the reaction with imidazole-based P,N-ligand does not present a non-linear effect and a monomeric copper complex could be catalyzing the reaction. Therefore, it is difficult at this moment to draw any conclusion with respect to the mechanism of the copper-catalyzed A$_3$-coupling reaction employing 4-1.

Regarding the more basic imidazole nitrogen in 4-1, a comparison to the isoquinoline nitrogen of QUINAP was considered. The shorter reaction times observed with 4-1 could be related to a faster deprotonation of the terminal alkyne during the A$_3$-coupling reaction. If a nitrogen of the imidazole is in close proximity to the π-metal-alkyne complex 4-106 during the reaction, it could deprotonate the alkyne and accelerate the transformation (Figure 4-29). Interesting evidence for this possibility could be obtained by studying the P,N-ligand-copper-alkyne complex 4-107. To this end, racemic P,N-ligand rac-4-1, phenylacetylene 4-50 and CuBr were mixed in CDCl$_3$ in hopes to observe a deprotonation of the terminal alkyne by $^1$H NMR, but it was difficult to analyze the spectrum due to very broad peaks.

![Figure 4-29. Speculative deprotonation of the terminal alkyne by the imidazole nitrogen](image)

In summary, the mechanism of the copper-catalyzed enantioselective A$_3$-coupling is still poorly understood. Efforts still need to be directed towards the investigation of which copper-complexes (monomeric, dimeric, etc.) are involved in the reaction. In addition, studying the
difference between imidazole-based ligand 4-1 and QUINAP 4-2 in the A²-coupling will be important.

4.3.3. Copper-Catalyzed Acetylide Addition to Quinolinium Salts

The functionalization of pyridine aromatic rings through the formation of pyridinium salts is a very important tool for the synthesis of nitrogen heterocycles. In 2008, Arndsten and co-workers reported the copper-catalyzed coupling between quinolinium salts and terminal alkynes to give cyclic propargylcarbamates (Figure 4-30). The reaction requires the in situ formation of the iminium salt from quinoline 4-108 and ethylchloroformate 4-109 which reacts smoothly with the copper phenylacetylide to furnish 4-110. They observed higher reactivity for quinolines when compared to simple pyridines and the chosen catalyst system was CuCl along with a PINAP ligand 4-113. Interestingly, the introduction of an electron-donor methoxy group on the 7-position of the naphthalene ring increased significantly the enantioselectivity of the reaction from 53% to 81% (Compare results with ligands 4-112 vs 4-113). The optimized conditions employed catalytic 4-113/CuCl, CH₂Cl₂/CH₃CN as the solvent system at -78 °C and Hunig’s base.

Figure 4-30. Enantioselective copper-catalyzed coupling of quinolines and alkynes

During the course of our work on copper-catalyzed acetylide addition with imidazole-based P,N-ligand 4-1, the reaction developed by Arndsten appeared to be a good candidate to
study as the reported enantioselectivities were not high enough to be synthetically useful, leaving room for improvement. At the outset, an experiment using the optimal conditions from the A\textsuperscript{3}-coupling was performed. Quinoline 4-108, ethylchloroformate 4-109, and TMS-acetylene 4-46 were exposed to ligand 4-1 and CuBr in toluene, and upon addition of Hunig’s base the reaction provided the product in 55% yield (Figure 4-31). Although the conversion was not ideal, to our delight the product 4-114 was isolated in excellent 95% enantiomeric excess. Isoquinoline 4-115 was also used as starting material under the same conditions providing the product in lower enantiomeric excess of 82%, but still higher than the 72% observed by Arndtsen with the same substrate.\textsuperscript{138b}

![Reaction Scheme](image)

Figure 4-31. Enantioselective copper-catalyzed coupling of quinolines and alkynes employing P,N-ligand 4-1

The present method allows for the synthesis of alkaloids 4-117, 4-118 and 4-119 in only three steps from commercially available materials (Figure 4-32). These natural products were isolated from the bark of \textit{Galipea officinalis} Hancock in Venezuela.\textsuperscript{139,140,141} Despite the interesting biological activities of these compounds,\textsuperscript{139,140,141} we were interested in preparing them so that the absolute configuration of the products of our reaction could be determined. The use of arylalkyne 4-62 in the three-component reaction gave the product 4-120 in 86% yield and
95% ee using reaction conditions optimized by our group member Mukesh Pappoppula. The higher yield obtained in this reaction was probably due to better solubility of the catalyst in dichloromethane, when compared to toluene. Global hydrogenation of 4-120 using Pd/C and H₂, followed by LAH reduction of the carbamate furnished (+)-cuspareine 4-121, the unnatural version of the natural product, in 77% yield over two steps. The observed positive value for the optical rotation allowed for the assignment of the absolute configuration of the product by comparison to the known value for the natural (-)-cuspareine.¹⁴² This work is being further developed by graduate students Mukesh Pappoppula and Owen Garrett.

Figure 4-32. Determination of the absolute configuration through the synthesis of (+)-cuspareine

4.3.4. Asymmetric Alkynylation of Alkylidene Derivatives of Meldrum’s Acid

The asymmetric conjugate addition of alkynes to Meldrum’s acid derivatives was discussed in Section 4.2.5. The employment of PINAP type ligands in the reaction was widely studied for a variety of substrates.¹⁰⁵,¹³¹
In view of the success of ligand 4-1 in copper-catalyzed acetylide additions, an evaluation of 4-1 in this powerful carbon-carbon bond formation reaction was performed. Since PINAP type ligands possess one chiral center and one chiral axis, the examination of a purely axially chiral ligand such as 4-1 was worthwhile. The preparation of substrate 4-123 was done through a Knoevenagel condensation between Meldrum’s acid 4-122 and p-anisaldehyde 4-80 (Figure 4-33). By analogy to Carreira’s work, Cu(OAc)$_2$, (+)-sodium ascorbate, and ligand 4-1 were employed. The reaction is performed in water and with excess of phenylacetylene (10 molar equivalents) generating a biphasic medium. After 18 hours of vigorous stirring at 0 °C, an excellent yield of 95% and a good 80% enantiomeric excess were obtained. In a patent,$^{143}$ Carreira and co-workers report 27% yield and 80% ee for the same reaction. This represents a very good preliminary result since QUINAP gave only 42% ee in a similar reaction (Figure 4-14). For practical matters, the product is submitted to an amidation/decarboxylation reaction using aniline in DMF to give amide 4-125, which can be separated by HPLC.

Figure 4-33. Asymmetric conjugate addition of alkynes to Meldrum’s acid derivatives

The higher reactivity observed with our ligand calls attention to the fact that this substrate presents an aromatic ring substituted on the electrophilic carbon. This is somewhat similar to the higher reactivity observed for the aromatic aldehydes in the A$^3$-coupling. This preliminary result
is encouraging since a good enantiomeric excess was observed with axially chiral ligand 4-1, showing that the biaryl moiety dictates stereoinduction in this reaction and there is no requirement for the additional stereocenters as in PINAP. Studies on this reaction are ongoing in the laboratory.

4.3.5 Palladium-Catalyzed Asymmetric Allylic Alkylation

In the beginning of Chapter 3, the application of QUINAP in palladium-catalyzed asymmetric allylic alkylation was briefly discussed. In parallel to the first appearance of QUINAP, PHOX and Trost ligands were discovered and were also found to be excellent for this reaction. All these examples represent an important improvement for this reaction since well-known C₂-symmetric ligands were not as successful.

The approach adopted in the development of QUINAP and PHOX have some similarities. The success of PHOX in the asymmetric allylic alkylation was rationalized by Helmchen and Pfaltz using the electronic differentiation concept which can also be applied to other P,N-ligands such as QUINAP (Figure 4-34).

Figure 4-34. Concept of electronic differentiation proposed by Pfaltz

Inspired by previous work on C₂-symmetric BOX type N,N-ligands, Pfaltz thought that changing one of the hard nitrogens to a soft phosphorus donor would be useful, giving rise to a P,N-ligand. At that time, C₁-symmetric ligands were not widely explored because reduced
symmetry increases the number of possible reaction intermediates and predicting the reaction outcome can be more difficult. Interestingly, the differentiation proposed by Pfaltz was extremely successful as exemplified by the reaction in Figure 4-34.

To gain insight into the mechanism of the reaction catalyzed by PHOX ligands, a combination of NMR and X-ray studies were performed.\textsuperscript{146} X-ray structure of a PHOX-\pi-allyl complex 4-132 reveals a longer Pd-C bond \textit{trans} to the phosphorus atom (\textit{trans} influence), when compared to the Pd-C bond \textit{trans} to the nitrogen atom, which illustrates the electronic differentiation governed by the P,N-ligand. As a consequence, it is believed that this directs the nucleophilic attack \textit{trans} to the phosphorus, controlling the regioselectivity of the reaction (Figure 4-35).

![Figure 4-35. Trans influence on nucleophilic substitution](image)

Although there are excellent ligands for the palladium-catalyzed allylic alkylation, a test with ligand 4-1 was desired in order to analyze the feasibility of this ligand with other metals. For direct comparison with QUINAP,\textsuperscript{82} the same conditions that were optimized by Brown and co-workers were employed.

![Figure 4-36. Palladium-catalyzed allylic alkylation with axially chiral P,N-ligands](image)
The observed enantioselectivity was 94%, lower than the 98% obtained with QUINAP (Figure 4-36). Although this results is not excellent, it shows the compatibility of ligand 4-1 with palladium catalysis. Studies on the optimization of this reaction as well as the development of other palladium-catalyzed transformations are ongoing.

By analogy to PHOX and QUINAP, P,N-ligand 4-1 should also present an electronic differentiation. To rationalize the stereoselectivity observed in the reaction, the X-ray structure of complex 4-134, obtained during the deracemization studies (Chapter 3) was used. The conformation of the P,N-ligand and palladium (in the absence of the chiral auxiliary) is shown in structure 4-135. Using that structure, transition states 4-136 and 4-137 can be suggested (note the opposite ligand enantiomer). In each structure, the π-allyl approaches the metal in a different orientation and transition state 4-136 leads to the observed product 4-133, so presumably it should be favored. This reaction outcome can be rationalized by possible steric interactions between the phenyl groups of the π-allyl and of the imidazole ring.

![Diagram](image)

Figure 4-37. Stereoselectivity of the palladium-catalyzed allylic alkylation with ligand 4-1
In summary, product 4-133 was obtained in very good yield and excellent enantiomeric excess in the asymmetric palladium-catalyzed allylic alkylation with 4-1. Although there are many ligands that can catalyze this reaction, this result shows that this reaction is also feasible with imidazole-based P,N-ligand 4-1. Current work is focused on expanding the substrate scope of this reaction.

**4.4 Outcome and Current Work**

In summary, the set of experiments presented in Chapter 4 illustrates the utility of P,N-ligand 4-1. For instance, in the A³-coupling reaction our ligand furnished the products in 24h at 0°C with high yields and enantioselectivities for a broad range of substrates (alkyl and aryl aldehydes), whereas when QUINAP 4-2 was employed the reaction times were much longer and the less reactive aryl substrates were more challenging to achieve high enantioselectivities. This higher reactivity of our catalytic system might be related with the electron-rich five-membered imidazole heteroaromatic. Moreover, copper catalyzed acetylide additions to pyridinium ions or Michael acceptors were explored giving good results. The ligand can also be employed in palladium catalyzed allylic alkylations. The research in this area is still in progress in our group towards the expansion of these methodologies and also development of analogues of ligand 4-1.

Figure 4-38. Enantioselective reactions employing 4-1
CHAPTER 5
CONCLUSION AND OUTLOOK

The development of new chiral ligands for enantioselective catalysis has been an important topic in organic synthesis because the preparation of chiral molecules as single enantiomers plays an important role in the fields of pharmaceuticals, agriculture and materials science. Therefore, discovery of new reaction methodologies and chiral catalysts is an ongoing research topic. Among the chiral ligands for metal-catalyzed reactions, the existence of axially chiral P,N-ligands comprised of five-membered heteroaromatics in the biaryl backbone is rare, probably due to difficulties in isolating enantiopure materials. The work described in this dissertation focused on the development of a new strategy to increase the barrier to rotation in axially chiral compounds. The approach was based on intramolecular π-stacking interactions that would stabilize the ground state conformation of biaryls. The synthesis and NMR studies of many compounds showed a significant stabilization (2.0 - 2.4 kcal/mol) when a pentafluorinated benzyl ring was employed, as in 5-2.

![Figure 5-1. New approach to axial chirality in biaryl compounds](image)

In light of this, our new approach to atropisomers was applied to the design and preparation of an imidazole-based P,N-ligand 5-4. The invention of 5-4 allows for the exploration of a new class of ligands that were previously unexplored in asymmetric catalysis. In fact, ligand 5-4 proved to be very efficient in copper-catalyzed acetylide additions, as exemplified by the results obtained in the A³-coupling reaction (Figure 6-2).
Figure 5-2. Copper-catalyzed $A_3$-coupling reaction employing 5-4

Although the employment of 5-4 for asymmetric reactions gave very good results there are many aspects to be improved. The synthesis and deracemization to provide 5-4 as a single enantiomer are not ideal, and efforts have to be made to provide a more efficient and less expensive method. In addition, the preparation of analogues of 5-4 for fine tuning will be crucial when developing new enantioselective reactions.

From a broader perspective, this previously unexplored class of compounds in asymmetric catalysis encourages for the development of other types of chiral ligands or catalysts. The expansion of this new design element to the synthesis of new ligands and catalysts has emerged in our group along with the investigation of new organic reactions. Therefore, new reports along these lines will be reported in due course.
CHAPTER 6
EXPERIMENTAL SECTION

6.1 General Remarks

All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Anhydrous solvents were transferred via syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Anhydrous tetrahydrofuran (THF), acetonitrile, ether, dichloromethane, and pentane were dried using a mBraun solvent purification system. Analytical thin layer chromatography (TLC) was performed using 250 μm Silica Gel 60 F254 pre-coated plates (EMD Chemicals Inc.). Flash column chromatography was performed using 230-400 Mesh 60Å Silica Gel (Whatman Inc.). The eluents employed are reported as volume/volume percentages. Melting points were recorded on a MEL-TEMP® capillary melting point apparatus and are uncorrected. High performance liquid chromatography (HPLC) was performed on a Shimadzu LC-20AT. Gas Chromatography analyses were obtained using a Hewlett Packard HP 5890 Series II - FID Detector. Proton nuclear magnetic resonance (1H NMR) spectra were recorded using Varian Unity Inova 500 MHz and Varian Mercury 300 MHz spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.0 ppm) or CDCl₃ (7.26 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Varian Unity Inova 500 MHz and Varian Unity Mercury 300 spectrometer at 75 MHz. Chemical shift is reported in ppm relative to the carbon resonance of CDCl₃ (77.00 ppm). Phosphorus-31 (³¹P NMR) and Fluorine-19 (¹⁹F NMR) nuclear magnetic resonance spectra were recorded using Varian Unity Mercury 300 spectrometer at 121 MHz, and 281 MHz, respectively. The ³¹P NMR chemical shifts were calibrated using an external reference sample of
85% H$_3$PO$_4$ in D$_2$O. The $^{19}$F NMR chemical shifts were calibrated using an external reference sample of CCl$_3$F in CDCl$_3$ (δ 0.0 ppm). Specific Optical rotations were obtained on a JASCO P-2000 Series Polarimeter (wavelength = 589 nm). Infrared 111 spectra were obtained on a Perkin Elmer Spectrum RX-1 at 0.5 cm$^{-1}$ resolution and are reported in wave numbers. High resolution mass spectra (HRMS) were obtained by The Mass Spectrometry Core Laboratory of University of Florida, and are reported as m/e (relative ratio). Accurate masses are reported for the molecular ion (M+) or a suitable fragment ion.

6.2 Chemical Procedures

6.2.1 Synthesis of Model Compounds

5-methoxynaphthalen-1-yl trifluoromethanesulfonate (2-39). A solution of Tf$_2$O (0.73 mL, 4.32 mmol) in DCM (5 mL) was added dropwise to a solution of pyridine (0.6 mL, 7.2 mmol) and 2-38$^{147}$ (625 mg, 3.6 mmol) in DCM (10 mL) at 0°C. After complete addition, the mixture was warmed to room temperature and allowed to stir for 1 hour the mixture was then diluted with Et$_2$O (20 mL), quenched with 10% HCl (10 mL) and washed with NaHCO$_3$ (2 x 10 mL) saturated solution and twice with brine (2 x 10 mL). After drying this solution with MgSO$_4$, the solvent was removed and a column run at 20% EtOAc/Hexanes gave the triflate 2-39 as a yellow solid (921 mg, 84%); MP = 47-48°C. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.28 (d, J = 9Hz, 1H), 7.25 (d, J = 9Hz, 1H), 7.53-7.38(m, 3H), 6.87 (d, J = 6Hz, 1H), 3.96 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.6, 145.7, 128.3, 127.7, 127.45, 125.3, 124.4, 123.0, 121.1, 118.5, 116.8, 114.4, 112.9, 105.4, 104.7, 55.9. HRMS (DART) Calcd for C$_{12}$H$_{10}$F$_3$O$_4$S (M+H)$^+$ 307.0246, found 307.0519.
2-(naphthalen-1-yl)-1H-pyrrole (2-35). N-Boc-pyrrole-2-boronic acid 2-34 (0.0912 g, 0.432 mmol), 1-bromonaphthalene 2-33 (30 µL, 0.216 mmol), Pd(PPh₃)₄ (0.05 g, 0.0432 mmol) and LiCl (0.018 g, 0.432 mmol) were added sequentially to a test tube that then evacuated and refilled with argon. Degassed DME was then added and the mixture was heated at 80 °C before the degassed 2M Na₂CO₃ (0.5 mL) was added dropwise. The mixture was stirred for 1h and cooled to room temperature. The mixture was diluted with CHCl₃ and NaHCO₃ (saturated solution) was added. The aqueous phase was washed with CHCl₃ twice. The organic phase was dried with MgSO₄ and concentrated under vacuum. The crude mixture was filtrated through a short plug of silica using 20% EtOAc/hexanes. After the short column, the solution was concentrated and dissolved in THF (6 mL). MeONa 25% in MeOH (0.25 mL) was added dropwise at room temperature and let to stir for 12 hours. After dilution in water (10 mL), the crude product was extracted with Et₂O (2x10 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. Flash chromatography (gradient 5-20% EtOAc/hexanes) afforded the product as a colorless oil that crystalizes upon standing (25 mg, 59% yield over two steps). Compound 2-35 has been described in the literature and when prepared here satisfactorily matched all previously reported data.

2-(5-methoxynaphthalen-1-yl)-1H-pyrrole (2-40). The typical Suzuki coupling procedure was followed with triflate 2-39 (0.236 g, 0.77 mmol) to give the title compound as a
white solid (45 mg, 26% yield over two steps); MP = 114-115 °C. 1H NMR (300 MHz, CDCl3) δ 8.36 (s, 1H), 8.25 (ddd, \( J = 7.6, 2.2, 0.9 \) Hz, 1H), 7.83 (dt, \( J = 8.6, 1.0 \) Hz, 1H), 7.57 – 7.28 (m, 3H), 6.92 (td, \( J = 2.7, 1.5 \) Hz, 1H), 6.83 (dd, \( J = 7.6, 0.9 \) Hz, 1H), 6.48 (ddd, \( J = 3.9, 2.6, 1.5 \) Hz, 1H), 6.38 (dt, \( J = 3.5, 2.7 \) Hz, 1H), 4.00 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 155.8, 132.7, 131.3, 131.1, 127.1, 126.4, 126.4, 124.9, 121.6, 118.5, 118.2, 109.6, 109.6, 104.1, 55.8. HRMS (DART) Calcd for C15H14NO (M+H)+ 224.1070, found 224.1081.

2-(2-methoxynaphthalen-1-yl)-1H-pyrrole (2-42). The typical Suzuki coupling procedure was followed with bromide 2-41 (0.280 g, 1.18 mmol) to give the title compound as a colorless oil (90 mg, 34% yield over two steps); 1H NMR (300 MHz, CDCl3) δ 8.76 (s, 1H), 8.20 (ddt, \( J = 8.6, 1.4, 0.8 \) Hz, 1H), 7.86 – 7.74 (m, 2H), 7.48 – 7.27 (m, 3H), 6.98 (td, \( J = 2.7, 1.5 \) Hz, 1H), 6.53 – 6.37 (m, 2H), 3.88 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 154.3, 133.5, 129.6, 129.2, 128.1, 126.8, 125.8, 125.5, 123.97, 117.9, 116.82, 113.7, 111.1, 108.7, 56.5. HRMS (DART) Calcd for C15H14NO (M+H)+ 224.1070, found 224.1074.

1-benzyl-2-(naphthalen-1-yl)-1H-pyrrole (2-10). A solution of 2-35 (0.025 g, 0.13 mmol) in DMF (3 mL) was added dropwise to a suspension of NaH (5 mg, 0.208 mmol) in DMF (2 mL) at 0 °C. After 15 minutes, benzylbromide (15 μL, 0.13 mmol) was added at 0°C and the reaction was allowed to warm to room temperature over 1 hour. The mixture was diluted with Et2O (10 mL) and washed with water (2 x 10mL) and brine (10 mL). The organic layer was dried
with MgSO₄ and concentrated under vacuum. The crude was purified by flash chromatography
(10% EtOAc/Hexanes) giving the title compound as a colorless oil (31 mg, 84%). ¹H NMR (300
MHz, CDCl₃) δ 7.92 – 7.71 (m, 3H), 7.52 – 7.31 (m, 4H), 7.21 - 7.08 (m, 3H), 6.88 – 6.74 (m,
3H), 6.35 (t, J = 3.1 Hz, 1H), 6.30 (dd, J = 3.5, 1.7 Hz, 1H), 4.83 (s, 2H). ¹³C NMR (75 MHz,
CDCl₃) δ 138.9, 133.8, 133.6, 132.3, 131.2, 129.2, 128.6, 128.5, 128.3, 127.4, 127.1, 126.5,
126.4, 126.0, 125.3, 121.9, 110.6, 108.4, 51.1. HRMS (APCI) Calcd for C₂₁H₁₈N (M+H)+
284.1434, found 284.1444.

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2-(naphthalen-1-yl)-1-(perfluorobenzyl)-1H-pyrrole (2-32). The typical benzylation
procedure was followed with 2-35 (0.025 g, 0.13 mmol) and pentafluorobenzylbromide (20 μL,
0.13 mmol) to give the title compound as a white solid (28 mg, 57%); recrystallization from
chloroform gave white needles that were submitted to X-Ray crystallography. MP = 89-90 ºC; ¹H
NMR (300 MHz, CDCl₃): δ 7.89 (t, J = 6 Hz, 2H), 7.54-7.35 (m, 5H), 6.87 (s, 1H), 6.33 (t, J =
3Hz, 1H), 6.26-6.24 (m, 1H), 4.92 (ABq, J = 15Hz, Δυ = 52 Hz, 2H). ¹⁹F NMR (282 MHz,
CDCl₃) δ -142.3 (dd, J = 22.5, 8.2 Hz), -155.1 (t, J = 20.9 Hz), -162.7 (td, J = 22.0, 7.7 Hz).
HRMS (APCI) Calcd for C₂₁H₁₃F₅N (M+H)+ 374.0963, found 374.0972.

Crystal structure 2-32: Data were collected at 173 K on a Siemens SMART
PLATFORM equipped with a CCD area detector and a graphite monochromator utilizing
MoKα radiation (λ = 0.71073 Å). Cell parameters were refined using up to 8192 reflections. A
full sphere of data (1850 frames) was collected using the ω-scan method (0.3° frame width). The
first 50 frames were re-measured at the end of data collection to monitor instrument and crystal
stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in SHELXTL6, and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 244 parameters were refined in the final cycle of refinement using 3078 reflections with I > 2σ(I) to yield R1 and wR2 of 3.58% and 9.42%, respectively. Refinement was done using F2.

Table 6-1. Crystal data and structure refinement for 2-32.

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Table 6-1. Continued

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2-(5-methoxynaphthalen-1-yl)-1-(perfluorobenzyl)-1H-pyrrole (2-36). The typical benzylation procedure was followed with 2-36 (0.018 g, 0.08 mmol) and pentafluorobenzylbromide (12 μL, 0.08 mmol) to give the title compound as a colorless oil (30 mg, 92 %). ^1H NMR (300 MHz, CDCl₃) δ 8.26 (dd, J = 8.3, 1.6 Hz, 1H), 7.53 – 7.33 (m, 2H), 7.28 – 7.12 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.85 – 6.65 (m, 2H), 6.22 (td, J = 3.3, 1.3 Hz, 1H),
6.13 (dt, $J = 3.4$, 1.7 Hz, 1H), 4.82 (ABq, $J = 15$ Hz, $\Delta \nu = 47.89$ Hz, 2H), 3.93 (s, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -142.8 (dd, $J = 22.4$, 8.6 Hz), -154.8 (t, $J = 20.8$ Hz), -162.5 (td, $J = 21.9$, 8.0 Hz). HRMS (DART) Calcd for C$_{22}$H$_{15}$F$_5$NO ($M+$H)$^+$ 404.1068, found 404.1068.

1-benzyl-2-(2-methoxynaphthalen-1-yl)-1H-pyrrole (2-37). The typical benzylation procedure was followed with 2-42 (0.029 g, 0.13 mmol) and benzylbromide (15 $\mu$L, 0.13 mmol) to give the title compound as a colorless oil (28 mg, 70%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 9.0$ Hz, 1H), 7.81 – 7.74 (m, 1H), 7.63 – 7.55 (m, 1H), 7.41 – 7.19 (m, 3H), 7.11 (dt, $J = 4.7$, 3.4, 2.7, 1.7 Hz, 2H), 6.97 – 6.86 (m, 1H), 6.83 (dd, $J = 2.8$, 1.6 Hz, 1H), 6.39 (ddd, $J = 3.7$, 2.7, 1.0 Hz, 1H), 6.23 (dd, $J = 3.5$, 1.7 Hz, 1H), 4.76 (ABq, $J = 15$Hz, $\Delta \nu = 9.95$ Hz, 2H), 3.72 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 155.6, 138.6, 135.5, 130.4, 129.0, 128.6, 128.4, 127.9, 127.5, 127.2, 126.8, 125.6, 123.8, 121.4, 116.1, 113.2, 110.5, 108.3, 56.4, 51.1. HRMS (EI) Calcd for C$_{22}$H$_{19}$NO ($M^+$) 313.1467, found 313.1469.

2-(naphthalen-1-yl)-1H-indole (2-45). Phenylhydrazine 2-44 (5.91 mL, 60 mmol) was added dropwise to a solution of 2-acetynaphthalene 2-43 (7.61 g, 50 mmol) in phosphoric acid 85% (10 mL). The resulting mixture was stirred at 40 °C for one hour. Polyphosphoric acid (50 g) was carefully added to the mixture. The viscous mass was mixed while temperature was increased from room temperature to 120 °C (keep for 1 hour). The black reaction mixture was poured into crushed ice (~150 mL) and the product extracted with EtOAc (3 x 50 mL). The
organic layer was dried with MgSO₄ and concentrated under vacuum. The crude was purified by flash chromatography (10% EtOAc/Hexanes) giving the title compound as a light brown solid (8.9 g, 73%). Compound 2-45¹⁴⁹ has been described in the literature and when prepared here satisfactorily matched all previously reported data.

2-(naphthalen-1-yl)-1-(perfluorobenzyl)-1H-indole (2-46). The typical benzylation procedure was followed with 2-45 (0.19 g, 0.78 mmol) and pentafluorobenzylbromide (0.12 mL, 0.78 mmol) to give the title compound as a white solid (0.314 g, 95%). MP = 157-158. ¹H NMR (300 MHz, CDCl₃) δ 8.01 – 7.76 (m, 2H), 7.68 (dd, J = 7.8, 1.2 Hz, 1H), 7.60 – 7.12 (m, 8H), 6.64 (s, 1H), 5.16 (ABq, J = 15Hz, Δν = 38 Hz, 2H). ¹⁹F NMR (282 MHz, CDCl₃) δ -142.3 (dd, J = 22.4, 8.1 Hz), -155.1 (t, J = 20.9 Hz), -162.7 (td, J = 22.6, 8.5). HRMS (APCI) Calcd for C₂₅H₁₅F₅N (M+H)⁺ 424.1119, found 424.1138.

1-benzyl-2-(naphthalen-1-yl)-1H-indole (2-47). The typical benzylation procedure was followed with 2-45 (0.21 g, 0.863 mmol) and benzylbromide (0.1 mL, 0.863 mmol) to give the title compound as a colorless oil (0.24 g, 84 %). ¹H NMR (300 MHz, CDCl₃): δ 8.06 (d, J = 4.8 Hz, 2H), 7.99 (d, J = 3.0 Hz, 1H), 7.93 (d, J = 5.1 Hz, 1H), 7.66-7.56 (m, 4H), 7.48 (d, J = 3.0 Hz, 1H), 7.40-7.38 (m, 2H), 7.28 (s, 3H), 6.99-6.98 (m, 2H), 6.91 (s, 1H), 4.54 (bd, J = 18Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 139.3, 138.1, 137.4, 133.7, 133.2, 130.4, 129.2, 129.2, 128.6,
128.6, 128.4, 127.2, 126.8, 126.4, 126.3, 126.2, 125.3, 122.0, 120.8, 120.2, 110.7, 104.2, 47.9.

HRMS (APCI) Calcd for C_{26}H_{19}N (M+H)^+ 334.1590, found 334.1603.

(\textit{perfluorophenyl})methanamine hydrochloride (6-1). Pd/C (200 mg) was added to a solution of pentafluorobenzonitrile (1.0 g, 5.18 mmol) in a mixture of MeOH (10 mL) and 37% HCl (1 mL). The reaction mixture was stirred overnight under H\textsubscript{2} (1 atm). Filtration over a plug of cotton and removal of the solvent afforded 37 as a white solid (1.077 g, 89%). Compound 6-1\textsuperscript{150} has been described in the literature and when prepared here satisfactorily matched all previously reported data.

2-methyl-5-(naphthalen-1-yl)-1-(perfluorobenzyl)-1H-pyrrole (2-52). Diketone 2-51\textsuperscript{74} (0.039 g, 0.172 mmol) and 2,3,4,5,6-pentafluorobenzylamine hydrochloride 6-1 (0.040 g, 0.172 mmol) were added to toluene (3 mL) and the resulting mixture was refluxed overnight. The mixture was cooled to room temperature, water (10 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The organic layers were dried over MgSO\textsubscript{4} and then purified by flash chromatography (5% EtOAc in Hexanes) to give the title compound as a white solid (0.067 g, 74%). MP = 174-175 °C. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.90 – 7.75 (m, 2H), 7.55 – 7.27 (m, 5H), 6.15 (d, \(J = 3.4\) Hz, 1H), 6.07 (dd, \(J = 3.4, 1.0\) Hz, 1H), 4.94 (ABq, \(J = 15\)Hz, \(\Delta\nu = 39.00\) Hz, 2H), 2.38 (s, 3H). \textsuperscript{19}F NMR (282 MHz, CDCl\textsubscript{3}) \(\delta\) -143.7 (dd, \(J = 22.1, 8.0\) Hz), -155.9

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(t, J = 20.8 Hz), -163.5 (td, J = 21.7, 7.7 Hz). HRMS (DART) Calcd for C_{22}H_{15}F_{5}N (M+H)^+ 388.1119, found 388.1128.

1-benzyl-2-methyl-5-(naphthalen-1-yl)-1H-pyrrole (2-53). The typical Paal-Knorr procedure was followed with 2-51 (0.665 g, 2.94 mmol) and benzylamine (0.32 mL, 2.94 mmol) to give the title compound as a colorless oil (0.446 g, 51 %). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.89 – 7.86 (m, 1H), 7.81 – 7.78 (m, 1H), 7.74 (ddt, \(J = 7.3, 2.2, 0.6\) Hz, 1H), 7.46 – 7.30 (m, 4H), 7.17 – 7.05 (m, 3H), 6.72 (ddt, \(J = 7.2, 1.3, 0.7\) Hz, 2H), 6.25 (d, \(J = 3.4\) Hz, 1H), 6.13 (dq, \(J = 3.3, 0.9\) Hz, 1H), 5.08 – 4.55 (m, 2H), 2.18 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 139.0, 133.8, 133.6, 131.8, 131.7, 129.8, 129.0, 128.6, 128.3, 128.1, 126.9, 126.4, 126.3, 126.0, 125.9, 125.3, 109.7, 107.2, 48.0, 13.0. HRMS (DART) Calcd for C_{22}H_{20}N (M+H)^+ 298.1590, found 298.1604.

1-(4-fluorobenzyl)-2-(naphthalen-1-yl)-1H-indole (2-54). The typical benzylation procedure was followed with 2-45 (0.1 g, 0.42 mmol) and 4-fluorobenzylbromide (0.079 g, 0.42 mmol) to give the title compound as a colorless oil (0.1 g, 71 %). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.94 – 7.86 (m, 2H), 7.77 – 7.66 (m, 2H), 7.53 – 7.37 (m, 4H), 7.31 – 7.26 (m, 1H), 7.24 – 7.17 (m, 2H), 6.82 – 6.71 (m, 4H), 6.69 (d, \(J = 0.8\) Hz, 1H), 5.08 (ABq, \(J = 15\)Hz, \(\Delta\nu = 119.10\) Hz, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 163.5, 161.5, 139.7, 137.7, 134.3, 134.3, 134.2, 133.6, 130.9, 129.8, 129.7, 129.1, 128.9, 128.7, 128.6, 127.3, 126.8, 126.6, 125.8, 122.6, 121.4, 120.8,
116.0, 115.9, 111.0, 104.8, 47.7. HRMS (DART) Calcd for C_{26}H_{19}FN \text{ (M+H)}^+ 352.1496, found 352.1500.

1-(4-methoxybenzyl)-2-(naphthalen-1-yl)-1H-indole (2-55). The typical benzylation procedure was followed with 2-45 (0.1 g, 0.42 mmol) and 4-methoxybenzylbromide (0.084 g, 0.42 mmol) to give the title compound as a colorless oil (0.073 g, 48 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.02 – 7.83 (m, 2H), 7.79 – 7.64 (m, 2H), 7.53 – 7.10 (m, 7H), 6.78 – 6.57 (m, 5H), 5.10 (ABq, $J = 15$ Hz, $\Delta \nu = 70.42$ Hz, 2H), 3.67 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.8, 139.3, 137.3, 133.7, 133.2, 130.6, 130.2, 129.2, 129.2, 128.6, 128.4, 127.8, 126.8, 126.3, 126.2, 125.3, 121.9, 120.8, 120.1, 114.0, 110.7, 104.1, 55.4, 47.4. HRMS (DART) Calcd for C$_{26}$H$_{22}$NO \text{ (M+H)}^+ 364.1696, found 364.1706.

2-(naphthalen-1-yl)-1-(pyridin-4-ylmethyl)-1H-indole (2-56). The typical benzylation procedure was followed with 2-45 (0.613 g, 2.52 mmol), 4-(bromomethyl)pyridine hydrobromide (0.637 g, 0.42 mmol) and NaH (0.121 g, 5.02 mmol) to give the title compound as a yellow solid (0.447 g, 53 %). MP = 60-62 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.38 (bs, 2H), 7.98 – 7.80 (m, 2H), 7.79 – 7.65 (m, 2H), 7.55 – 7.32 (m, 4H), 7.29 – 7.14 (m, 3H), 6.71 (m, 3H), 5.07 (ABq, $J = 15$ Hz, $\Delta \nu = 70.42$ Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 149.4, 147.5, 139.0, 137.1, 133.6, 132.8, 129.7, 129.4, 129.1, 128.5, 128.4, 126.9, 126.3, 125.7, 125.2, 122.3,
121.5, 121.0, 120.6, 110.1, 104.6, 46.7. HRMS (DART) Calcd for C_{24}H_{19}N_{2} (M+H)^+ 335.1543, found 335.1559.

![Diagram](image)

**1-(1H-indol-2-yl)isoquinoline (2-61).** This compound was prepared according to a modified procedure from the literature. Phenylhydrazine 2-44 (3.0 mL, 30 mmol) was added to a solution of 1-(isoquinolin-1-yl)ethan-1-one 2-60 (5.1 g, 30 mmol) in ethanol (20 mL). 3 drops of glacial acetic acid was added and the mixture was refluxed for 2 hours. A yellow solid precipitated when the solution was cooled to 0 °C and it was filtrated. Polyphosphoric acid (20 g) was mixed with the solid. The viscous mass was mixed while temperature was increased from room temperature to 100 °C forming a homogeneous red solution. After 1 hour at this temperature, the mixture was cooled to room temperature and water (300 mL) was added. The formed yellow solid was filtered and washed with 25% NaOH aqueous solution. The crude was purified by flash chromatography (5% EtOAc/Hexanes) giving the title compound as a yellow solid (5.5 g, 75%). ^{1}H NMR (500 MHz, CDCl_{3}) δ 9.92 (s, 1H), 8.85 (d, J = 8.4 Hz, 1H), 8.53 (d, J = 5.6 Hz, 1H), 7.87 (dd, J = 8.0, 1.5 Hz, 1H), 7.71 (dddd, J = 22.5, 8.3, 6.8, 1.4 Hz, 3H), 7.63 – 7.55 (m, 1H), 7.47 (dq, J = 8.2, 1.0 Hz, 1H), 7.34 – 7.22 (m, 2H), 7.15 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H).
1-(1-(perfluorobenzyl)-1H-indol-2-yl)isoquinoline (2-57). The typical benzylation procedure was followed with 2-61 (0.50 g, 2.05 mmol) and pentafluorobenzylbromide (0.32 mL, 2.05 mmol) in THF to give the title compound as a white solid (0.696 g, 80%). MP = 173-174 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.63 (d, J = 5.7 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.77 - 7.62 (m, 3H), 7.56 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 6.88 (s, 1H), 5.84 (s, 2H). ¹⁹F NMR (282 MHz, CDCl₃) δ -142.2 (dd, J = 22.5, 8.4 Hz), -155.2 (t, J = 20.9 Hz), -162.4 (td, J = 22.5, 8.5). HRMS (DART) Calcd for C₂₄H₁₄F₅N₂ (M+H)+ 425.1072, found 425.1087.

2-(isoquinolin-1-yl)-1-((perfluorophenyl)methyl)-1H-indol-3-yl acetate (2-62). Pd(OAc)₂ (12 mg, 0.518 mmol), PhI(OAc)₂ (0.334 g, 1.0 mmol), indole 2-57 (0.220 g, 0.518 mmol), and KOAc (51 mg, 0.518 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. Acetonitrile (5.0 mL) was then added with stirring at room temperature for several minutes. The tube was then placed into a preheated oil bath (70 °C) and stirred for 1 h. After completion of the reaction as judged by TLC analysis, the reaction tube was allowed to cool to room temperature and quenched with sodium bisulfate saturated solution (5 mL) and water (5 mL). EtOAc (10 mL) was then added for dilution. The organic layer was separated, and the aqueous layer was washed with EtOAc (2 x 10 mL). The organic layers were
dried over MgSO₄ and then purified by flash chromatography (10% EtOAc/hexanes) to give the title compound as a yellowish oil (0.170 g, 68%). ¹H NMR (500 MHz, CDCl₃) δ 8.71 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.56 (t, J = 7.7 Hz, 1H), 7.50 (t, J = 8.3 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 5.70 (ABq, J = 15Hz, Δν = 134.36 Hz, 2H), 1.97 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 168.8, 150.4, 145.2 (d, J = 250.0 Hz), 142.6, 140.9 (d, J = 255.3 Hz), 137.3 (d, J = 253.0 Hz), 136.7, 135.5, 130.7, 130.5, 128.1, 127.9, 127.2, 125.9, 124.2, 121.1, 121.0, 120.6, 119.0, 111.1 (t, J = 17.0 Hz), 110.0, 36.0, 20.6. ¹⁹F NMR (282 MHz, CDCl₃) δ -141.9 (dd, J = 22.7, 8.1 Hz), -154.8 (t, J = 20.9 Hz), -162.3 (td, J = 22.1, 8.0 Hz). HRMS (DART) Calcd for C₂₆H₁₆F₅N₂O₂ (M+H)+ 483.1126, found 483.1127.

**Variable temperature ¹H NMR:** The variable temperature ¹H NMR spectra were collected in C₂D₂Cl₄ (δ = 5.91 ppm) or CDCl₃ (δ = 7.26 ppm). Samples were prepared in a 0.05M concentration allowed to equilibrate for ~5 min at each set temperature. The recorded NMR data were analyzed as described in Chapter 2.

### 6.2.2 Synthesis and Deracemization of 3-1 and 3-111

![Structure](image)

**1-(4,5-diphenyl-1H-imidazol-2-yl)naphthalen-2-ol (3-39).** Prepared according to a modified procedure by Eseola et al.⁹³ To a flask containing benzyl 3-37 (6.1 g, 29 mmol), 2-hydroxynaphthalene-1-carbaldehyde 3-38 (5 g, 29 mmol) and ammonium acetate (45 g, 584 mmol) was added glacial acetic acid (40 mL). The mixture was heated from room temperature to 140 °C over 1 hour when a yellow solid was formed. After cooling to room temperature, the mixture was filtered and washed with excess of water. The remaining residue was recrystallized...
from ethanol to give 8.41 g (80%) of the title compound as a yellow solid. MP: 202-203 °C. \(^1\)H NMR (500 MHz, DMSO-d6) \(\delta\) 12.04 (s, 1H), 8.21 (d, \(J = 8.6\) Hz, 1H), 7.88 (dd, \(J = 11.3, 8.5\) Hz, 2H), 7.58 (d, \(J = 7.1\) Hz, 4H), 7.48 (td, \(J = 6.8, 3.3\) Hz, 1H), 7.44 – 7.25 (m, 8H), 3.42 (s, 1H). \(^{13}\)C NMR (125 MHz, DMSO-d6) \(\delta\) 154.6, 143.02, 132.3, 130.6, 128.5, 128.1, 128.0, 127.7, 127.1, 127.0, 124.5, 123.0, 118.4, 109.2. IR (Neat): 3392, 2098, 1643 cm\(^{-1}\). HRMS (DART) Calcd for \(\text{C}_{25}\text{H}_{18}\text{N}_{2}\text{O}(\text{M+H})^+\) 363.1492, found 363.1489.

2-(2-(tert-butyldimethylsilyloxy)naphthalen-1-yl)-4,5-diphenyl-1H-imidazole (3-112).

To a suspension of 3-39 (7.5 g, 20.7 mmol) and triethylamine (2.9 ml, 20.7 mmol) in DCM (90 mL) was added TBSCl (3.2 g, 20.7 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 hours and quenched with \(\text{H}_2\text{O}\) (30 mL). The crude product was extracted with DCM (2 x 20 mL), dried over \(\text{MgSO}_4\) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (5-20% EtOAc/Hexanes, gradient) to yield 7.7 g (78%) of the title compound as a white solid. \(R_f = 0.59\) (20% EtOAc/hexanes). MP: 145-146 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.58 (s, 1H), 8.79 (d, \(J = 8.6\) Hz, 1H), 7.87 – 7.73 (m, 4H), 7.50 (ddd, \(J = 8.5, 6.8, 1.3\) Hz, 2H), 7.45 – 7.25 (m, 8H), 7.13 (d, \(J = 8.9\) Hz, 1H), 0.84 (s, 9H), 0.09 (s, 6H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 151.9, 142.4, 133.5, 130.9, 130.1, 130.0, 128.0, 128.0, 127.6, 126.3, 124.6, 121.2, 116.4, 110.2, 25.7, 18.3, -4.3. IR (Neat): 3059, 2858, 1594, 1462, 1361, 1244, 991, 837, 696 cm\(^{-1}\). HRMS (DART) Calcd for \(\text{C}_{31}\text{H}_{32}\text{N}_2\text{OSi}(\text{M+H})^+\) 477.2357, found 477.2360.
2-(2-(tert-butyldimethylsilyloxy)naphthalen-1-yl)-1-(perfluorobenzyl)-4,5-diphenyl-1H-imidazole (3-42). A solution of the silyl ether 3-112 (7.43 g, 15.6 mmol) in THF (30 mL) was added dropwise to a suspension of sodium hydride (413 mg, 17.2 mmol) in THF (20 mL) at -78 °C. The mixture was stirred for 10 min and pentafluorobenzyl bromide (2.4 mL, 15.9 mmol) was added in a dropwise fashion. The reaction was allowed to warm up to room temperature over 18h at which point the solution was cooled to 0 °C and water was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 50 ml). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (5-20% EtOAc/Hexanes, gradient) to yield 9.63 g (94%) of the title compound as a colorless oil that crystallizes upon standing. R$_f$ = 0.68 (20% EtOAc/hexanes). MP: 148-149 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.77 (d, $J$ = 8.9 Hz, 1H), 7.68 (d, $J$ = 7.8 Hz, 1H), 7.59 (d, $J$ = 7.5 Hz, 1H), 7.54 – 7.43 (m, 6H), 7.31 (dt, $J$ = 15.1, 6.6 Hz, 2H), 7.21 (t, $J$ = 7.4 Hz, 2H), 7.18 – 7.08 (m, 2H), 4.95 (ABq, $J$ = 15.4 Hz, $\Delta \nu$ = 109.55 Hz, 2H), 0.94 (s, 9H), 0.30 (s, 3H), 0.07 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 152.8, 144.7 (d, $J$ = 253 Hz), 142.9, 140.2 (d, $J$ = 255 Hz), 137.7, 136.6 (d, $J$ = 252 Hz), 134.9, 133.8, 131.5, 131.3, 129.3, 129.4, 129.2, 129.1, 128.2, 127.6, 127.0, 126.4, 124.5, 124.4, 120.8, 116.8, 110.2 (t, $J$ = 15 Hz), 36.7, 25.7, 18.2, -3.9, -4.6. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -142.1 (dd, $J$ = 22.2, 7.5 Hz), -156.1 (t, $J$ = 20.7 Hz), -163.5 (td, $J$ = 21.2, 6.7 Hz). (Neat): 3061, 2859, 2361, 1595, 1506, 1249, 1132, 1020, 838, 701 cm$^{-1}$. HRMS (DART) Calcd for C$_{38}$H$_{33}$F$_5$N$_2$OSi (M+H)$^+$ 657.2355, found 657.2345.
1-(1-(perfluorobenzyl)-4,5-diphenyl-1H-imidazol-2-yl)naphthalen-2-yl trifluoromethanesulfonate (3-44). To a solution of compound 3-42 (6.50 g, 9.89 mmol) in MeOH (100 ml) was added K$_2$CO$_3$ (2.73 g, 19.78 mmol) at room temperature. After 30 minutes, the mixture was filtered and concentrated under reduced pressure to ~10ml. The residue was dissolved in EtOAc (50 ml) and poured into water (50 ml). The organic phase was separated and the water phase was extracted with EtOAc (2 x 50 ml). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure to give the deprotected product as a white solid that was used in the next step without further purification.

To a solution of the free alcohol obtained above and DMAP (121 mg, 0.989 mmol) in DCM (100 mL) was added triethylamine (1.38 mL, 9.89 mmol) followed by N-phenyl-bis(trifluoromethanesulfonimide) 3-43 (3.68 g, 9.89 mmol) at room temperature. The resulting solution was stirred at room temperature for 6h and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/Hexanes) to yield 5.34 g (95%, 2 steps) of the triflate 3-44 as a white solid. R$_f$ = 0.51 (20% EtOAc/hexanes). MP: 163-164 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.01 (d, $J$ = 9.1 Hz, 1H), 7.87 (d, $J$ = 8.2 Hz, 1H), 7.73 (d, $J$ = 8.3 Hz, 1H), 7.62 – 7.41 (m, 10H), 7.21 (t, $J$ = 7.5 Hz, 2H), 7.16 (d, $J$ = 7.2 Hz, 1H), 4.96 (ABq, $J$ = 15Hz, $\Delta$$\nu$ = 13.23 Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 146.5, 144.8 (d, $J$ = 250.9 Hz), 140.7 (d, $J$ = 255 Hz), 139.1 , 138.6 , 136.8 (d, $J$ = 254 Hz), 134.2, 133.1, 132.6, 132.3, 131.3, 130.8, 130.5, 129.5, 128.4, 128.3, 128.1, 127.6, 127.0, 126.9, 126.1, 121.2, 119.3, 118.6 (q, $J$ = 321 Hz), 109.7 (t, $J$ = 16 Hz), 37.0. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -74.5 , -142.2 (dd, $J$ = 21.2, 7.0
Hz), -154.4 (t, J = 20.8 Hz), -162.7 (td, J = 20.7, 6.6 Hz). IR (Neat): 3056, 1521, 1510, 1211, 1138, 1021, 944, 829, 745, 702 cm\(^{-1}\). HRMS (DART) Calcd for C\(_{33}\)H\(_{19}\)F\(_8\)N\(_2\)O\(_3\)S (M+H)\(^+\) 675.0983, found 675.0968.

(±)-2-(2-(diphenylphosphino)naphthalen-1-yl)-1-(perfluorobenzyl)-4,5-diphenyl-1H-imidazole (3-1). To a solution of 3-44 (6.34 g, 9.4 mmol), NiCl\(_2\)(PPh\(_3\))\(_2\) (3.08 g, 4.7 mmol) and Ph\(_2\)PCl (2.10 ml, 11.4 mmol) in anhydrous DMF (40 ml) was added activated Zn (1.23 g, 18.8 mmol) in three portions at room temperature which resulted in a brown solution (Zinc dust was activated by washing the solid with aqueous HCl, water, ethanol and dry ether). The mixture was heated to 110 °C for 48h, cooled to room temperature, diluted with EtOAc and filtered through a short plug of silica. The resulting solution was washed with water (3 x 50 ml) and brine (50 ml), dried over MgSO\(_4\), and concentrated under reduced pressure. Flash chromatography (5-20% EtOAc/Hexanes, gradient) afforded 4.00 g (60%) of the phoshine 3-1 as a white foam. R\(_f\) = 0.57 (20% EtOAc/hexanes). MP = 88-90°C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.81 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.62 – 7.19 (m, 20H), 7.19 – 7.10 (m, 4H), 5.00 (ABq, J = 15Hz, \(\Delta\nu = 144.22\) Hz, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.9 (d, J = 248 Hz), 144.3, 144.3, 140.4 (d, J = 255 Hz), 138.7, 138.6, 137.5, 136.7 (d, J = 254 Hz), 136.6, 136.5, 135.8, 135.7, 134.7, 134.7, 134.5, 134.4, 134.4, 134.3, 134.2, 133.12, 133.10, 133.05, 131.9, 131.2, 129.9, 129.8, 129.3, 129.2, 129.0, 128.9, 128.7, 128.6, 128.6, 128.0, 127.7, 127.1, 126.9, 126.8, 126.4, 125.6, 125.6, 109.9 (t, J = 16 Hz), 37.3, 37.2. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -141.2 (dt, J = 22.1, 6.6 Hz), -155.4 (t, J = 20.8 Hz), -163.1 (td, J = 21.8, 7.6 Hz). \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) -7.69 (t, J = 5.8 Hz). IR

Crystal structure 3-1: X-Ray Intensity data were collected at 100 K on a Bruker DUO diffractometer using CuKα radiation (λ = 1.54178 Å), from an ImuS power source, and an APEXII CCD area detector.

Raw data frames were read by program SAINT¹ and integrated using 3D profiling algorithms. The resulting data were reduced to produce hkl reflections and their intensities and estimated standard deviations. The data were corrected for Lorentz and polarization effects and numerical absorption corrections were applied based on indexed and measured faces.

The structure was solved and refined in SHELXTL6.1, using full-matrix least-squares refinement. The non-H atoms were refined with anisotropic thermal parameters and all of the H atoms were calculated in idealized positions and refined riding on their parent atoms. In the final cycle of refinement, 5959 reflections (of which 5586 are observed with I > 2σ(I)) were used to refine 469 parameters and the resulting R₁, wR₂ and S (goodness of fit) were 2.89%, 7.69% and 1.057, respectively. The refinement was carried out by minimizing the wR₂ function using F² rather than F values. R₁ is calculated to provide a reference to the conventional R value but its function is not minimized.

Table 6-2. Crystal data and structure refinement for 3-1.

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Table 6-2. Continued

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<td></td>
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<tr>
<td>Largest diff. peak and hole</td>
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(S,R)-cis-[Dimethyl(1-(-(Naphthyl)Ethyl)Aminato-C$_2$N)-2-(2-(diphenylphosphino)naphthalen-1-yl)-1-(perfluorobenzyl)-4,5-diphenyl-1H-imidazole]

**Palladium (II) Hexafluorophosphate (3-93).** Acetone (12 mL) was added to a flask containing 3-1 (500 mg, 0.704 mmol), (+)-Di-μ-chlorobis[(R)-dimethyl(1-(1-naphthyl)ethyl)aminato-C$_2$N]dipalladium (II)$^{100}$ 3-52 (240 mg, 0.352 mmol) and potassium hexafluorophosphate (130 mg, 0.704 mmol). The resulting mixture was stirred at 60 ºC for 12 h. The mixture was then cooled, concentrated under reduced pressure, and filtered through a plug of celite washing with dichloromethane. The resulting yellow solution was concentrated under vacuum and dissolved in acetone (12 mL) before stirring for an additional 12 h at 60 ºC. The solution was then concentrated under vacuum to give a yellow solid. Recrystallization from ether/dichloromethane gave 662 mg of the palladium complex 3-93 as a light yellow powder (81% yield). $[^{27}]_{D}^{o} = -205.4$ (c 1.00, CHCl$_3$). MP: 212-214 ºC (dec.). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.45 (d, $J = 8.7$ Hz, 1H), 8.11 (t, $J = 7.9$ Hz, 1H), 7.99 (d, $J = 8.3$ Hz, 1H), 7.93 (d, $J = 8.6$ Hz, 1H), 7.88 (d, $J = 7.9$ Hz, 2H), 7.78 (t, $J = 7.7$ Hz, 1H), 7.72 (t, $J = 7.4$ Hz, 1H), 7.67 – 7.62 (m, 2H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 8.2$ Hz, 1H), 7.39 – 7.19 (m, 12H), 7.09 (td, $J = 8.7$, 2.0 Hz, 2H), 6.89 (d, $J = 8.5$ Hz, 3H), 6.82 (dd, $J = 11.7$, 7.7 Hz, 2H), 6.56 (ddd, $J = 8.1$, 6.1, 1.8 Hz, 1H), 4.96 (ABq, $J = 15.9$ Hz, Δν = 204.45 Hz, 2H), 4.01 (p, $J = 6.5$ Hz, 1H), 2.40 (d, $J = 3.6$ Hz, 3H), 1.67 (d, $J = 6.4$ Hz, 3H), 1.36 (d, $J = 2.5$ Hz, 3H). $^{31}$P NMR (121 MHz, CDCl$_3$) δ 32.83, -144.23 (hept, $J = 712.7$ Hz). IR (Neat): 3056, 2881, 1573, 1438, 841, 746, 700 cm$^{-1}$. HRMS (ESI) Calcd for C$_{58}$H$_{44}$F$_5$N$_3$PPd (M-PF$_6$)$^+$ 1014.2242, found 1014.2239.
Crystal structure 3-99: X-Ray Intensity data were collected at 100 K on a Bruker DUO diffractometer using MoKα radiation (λ = 0.71073 Å) and an APEXII CCD area detector.

Raw data frames were read by program SAINT\textsuperscript{1} and integrated using 3D profiling algorithms. The resulting data were reduced to produce hkl reflections and their intensities and estimated standard deviations. The data were corrected for Lorentz and polarization effects and numerical absorption corrections were applied based on indexed and measured faces.

The structure was solved and refined in SHELXTL6.1, using full-matrix least-squares refinement. The non-H atoms were refined with anisotropic thermal parameters and all of the H atoms were calculated in idealized positions and refined riding on their parent atoms. In the final cycle of refinement, 11122 reflections (of which 10515 are observed with I > 2σ(I)) were used to refine 679 parameters and the resulting R\textsubscript{1}, wR\textsubscript{2} and S (goodness of fit) were 2.18\%, 5.21\% and 1.039, respectively. The refinement was carried out by minimizing the wR\textsubscript{2} function using F\textsuperscript{2} rather than F values. R\textsubscript{1} is calculated to provide a reference to the conventional R value but its function is not minimized.

Table 6-3. Crystal data and structure refinement for 3-99.

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<td>Space group</td>
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<td>c = 14.9347(16) Å γ = 90°.</td>
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(-)-2-(2-(diphenylphosphino)naphthalen-1-yl)-1-(perfluorobenzyl)-4,5-diphenyl-1H-imidazole (3-2). 1,2-bis(diphenylphosphino)ethane 3-61 (60 mg, 0.151 mmol) was added as a solid to a solution of 3-93 (170 mg, 0.147 mmol) at -78 °C. After 5 minutes, the solution was warmed up to 0 °C and allowed to stir for 1 hour at the same temperature. The mixture was submitted directly to flash chromatography (20% EtOAc/Hexanes) to give 101 mg (97% yield) of 3-2 as a white foam. Rf = 0.57 (20% EtOAc/hexanes). [α]23D = -73.5 (c 3.03, CHCl3). The ee was determined after oxidation to phosphine oxide 3-97.

(-)-2-(2-(diphenylphosphoryl)naphthalen-1-yl)-1-(perfluorobenzyl)-4,5-diphenyl-1H-imidazole (3-97). Phosphine 3-2 (7 mg, 0.01 mmol) was dissolved in dichloromethane (2 mL) followed by the addition of hydrogen peroxide (0.05 mL), and the solution was stirred at room temperature for 5 min. The mixture was diluted with dichloromethane, washed with water and dried over MgSO4. The solvent was removed under reduced pressure, and the residue was purified using a plug of silica gel (hexane/ethyl acetate 1:1) to yield 3-97 as a white solid (7 mg, 96% yield). Rf = 0.16 (20% EtOAc/hexanes). [α]23D = -5.1 (c 0.60, CHCl3). MP: 265-266 °C. 1H NMR (500 MHz, CDCl3) δ 7.91 – 7.86 (m, 3H), 7.79 (d, J = 8.3 Hz, 1H), 7.69 – 7.43 (m, 11H), 7.43 – 7.31 (m, 3H), 7.25 – 7.05 (m, 8H), 5.94 (d, J = 15.5 Hz, 1H), 4.86 (d, J = 15.4 Hz, 1H). 13C NMR (125 MHz, CDCl3) δ 145.0 (d, J = 248 Hz), 142.3, 142.3, 140.3 (d, J = 249 Hz), 137.2, 136.6 (d, J = 253 Hz), 134.7, 134.7, 134.5, 134.4, 133.7, 133.5, 133.5, 133.4, 132.9, 132.5, 132.1, 131.7, 131.6,
131.6, 131.4, 131.3, 131.2, 131.0, 130.4, 129.6, 129.5, 129.2, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 128.3, 127.8, 127.7, 127.3, 127.0, 126.4, 126.2, 110.3 (t, \( J = 18 \) Hz), 37.4. \(^{19}\)F NMR (281 MHz, CDCl\(_3\)) \( \delta \) -140.9 (dd, \( J = 22.4, 7.8 \) Hz), -155.8 (t, \( J = 20.7 \) Hz), -163.3 (td, \( J = 21.5, 7.1 \) Hz). \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \( \delta \) 27.37. IR (Neat): 3058, 1652, 1521, 1508, 1438, 1192, 1118, 1022, 700 cm\(^{-1}\). HRMS (DART) Calcd for C\(_{44}\)H\(_{28}\)F\(_5\)N\(_2\)OP (M+H)\(^+\) 727.1932, found 727.1920. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (90:10 \( n\)-hexane:isopropanol, 1 mL/min, 215 nm); major \( t_r = 13.77 \) min; minor \( t_r = 25.59 \) min; 98% ee.

**Crystal structure 3-99/3-101:** X-Ray Intensity data were collected at 100 K on a Bruker DUO diffractometer using MoK\( \alpha \) radiation (\( \lambda = 0.71073 \) Å) and an APEXII CCD area detector.

Raw data frames were read by program SAINT\(^1\) and integrated using 3D profiling algorithms. The resulting data were reduced to produce hkl reflections and their intensities and estimated standard deviations. The data were corrected for Lorentz and polarization effects and numerical absorption corrections were applied based on indexed and measured faces.

The structure was solved and refined in SHELXTL6.1, using full-matrix least-squares refinement. The non-H atoms were refined with anisotropic thermal parameters and all of the H atoms were calculated in idealized positions and refined riding on their parent atoms. The asymmetric unit consists of two Pd Complex cations and two hexafluorophosphate anions. The correct enantiomer are refined as can be seen from the value of the Flack \( x \) parameter of -0.02(3). In the final cycle of refinement, 43677 reflections (of which 13112 are observed with \( I > 2\sigma(I) \)) were used to refine 1339 parameters and the resulting \( R_1, wR_2 \) and \( S \) (goodness of fit) were 5.61\%, 12.25\% and 1.143, respectively. The refinement was carried out by minimizing the \( wR_2 \) function using \( F^2 \) rather than \( F \) values. \( R_1 \) is calculated to provide a reference to the conventional \( R \) value but its function is not minimized.
Table 6-4. Crystal data and structure refinement for 3-99/3-101.

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![Chemical Structure](image)

**1-(1-benzyl-4,5-diphenyl-1H-imidazol-2-yl)naphthalen-2-ol (3-113).** A solution of the silyl ether 3-112 (3.43 g, 7.2 mmol) in THF (15 mL) was added dropwise to a suspension of sodium hydride (190 mg, 7.92 mmol) in THF (10 mL) at -78 °C. The mixture was stirred for 10 min and benzyl bromide (0.94 mL, 7.90 mmol) was added in a dropwise fashion. The reaction was allowed to warm up to room temperature over 18h at which point the solution was cooled to 0 °C and water was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 25 ml). The organic layers were dried over MgSO₄ and the crude product was recovered as a colorless oil which was used for the next step without further purification.

To a solution of the silane obtained above in MeOH (50 ml) was added K₂CO₃ (2.0 g, 14.4 mmol) at room temperature. After 30 minutes, the mixture was filtered and concentrated under reduced pressure to ~10ml. The residue was dissolved in EtOAc (25 ml) and poured into water (25 ml). The organic phase was separated and the water phase was extracted with EtOAc.
(2 x 25 ml). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure to give 2.51 g of 3-113 as a white solid (70%, 2 steps). $R_f = 0.29$ (20% EtOAc/hexanes). MP: 227-228 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.72 (d, $J = 8.4$ Hz, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.49 (dd, $J = 6.9$, 2.2 Hz, 2H), 7.42 (ddd, $J = 8.3$, 6.8, 1.3 Hz, 1H), 7.35 – 7.20 (m, 7H), 7.15 (t, $J = 7.7$ Hz, 2H), 6.79 (t, $J = 7.4$ Hz, 1H), 6.70 (t, $J = 7.6$ Hz, 2H), 6.53 (d, $J = 7.4$ Hz, 2H), 6.42 (d, $J = 8.8$ Hz, 1H), 6.15 (d, $J = 7.6$ Hz, 2H), 4.74 (ABq, $J = 15.6$ Hz, $\Delta\nu = 97.98$ Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.9, 144.4, 136.4, 136.2, 134.1, 133.4, 131.3, 131.2, 130.7, 129.9, 129.2, 128.8, 128.5, 128.0, 127.9, 127.0, 126.8, 126.7, 126.6, 124.3, 123.3, 120.6, 48.6. HRMS (DART) Calcd for C$_{32}$H$_{25}$N$_2$O (M+H)$^+$ 453.1961, found 453.1959.

![1-(1-benzyl-4,5-diphenyl-1H-imidazol-2-yl)naphthalen-2-yl trifluoromethanesulfonate (6-2).](image)

To a solution of the free alcohol 3-113 (2.07 g, 4.57 mmol) and DMAP (56 mg, 0.46 mmol) in DCM (50 mL) was added triethylamine (0.64 mL, 4.57 mmol) followed by N-phenyl-bis(trifluoromethanesulfonimide) (1.70 g, 4.57 mmol) at room temperature. The resulting solution was stirred at room temperature for 6h and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/Hexanes) to yield 2.54 g (95%) of the triflate 6-2 as a white solid. $R_f = 0.41$ (20% EtOAc/hexanes). MP: 63-64°C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.95 (d, $J = 8.9$ Hz, 1H), 7.84 (dd, $J = 21.5$, 7.3 Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 7.54 – 7.31 (m, 7H), 7.25 – 7.10 (m, 3H), 7.07 – 6.98 (m, 1H), 6.97 – 6.71 (m, 3H), 6.48 (d, $J = 7.6$ Hz, 2H), 4.86 (s, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 146.2, 139.8, 139.0, 136.1, 134.4, 133.7, 132.5, 131.3, 130.9, 130.7, 129.2, 129.0, 128.4, 128.3, 128.2, 127.5, 127.2, 126.9,
126.7, 124.3, 121.5, 119.0, 48.8. HRMS (DART) Calcd for C_{33}H_{24}FN_{2}O_{3}S (M+H)^{+} 585.1454, found 585.1461.

1-benzyl-2-(2-(diphenylphosphino)naphthalen-1-yl)-4,5-diphenyl-1H-imidazole (3-111). To a solution of triflate 6-2 (2.3 g, 3.93 mmol), NiCl_{2}(PPh_{3})_{2} (1.29 g, 1.97 mmol) and Ph_{2}PCl (0.87 ml, 4.72 mmol) in anhydrous DMF (20 ml) was added activated Zn (0.51 g, 7.86 mmol) in three portions at room temperature which resulted in a brown solution (Zinc dust was activated by washing the solid with aqueous HCl, water, ethanol and dry ether). The mixture was heated to 110 °C for 48h, cooled to room temperature, diluted with EtOAc and filtered through a short plug of silica. The resulting solution was washed with water (3 x 25 ml) and brine (25 ml), dried over MgSO_{4}, and concentrated under reduced pressure. Flash chromatography (5-20% EtOAc/Hexanes, gradient) afforded 1.29 g (53%) of the phosphine 3-111 as a white foam. R_{f} = 0.47 (20% EtOAc/hexanes). MP = 68-69 °C. 1H NMR (500 MHz, CDCl_{3}) δ 7.80 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.41 – 7.25 (m, 19H), 7.16 – 7.06 (m, 5H), 6.96 – 6.82 (m, 6H), 6.55 (d, J = 7.5 Hz, 2H), 4.63 (ABq, J = 15 Hz, Δν = 52.92 Hz, 2H). 13C NMR (125 MHz, CDCl_{3}) δ 145.7, 145.6, 138.4, 138.3, 138.0, 137.8, 137.7, 137.0, 136.9, 136.3, 135.5, 135.2, 134.5, 134.4, 134.2, 134.0, 134.0, 133.9, 133.6, 133.6, 131.5, 131.3, 130.0, 129.8, 129.5, 129.2, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.6, 128.5, 128.1, 128.0, 128.0, 127.4, 127.4, 127.3, 127.3, 127.2, 127.2, 126.9, 126.6, 126.4, 124.2, 121.2, 49.0, 49.0. 31P NMR (121 MHz, C_{2}D_{2}Cl_{4}) δ -10.07. Calcd for C_{44}H_{34}N_{2}P (M+H)^{+} 621.2454, found 621.2459.
(S,R)-cis-[Dimethyl(1-(-Naphthyl)Ethyl)Aminato-C$_2$N]-[1-benzyl-2-(2-(diphenylphosphino)naphthalen-1-yl)-4,5-diphenyl-1H-imidazole] Palladium (II)

**Hexafluorophosphate (3-114).** Acetone (12 mL) was added to a flask containing 3-111 (410 mg, 0.661 mmol), (+)-Di-$\mu$-chlorobis[(R)-dimethyl(1-(1-naphthyl)ethyl)aminato-C$_2$N]dipalladium (II)$^{100}$ 14 (225 mg, 0.331 mmol) and potassium hexafluorophosphate (121.3 mg, 0.659 mmol). The resulting mixture was stirred at room temperature for 12 h. The mixture concentrated under reduced pressure, and filtered through a plug of celite washing with dichloromethane. The resulting yellow solution was concentrated under vacuum and dissolved in acetone (12 mL) before stirring for an additional 12 h at room temperature. The solution was then concentrated under vacuum to give a yellow solid. Recrystallization from ether/dichloromethane gave 410 mg of the palladium complex 3-114 as a light yellow powder (58% yield). $[\alpha]^{23}_D$ = -75.44 (c 2.00, CHCl$_3$). MP: 214-216 ºC (dec.). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.46 (d, $J = 8.5$ Hz, 1H), 8.10 (t, $J = 7.8$ Hz, 1H), 8.00 (d, $J = 8.3$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.84 – 7.73 (m, 4H), 7.70 – 7.49 (m, 4H), 7.48 – 7.04 (m, 14H), 7.01 – 6.71 (m, 8H), 6.62 (dd, $J = 8.4$, 5.8 Hz, 1H), 5.66 (d, $J = 7.6$ Hz, 2H), 4.98 (ABq, $J = 15.0$ Hz, $\Delta\nu = 64.3$ Hz, 2H), 4.02 (p, $J = 6.5$ Hz, 1H), 2.38 (d, $J = 3.7$ Hz, 3H), 1.92 (d, $J = 6.3$ Hz, 3H), 1.37 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 152.3, 149.5, 143.3, 143.3, 138.1, 136.6, 136.5, 135.7, 135.2, 134.78, 134.3, 133.6, 133.5, 132.5, 132.2, 132.0, 132.0, 131.7, 131.6, 131.5, 131.3, 131.2, 130.9, 130.9, 130.6, 130.1, 130.1, 129.7, 129.2, 129.1, 129.0, 128.8, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.2, 127.9, 127.7, 127.5, 127.2, 127.0, 126.7, 126.4, 126.3, 126.1, 126.0, 125.9, 125.3, 125.3, 124.6, 123.1, 122.6, 73.6, 51.0, 50.7, 47.9, 24.0. $^{31}$P NMR (121
MHz, CDCl$_3$) $\delta$ 34.03, -141.16 (h, $J = 712.9$ Hz). HRMS (ESI) Calcd for C$_{58}$H$_{49}$N$_3$PPd (M-PF$_6$)$^+$ 924.2713, found 924.2720.

**(-)-1-benzyl-2-(2-(diphenylphosphino)naphthalen-1-yl)-4,5-diphenyl-1H-imidazole** (3-115). 1,2-bis(diphenylphosphino)ethane 3-61 (49.4 mg, 0.124 mmol) was added as a solid to a solution of 3-114 (132.4 mg, 0.124 mmol) at -78 °C. After 5 minutes, the solution was warmed up to 0 °C and allowed to stir for 1 hour at the same temperature. The mixture was submitted directly to flash chromatography (20% EtOAc/Hexanes) to give 68 mg (88% yield) of 3-115 as a white foam. R$_f$ = 0.47 (20% EtOAc/hexanes). $[\alpha]^{23}_D$ = -19.0 (c 1.09, CHCl$_3$). The ee was determined after oxidation to phosphine oxide 3-117.

**(-)-1-benzyl-2-(2-(diphenylphosphoryl)naphthalen-1-yl)-4,5-diphenyl-1H-imidazole** (3-117). Phosphine 3-115 (10.9 mg, 0.017 mmol) was dissolved in dichloromethane (2 mL) followed by the addition of hydrogen peroxide (0.05 mL), and the solution was stirred at room temperature for 5 min. The mixture was diluted with dichloromethane, washed with water and dried over MgSO$_4$. The solvent was removed under reduced pressure, and the residue was purified using a plug of silica gel (hexane/ethyl acetate 1:1) to yield 3-117 as a white solid (10 mg, 90% yield). R$_f$ = 0.10 (20% EtOAc/hexanes). $[\alpha]^{25}_D$ = -25.4 (c 1.00, CHCl$_3$). MP: 89-90 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.95 (ddd, $J = 11.4, 7.9, 1.6$ Hz, 2H), 7.89 (dd, $J = 8.7, 2.2$ Hz, 1H), 7.82 – 7.70 (m, 3H), 7.62 – 7.44 (m, 6H), 7.44 – 7.34 (m, 5H), 7.33 – 7.20 (m, 3H), 7.20 – 7.06 (m, 5H),
7.02 (t, J = 7.4 Hz, 1H), 6.78 (t, J = 7.2 Hz, 1H), 6.71 (t, J = 7.5 Hz, 2H), 6.39 (d, J = 7.4 Hz, 2H), 5.18 (ABq, J = 15.0 Hz, Δν = 129.13 Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.9, 142.9, 137.7, 136.7, 135.0, 134.9, 134.9, 134.5, 134.0, 133.9, 133.9, 133.0, 132.3, 132.1, 132.0, 131.8, 131.8, 131.5, 131.5, 131.3, 131.2, 131.1, 131.0, 130.7, 129.6, 129.5, 129.4, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 128.3, 128.1, 128.0, 127.7, 127.7, 127.7, 127.6, 127.6, 127.3, 127.1, 126.8, 126.0, 49.7. $^{31}$P NMR (121 MHz, CDCl$_3$) δ 26.91. Calcd for C$_{44}$H$_{34}$N$_2$OP (M+H)$^+$ 637.2403, found 637.2397. Enantiomeric excess was determined by HPLC with a Chiralpak IA column (97:3 n-hexane:isopropanol, 1 mL/min, 254 nm); major t$_r$ = 66.43 min; minor t$_r$ = 80.49 min; 52% ee.

6.2.3 A$^3$-Coupling Reactions

$N,N$-dibenzyl-1-(trimethylsilyl)hex-1-yn-3-amine (4-85). CuBr (5.5 mg, 0.03834 mmol, 5 mol%), and activated MS 4Å sieves (450 mg) were added to a test tube in a glove box. The tube was fitted with a septum before being taken from the glove box and placed directly under dry nitrogen. rac-4-1 (30.0 mg, 0.0422 mmol, 5.5 mol %) in toluene (3 mL) was added to the tube and the mixture was stirred for 30 minutes at room temperature. The mixture was cooled to 0 °C and trimethylsilylacetylene 4-46 (0.767 mmol, 0.11 mL), butyraldehyde 4-84 (0.767 mmol, 0.069 mL), and dibenzylamine 4-47 (0.767 mmol, 0.15 mL) were added via syringe. The reaction mixture was stirred at 0 °C for 24 hours, filtered and subjected to flash column chromatography on silica gel (hexanes) giving the product as a colorless oil (247.2 mg, 92%) that matched previously reported spectral data. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 7.37 (d, J = 7.5 Hz, 4H), 7.29 (t, J = 7.6 Hz, 4H), 7.21 (t, J = 7.3 Hz, 2H), 3.78 (d, J = 13.8 Hz, 2H), 3.44 – 3.22 (m, 3H), 1.67 (dtd, J = 13.7, 8.9, 5.4 Hz, 1H), 1.62 – 1.48 (m, 1H), 1.49 – 1.30 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H), 0.23 (s, 9H). $^{13}$C
NMR (125 MHz, CDCl$_3$) $\delta$ 140.1, 129.0, 128.4, 127.0, 104.9, 89.2, 55.0, 52.3, 36.0, 19.7, 13.9, 0.7.

**General procedure (A) for enantioselective copper acetylide addition:**

$\text{(R)-N,N-dibenzyl-1-(trimethylsilyl)hex-1-yn-3-amine (4-93).}$ CuBr (1.8 mg, 0.0125 mmol, 5 mol%), and activated MS 4Å sieves (150 mg) were added to a test tube in a glove box. The tube was fitted with a septum before being taken from the glove box and placed directly under dry nitrogen. Phosphine 4-1 (9.7 mg, 0.0141 mmol, 5.5 mol%) in toluene (1 mL) was added to the tube and the mixture was stirred for 30 minutes at room temperature. The mixture was cooled to 0 °C and trimethylsilylacetylene 4-46 (0.25 mmol), butyraldehyde 4-84 (0.25 mmol), and dibenzylamine 4-47 (0.25 mmol) were added via syringe. The reaction mixture was stirred at 0 °C and monitored by TLC. The reaction mixture was directly subjected to flash column chromatography on silica gel.

**General procedure (B) for desilylation:**

The propargylamine obtained above was dissolved in MeOH (0.5 ml), and (KOH 1M in MeOH, 0.3 mL, 0.3 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 12 h, quenched with water (2 mL), and extracted with Et$_2$O (3 x 3 mL). The combined organic layers were dried over MgSO$_4$, concentrated under reduced pressure and purified by flash column chromatography.

$\text{(R)-N,N-dibenzyl-1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-amine (4-90).}$ The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 µL, 0.25
mmol), cyclohexanecarboxaldehyde 4-45 (30 µL, 0.25 mmol) and dibenzylamine 4-47 (48 µL, 0.25 mmol) at 0 °C for 24h. Purification by flash column chromatography (hexanes) yielded the product as a colorless solid (92.5 mg, 95%) that satisfactorily matched previously reported data.\(^\text{126}\) The \(ee\) was determined after desilylation (below). \([\alpha]^{24}_D = +180.5\ (c\ 0.77,\ \text{CHCl}_3)\). MP = 83-84 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.48 (s, 4H), 7.42 – 7.34 (m, 4H), 7.34 – 7.25 (m, 2H), 3.89 (d, \(J = 13.6\) Hz, 2H), 3.45 (d, \(J = 13.7\) Hz, 2H), 3.13 (d, \(J = 10.4\) Hz, 1H), 2.37 (d, \(J = 13.1\) Hz, 1H), 2.09 (d, \(J = 12.6\) Hz, 1H), 1.87 – 1.55 (m, 4H), 1.44 – 1.02 (m, 3H), 1.03 – 0.65 (m, 2H), 0.35 (s, 9H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 140.0, 129.0, 128.4, 127.0, 103.7, 90.3, 58.8, 55.1, 39.7, 31.5, 30.5, 26.9, 26.4, 26.2, 0.8. The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.\(^\text{126}\)

\(\text{(R)-N}N\text{-dibenzyl-1-cyclohexylprop-2-yn-1-amine.}\) The following compound was prepared via procedure B, with 4-90 (41 mg, 0.105 mmol), KOH (0.3 mmol) and MeOH (0.5 mL). Purification by flash column chromatography (hexanes) yielded the product as a colorless solid (32 mg, 96%) that satisfactorily matched previously reported data.\(^\text{126}\) \([\alpha]^{24}_D = +156.6\ (c\ 0.51,\ \text{CHCl}_3)\). MP = 75-76 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.31 (d, \(J = 7.4\) Hz, 4H), 7.21 (t, \(J = 7.3\) Hz, 4H), 7.13 (t, \(J = 7.2\) Hz, 2H), 3.73 (d, \(J = 13.8\) Hz, 2H), 3.29 (d, \(J = 13.8\) Hz, 2H), 2.95 (dd, \(J = 10.5,\ 2.2\) Hz, 1H), 2.30 – 2.13 (m, 2H), 1.92 (d, \(J = 13.5\) Hz, 1H), 1.71 – 1.42 (m, 4H), 1.29 – 0.86 (m, 3H), 0.86 – 0.50 (m, 2H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 139.8, 129.0, 128.4, 127.0, 81.16, 73.7, 57.8, 55.0, 39.7, 31.4, 30.4, 26.8, 26.3, 26.1. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (100:0 \(n\)-hexane:isopropanol, 0.1 mL/min, 215 nm); minor \(t_r = 66.22\) min; major \(t_r = 71.90\) min; 97% \(ee\). The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.\(^\text{126}\)
**State 1**

(R)-N,N-dibenzyl-4-methyl-1-(trimethylsilyl)pent-1-yn-3-amine (4-91). The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 µL, 0.25 mmol), isobutyraldehyde 4-53 (23 µL, 0.25 mmol) and dibenzylamine 4-47 (48 µL, 0.25 mmol) at 0 °C for 24h. Purification by flash column chromatography (hexanes) yielded the product as a clear colorless oil (80.0 mg, 92%) that satisfactorily matched previously reported data. The ee was determined after desilylation (below). [α]$_{24}^{D}$ = +263.6 (c 0.67, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.42 – 7.37 (m, 4H), 7.33 – 7.27 (m, 4H), 7.24 – 7.19 (m, 2H), 3.79 (d, $J$ = 13.7 Hz, 2H), 3.34 (dd, $J$ = 13.8, 0.8 Hz, 2H), 2.88 (dd, $J$ = 10.4, 0.9 Hz, 1H), 1.95 – 1.80 (m, 1H), 0.97 (dd, $J$ = 10.1, 6.9 Hz, 6H), 0.24 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 140.0, 129.1, 128.4, 127.0, 104.0, 90.1, 60.1, 55.2, 30.8, 21.1, 20.1, 0.7. The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.

(R)-N,N-dibenzyl-4-methyl-pent-1-yn-3-amine. The following compound was prepared via procedure B, with 4-91 (30 mg, 0.097 mmol), KOH (0.3 mmol) and MeOH (0.5 mL). Purification by flash column chromatography (hexanes) yielded the product as a clear colorless oil (22 mg, 92%) that satisfactorily matched previously reported data. [α]$_{24}^{D}$ = +232.1 (c 0.90, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.56 – 7.50 (m, 4H), 7.46 – 7.40 (m, 4H), 7.38 – 7.31 (m, 2H), 3.95 (d, $J$ = 13.7 Hz, 2H), 3.50 (d, $J$ = 13.8 Hz, 2H), 3.03 (dd, $J$ = 10.6, 2.2 Hz, 1H), 2.47 (d, 163
\[ J = 2.3 \text{ Hz, 1H}, \] 2.05 (dp, \[ J = 10.6, 6.6 \text{ Hz, 1H} \] ), 1.12 (dd, \[ J = 11.8, 6.6 \text{ Hz, 6H} \] ). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 134.8, 124.1, 123.4, 122.1, 76.4, 68.5, 54.2, 50.1, 25.8, 16.0, 15.0. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (100:0 n-hexane:isopropanol, 0.2 mL/min, 215 nm); minor \( t_r = 32.45 \text{ min} \); major \( t_r = 36.71 \text{ min} \); 95% ee. The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.  

**{(R)-N,N-dibenzyl-1-(1-tosylpiperidin-4-yl)-3-(trimethylsilyl)prop-2-yn-1-amine. (4-92).}** The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 \( \mu \text{L}, 0.25 \text{ mmol} \) ), 1-tosylpiperidine-4-carbaldehyde 4-88 (67 mg, 0.25 mmol) and dibenzylamine 4-47 (48 \( \mu \text{L}, 0.25 \text{ mmol} \) ) at 0 °C for 24 hours. Purification by flash column chromatography (20% EtOAc/Hexanes) yielded the product as a colorless solid (128.0 mg, 94%). 

\( [\alpha]_D^{24} = +88.1 \) (c 0.73, CHCl$_3$). MP = 128-129 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.59 (d, \( J = 8.2 \text{ Hz, 2H} \) ), 7.39 – 7.15 (m, 12H), 3.72 – 3.64 (m, 4H), 3.30 (d, \( J = 13.8 \text{ Hz, 2H} \) ), 3.00 (d, \( J = 10.5 \text{ Hz, 1H} \) ), 2.40 (s, 3H), 2.22 (td, \( J = 11.6, 2.9 \text{ Hz, 2H} \) ), 2.13 (td, \( J = 11.9, 2.7 \text{ Hz, 1H} \) ), 1.96 (d, \( J = 13.5 \text{ Hz, 1H} \) ), 1.54 – 1.36 (m, 1H), 1.14 (ddt, \( J = 49.0, 13.4, 12.7, 3.9 \text{ Hz, 2H} \) ), 0.21 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.5, 139.3, 133.1, 129.7, 128.9, 128.5, 127.9, 127.3, 102.1, 91.3, 57.4, 55.1, 46.5, 46.4, 37.5, 29.7, 29.0, 21.7, 0.5. HRMS (DART) Calcd for C$_{32}$H$_{41}$N$_2$O$_2$Si (M+H)$^+$ 545.2653, found 545.2646. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 n-hexane:isopropanol, 0.5 mL/min, 215 nm); minor \( t_r = 13.13 \text{ min} \); major \( t_r = 15.05 \text{ min} \); 91% ee. The absolute configuration was determined by analogy.

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(R)-N,N-dibenzyl-1-(trimethylsilyl)hex-1-yn-3-amine (4-93). The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 μL, 0.25 mmol), butyraldehyde 4-84 (22 μL, 0.25 mmol) and dibenzylamine 4-47 (48 μL, 0.25 mmol) at 0 °C for 24h. Purification by flash column chromatography (hexanes) yielded the product as a clear colorless oil (80.4 mg, 92%) that satisfactorily matched previously reported data. The ee was determined after desilylation (below). \([\alpha]^2_4\text{D} = +169.2\ (c\ 1.00,\ \text{CHCl}_3).\ 1^H\text{NMR (500 MHz, CDCl}_3)\ \delta\ 7.37\ (d,\ J = 7.5\ Hz,\ 4H),\ 7.29\ (t,\ J = 7.6\ Hz,\ 4H),\ 7.21\ (t,\ J = 7.3\ Hz,\ 2H),\ 3.78\ (d,\ J = 13.8\ Hz,\ 2H),\ 3.44 – 3.22\ (m,\ 3H),\ 1.67\ (dtd,\ J = 13.7,\ 8.9,\ 5.4\ Hz,\ 1H),\ 1.62 – 1.48\ (m,\ 1H),\ 1.49 – 1.30\ (m,\ 2H),\ 0.77\ (t,\ J = 7.4\ Hz,\ 3H),\ 0.23\ (s,\ 9H).\ 1^3\text{C NMR (125 MHz, CDCl}_3)\ \delta\ 140.1,\ 129.0,\ 128.4,\ 127.0,\ 104.9,\ 89.2,\ 55.0,\ 52.3,\ 36.0,\ 19.7,\ 13.9,\ 0.7.\ The\ absolute\ configuration\ was\ determined\ by\ comparing\ the\ sign\ of\ the\ optical\ rotation\ to\ that\ of\ a\ known\ sample.\ [\alpha]^2_4\text{D} = +159.5\ (c\ 0.73,\ \text{CHCl}_3).\ 1^H\text{NMR (500 MHz, CDCl}_3)\ \delta\ 7.41\ (d,\ J = 7.5\ Hz,\ 4H),\ 7.32\ (t,\ J = 7.5\ Hz,\ 4H),\ 7.24\ (t,\ J = 7.3\ Hz,\ 2H),\ 3.84\ (d,\ J = 13.8\ Hz,\ 2H),\ 3.47 – 3.31\ (m,\ 3H),\ 2.32\ (d,\ J = 2.3\ Hz,\ 1H),\ 1.80 – 1.69\ (m,\ 1H),
1.62 (ddt, \( J = 13.3, 8.9, 6.6 \) Hz, 1H), 1.44 (dtdd, \( J = 38.1, 13.5, 10.9, 6.7 \) Hz, 2H), 0.81 (t, \( J = 7.4 \) Hz, 3H). 13C NMR (125 MHz, CDCl3) \( \delta \) 139.9, 129.0, 128.4, 127.1, 82.4, 72.6, 55.0, 51.4, 36.1, 19.7, 13.9. Enantiomer ic excess was determined by HPLC with a Chiralcel OD-H column (100:0 \( n \)-hexane:isopropanol, 0.1 mL/min, 215 nm); major \( t_r = 84.62 \) min; minor \( t_r = 104.20 \) min; 89% ee. The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.134

\[
\begin{align*}
\( R \)-N,N-dibenzyl-1-phenyl-3-(trimethylsilyl)prop-2-yn-1-amine (4-94). The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 \( \mu \)L, 0.25 mmol), benzaldehyde 4-79 (25 \( \mu \)L, 0.25 mmol) and dibenzylationm 4-47 (48 \( \mu \)L, 0.25 mmol) at 0 °C for 24 hours. Purification by flash column chromatography (hexanes) yielded the product as a colorless solid (76.7 mg, 80%). The ee was determined after desilylation (below). \([\alpha]^{23}_{D} = +75.2 \) (c 1.00, CHCl3). \text{MP} = 100-101 °C. 1H NMR (500 MHz, CDCl3) \( \delta \) 7.68 – 7.59 (m, 2H), 7.42 – 7.36 (m, 4H), 7.35 – 7.26 (m, 6H), 7.26 – 7.18 (m, 3H), 4.70 (s, 1H), 3.70 (d, \( J = 13.5 \) Hz, 2H), 3.41 (d, \( J = 13.5 \) Hz, 1H), 0.32 (s, 9H). 13C NMR (125 MHz, CDCl3) \( \delta \) 139.8, 139.1, 129.1, 128.5, 128.3, 127.6, 127.2, 101.1, 93.4, 56.5, 54.7, 0.7. HRMS (DART) Calcd for C26H30NSi (M+H)+ 384.2142, found 384.2128. The absolute configuration was determined by analogy.
\]
(S)-N,N-dibenzyl-1-phenylprop-2-yn-1-amine. The following compound was prepared via procedure B, with 4-94 (26 mg, 0.078 mmol), KOH (0.3 mmol) and MeOH (0.5 mL). Purification by flash column chromatography (hexanes) yielded the product as a clear colorless oil (19.7 mg, 93%). $[\alpha]^{24}_D = +28.9 \ (c \ 0.50, \ \text{CHCl}_3)$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J = 8.1$ Hz, 2H), 7.39 (d, $J = 7.3$ Hz, 4H), 7.36 – 7.27 (m, 6H), 7.27 – 7.18 (m, 3H), 4.72 (s, 1H), 3.72 (d, $J = 13.4$ Hz, 2H), 3.44 (d, $J = 13.5$ Hz, 2H), 2.64 (d, $J = 2.3$ Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 139.6, 138.8, 129.1, 128.5, 128.4, 128.3, 127.7, 127.3, 79.0, 76.3, 55.6, 54.6. HRMS (DART) Calcd for C$_{23}$H$_{22}$N (M+H)$^+$ 312.1747, found 312.1747. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (100:0 n-hexane:isopropanol, 0.4 mL/min, 215 nm); minor $t_r = 27.50$ min; major $t_r = 35.34$ min; 94% ee. The absolute configuration was determined by analogy.

(S)-N,N-dibenzyl-1-(thiophen-2-yl)-3-(trimethylsilyl)prop-2-yn-1-amine (4-95). The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 µL, 0.25 mmol), 2-thiophenecarboxaldehyde 4-89 (23 µL, 0.25 mmol) and dibenzylamine 4-47 (48 µL, 0.25 mmol) at 0 °C for 4 days. Purification by flash column chromatography (hexanes) yielded the product as a colorless solid (58.4 mg, 60%) that satisfactorily matched previously reported data.$^{127}$ The ee was determined after desilylation (below). $[\alpha]^{24}_D = +415.5 \ (c \ 0.12 \ \text{CHCl}_3)$. MP = 89-90 °C.
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.54 – 7.47 (m, 3H), 7.40 – 7.31 (m, 3H), 7.30 – 7.23 (m, 4H), 6.96 (ddd, \(J = 5.1, 3.5, 0.8\) Hz, 1H), 4.85 (d, \(J = 1.2\) Hz, 1H), 3.86 (d, \(J = 13.7\) Hz, 2H), 3.46 (d, \(J = 13.7\) Hz, 2H), 0.34 (s, 9H). 

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.7, 139.5, 128.9, 128.5, 127.7, 126.4, 126.2, 125.7, 100.5, 92.1, 54.6, 53.1, 0.5. The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.\(^{127}\)

\(\text{(S)-N,N-dibenzyl-1-(thiophen-2-yl)prop-2-yn-1-amine.}\) The following compound was prepared via procedure B, with \(4\)-\textbf{95}(20 mg, 0.051 mmol), KOH (0.3 mmol) and MeOH (0.5 mL). Purification by flash column chromatography (hexanes) yielded the product as a clear colorless oil (12.0 mg, 74%) that satisfactorily matched previously reported data.\(^6\) \([\alpha]^{24}_D = +143.5\) (c 0.11, CHCl\(_3\)). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.52 (d, 3H), 7.37 (t, 4H), 7.31 – 7.27 (m, 3H), 6.97 (dd, \(J = 5.0, 3.6\) Hz, 1H), 4.90 (t, \(J = 1.5\) Hz, 1H), 3.90 (d, \(J = 13.7\) Hz, 2H), 3.51 (d, \(J = 13.7\) Hz, 2H), 2.64 (d, \(J = 2.3\) Hz, 1H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.2, 139.3, 128.9, 128.6, 127.3, 126.4, 126.3, 125.8, 78.7, 75.0, 54.6, 52.3. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (100:0 n-hexane:isopropanol, 0.5 mL/min, 215 nm); minor \(t_r = 14.23\) min; major \(t_r = 18.66\) min; 94% \(ee\). The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.\(^{127}\)
(R)-N,N-dibenzyl-1-(4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-amine (4-96). The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 µL, 0.25 mmol), p-anisaldehyde 4-80 (30 µL, 0.25 mmol) and dibenzylamine 4-47 (48 µL, 0.25 mmol) at 0 °C for 4 days. Purification by flash column chromatography (5% EtOAc/Hexanes) yielded the product as a clear colorless oil (79.6 mg, 77%). \([\alpha]_{22}^D = +34.3\) (c 0.99, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.58 (d, \(J = 8.9\) Hz, 2H), 7.42 (s, 4H), 7.33 (t, \(J = 7.6\) Hz, 4H), 7.26 (d, \(J = 9.8\) Hz, 2H), 6.90 (d, \(J = 8.7\) Hz, 2H), 4.68 (s, 1H), 3.82 (s, 3H), 3.73 (d, \(J = 13.5\) Hz, 2H), 3.42 (d, \(J = 13.5\) Hz, 2H), 0.36 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl₃) δ 159.1, 139.8, 131.1, 129.5, 128.4, 127.1, 113.6, 101.4, 93.0, 55.8, 55.5, 54.5, 0.6. HRMS (DART) Calcd for C_{27}H_{32}NOSi (M+H)⁺ 414.2248, found 414.2230. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (100:0 n-hexane:isopropanol, 0.8 mL/min, 254 nm); minor \(t_r = 9.53\) min; major \(t_r = 13.96\) min; 94% ee. The absolute configuration was determined by analogy.

(R)-N,N-dibenzyl-1-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-amine (4-97). The following compound was prepared via procedure A, with trimethylsilylacetylene 4-46 (35 µL, 0.25 mmol), p-trifluoromethylbenzaldehyde 4-49 (39 µL, 0.25 mmol) and dibenzylamine 4-47 (48 µL, 0.25 mmol) at room temperature for 24 hours. Purification by flash column chromatography (hexanes) yielded the product as a clear colorless oil (79.0 mg, 70%). The ee was
determined after desilylation (below). \([\alpha]^{22}_D = +54.5 \ (c \ 1.50, \ \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.75 \ (d, \ J = 9.8 \ Hz, \ 2H), \ 7.57 \ (d, \ J = 9.3 \ Hz, \ 4H), \ 7.36 \ (d, \ J = 8.7 \ Hz, \ 4H), \ 7.30 \ (t, \ J = 7.6 \ Hz, \ 2H), \ 7.24 - 7.19 \ (m, \ 2H), \ 4.69 \ (s, \ 1H), \ 3.66 \ (d, \ J = 13.4 \ Hz, \ 2H), \ 3.40 \ (d, \ J = 13.5 \ Hz, \ 2H), \ 0.32 \ (s, \ 9H). \) \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 143.3, \ 139.3, \ 130.0, \ 129.8, \ 129.1, \ 128.7, \ 128.6, \ 127.4, \ 125.2 \ (q, \ J = 4 \ Hz), \ 100.0, \ 94.3, \ 56.3, \ 54.9, \ 0.6. \) HRMS (DART) Calcd for C\(_{27}\)H\(_{29}\)F\(_3\)NSi (M+H\(^+\)) 452.2016, found 452.2006. The absolute configuration was determined by analogy. 

(S)-N,N-dibenzyl-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-amine. The following compound was prepared via procedure B, with 4-97 (35 mg, 0.078 mmol), KOH (0.3 mmol) and MeOH (0.5 mL). Purification by short flash column chromatography (hexanes) yielded the product as a clear colorless oil (21 mg, 70%). \([\alpha]^{23}_D = +7.1 \ (c \ 1.00, \ \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.79 \ (d, \ J = 8.7 \ Hz, \ 2H), \ 7.59 \ (d, \ J = 8.4 \ Hz, \ 2H), \ 7.39 \ (d, \ J = 7.4 \ Hz, \ 4H), \ 7.32 \ (t, \ J = 7.5 \ Hz, \ 4H), \ 7.27 - 7.19 \ (m, \ 2H), \ 4.74 \ (s, \ 1H), \ 3.70 \ (d, \ J = 13.5 \ Hz, \ 2H), \ 3.45 \ (dd, \ J = 13.4, \ 1.7 \ Hz, \ 2H), \ 2.69 \ (d, \ J = 2.3 \ Hz, \ 1H). \) \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 143.0, \ 139.2, \ 130.2, \ 129.9, \ 129.1, \ 128.7, \ 128.6, \ 127.5, \ 125.5, \ 125.3 \ (q, \ J = 4 \ Hz), \ 123.3, \ 78.9, \ 77.1, \ 55.4, \ 54.8. \) HRMS (DART) Calcd for C\(_{24}\)H\(_{21}\)F\(_3\)N (M+H\(^+\)) 380.1621, found 380.1617. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (100:0 n-hexane:isopropanol, 0.5 mL/min, 215 nm); minor \(t_r = 16.08 \) min; major \(t_r = 23.19 \) min; 92% ee. The absolute configuration was determined by analogy.
(R)-1-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl)piperidin-4-one (4-90). CuBr (1.8 mg, 0.0125 mmol, 5 mol%), and activated MS 4Å sieves (150 mg) were added to a test tube in a glove box. The tube was fitted with a septum before being taken from the glove box and placed directly under dry nitrogen. Phosphine 4-1 (9.7 mg, 0.0141 mmol, 5.5 mol%) in dichloromethane (1 mL) was added to the tube and the mixture was stirred for 30 minutes at room temperature. The mixture was cooled to 0 °C and triethylamine (56 mg, 0.55 mmol, 2.2 equiv) was added via syringe. 4-piperidone hydrochloride monohydrate (38.4 mg, 0.25 mmol, 1.0 equiv) was added as a solid, followed by phenylacetylene (55 µL, 0.5 mmol, 2.0 equiv) and isobutyraldehyde (46 µL, 0.50 mmol, 2.0 equiv) via syringe. After addition of an additional 1 mL of dichloromethane the reaction was stirred at 0 °C for 24 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (3 mL) and transferred to a separatory funnel containing dichloromethane (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the crude material by flash column chromatography on silica gel (20% EtOAc/Hexanes) afforded the product (51.2 mg, 80%) as a yellowish solid that satisfactorily matched previously reported data. \[ [\alpha]^{25}_D = +15.7 \ (c 1.00, \text{CHCl}_3) \]. MP = 69-70 °C. $^1$H NMR (500 MHz, CDCl₃) δ 7.44 – 7.35 (m, 2H), 7.31 – 7.26 (m, 3H), 3.18 (d, $J = 10.0$ Hz, 1H), 2.98 (dt, $J = 11.8, 6.2$ Hz, 2H), 2.76 (dt, $J = 11.5, 6.0$ Hz, 2H), 2.48 (ddt, $J = 22.0, 14.8, 8.0$ Hz, 4H), 1.91 (dt, $J = 9.8, 6.5$ Hz, 1H), 1.10 (dd, $J = 33.1, 6.6$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl₃) δ 209.7, 131.9, 128.5, 128.2, 123.4, 86.7, 86.4, 64.7, 49.7, 41.8, 31.4, 171
Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (99:1 n-hexane:isopropanol, 0.5 mL/min, 254 nm); minor $t_r = 31.60$ min; major $t_r = 39.09$ min; 93% ee. The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.\(^2\)

\[(R)-1-(4-methyl-1-phenylpent-1-yn-3-yl)piperidin-4-one (4-91).\] CuBr (2.7 mg, 0.0188 mmol, 7.5 mol%), and activated MS 4Å sieves (150 mg) were added to a test tube in a glove box. The tube was fitted with a septum before being taken from the glove box and placed directly under dry nitrogen. Phosphine 7 (14.2 mg, 0.02 mmol, 8 mol%) in dichloromethane (1 mL) was added to the tube and the mixture was stirred for 30 minutes at room temperature. The mixture was cooled to 0 °C and triethylamine (56 mg, 0.55 mmol, 2.2 equiv), 4-piperidone monohydrate (38.4 mg, 0.25 mmol, 1.0 equiv) was added as a solid, followed by trimethylsilylacetylene 4-46 (55 µL, 0.5 mmol, 2.0 equiv) and benzaldehyde (25 µL, 0.25 mmol, 1.0 equiv) via syringe. After addition of an additional 1 mL of dichloromethane the reaction was stirred at room temperature for 48 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (3 mL) and tranfered to a separatory funnel containing dichloromethane (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the crude material by flash column chromatography on silica gel (20% EtOAc/Hexanes) afforded
the product (49.0 mg, 69%) as a yellowish oil. \([\alpha]^{25}_{D} = -27.4 (c 1.00, \text{CHCl}_3).\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.61 (d, J = 7.6 \text{ Hz}, 2\text{H}), 7.37 (t, J = 7.5 \text{ Hz}, 2\text{H}), 7.31 (t, J = 7.3 \text{ Hz}, 1\text{H}), 4.80 (s, 1\text{H}), 2.80 (t, J = 6.2 \text{ Hz}, 4\text{H}), 2.46 (dtd, J = 20.9, 14.7, 7.1 \text{ Hz}, 4\text{H}), 0.23 (s, 9\text{H}).\) \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 209.4, 138.0, 128.4, 128.4, 128.0, 100.4, 93.5, 61.4, 49.3, 41.7, 0.4.\) HRMS (DART) Calcd for C\(_{17}\)H\(_{24}\)NOSi (M+H)\(^+\) 286.1622, found 286.1628. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 \text{n-hexane:isopropanol}, 1 mL/min, 215 nm); minor \(t_r = 21.31 \text{ min}; \) major \(t_r = 26.57 \text{ min}; 92\% \text{ ee}.\) The absolute configuration was determined by analogy.

**Crystal structure 4-103:** X-Ray Intensity data were collected at 100 K on a Bruker DUO diffractometer using CuK\(\alpha\) radiation (\(\lambda = 1.54178 \text{ Å}\)), from an ImuS power source, and an APEXII CCD area detector.

Raw data frames were read by program SAINT\(^1\) and integrated using 3D profiling algorithms. The resulting data were reduced to produce hkl reflections and their intensities and estimated standard deviations. The data were corrected for Lorentz and polarization effects and numerical absorption corrections were applied based on indexed and measured faces.

The structure was solved and refined in SHELXT2013, using full-matrix least-squares refinement. The non-H atoms were refined with anisotropic thermal parameters and all of the H atoms were calculated in idealized positions and refined riding on their parent atoms. The asymmetric unit consists of the Cu-dimer and a significantly disordered molecule. The latter is significantly disordered and could not be modeled properly, thus program SQUEEZE, a part of the PLATON package of crystallographic software, was used to calculate the solvent disorder.
area and remove its contribution to the overall intensity data. The molecules exhibit five
disordered phenyl rings. Those are located on C26, C79, C86, and P2. The latter are C101-C106
and C201-C206 and their disordered counter parts. The final cycle of refinement, 14276
reflections (of which 12641 are observed with I > 2σ(I)) were used to refine 822 parameters and
the resulting R₁, wR₂ and S (goodness of fit) were 4.88%, 12.32% and 1.065, respectively. The
refinement was carried out by minimizing the wR₂ function using F² rather than F values. R₁ is
calculated to provide a reference to the conventional R value but its function is not minimized.

Table 6-5. Crystal data and structure refinement for 4-103.

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Theta range for data collection 2.434 to 67.999°.

Table 6-5. Continued

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<td>Goodness-of-fit on F²</td>
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<td>R indices (all data)</td>
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<td>Extinction coefficient</td>
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</tr>
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<td>Largest diff. peak and hole</td>
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</table>

6.2.4 Synthesis of (+)-Cuspareine 4-121

\[ \text{Ethyl-(S)-2-((3,4-dimethoxyphenyl)ethynyl)quinoline-1(2H)-carboxylate (4-120).} \]

A solution of 4-1 (9.7 mg, 0.0141 mmol, 5.5 mol%) and alkyne 4-62 (41 mg, 0.25 mmol) in dichloromethane (1.0 mL) was added to CuBr (1.8 mg, 0.0125 mmol, 5 mol%) and stirred at
room temperature for 30 min. Quinoline 4-115 (30 µL, 0.25 mmol) and ethyl chloroformate 4-109 (24 µL, 0.25 mmol) were mixed in DCM (1.0 mL) for 5 min. at ambient temperature. Then the quinoline salt was added to the above reaction mixture at 0 °C followed by EtN\textsubscript{2}Pr\textsubscript{2} (60 µL, 0.35 mmol) and the reaction mixture was allowed to warm to room temperature. The reaction was stirred for three hours and directly subjected to flash column chromatography using dichloromethane. The solvent was removed under reduced pressure and the title product was obtained as a white solid (86%, 95% ee). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 n-hexane:isopropanol, 1.0 mL/min, 254 nm); minor t\textsubscript{R} = 14.54 min; major t\textsubscript{R} = 18.22 min. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.64 (s, 1H), 7.30 – 7.16 (m, 1H), 7.17 – 7.00 (m, 2H), 6.88 (dd, J = 8.3, 1.9 Hz, 1H), 6.77 (d, J = 1.9 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 6.60 – 6.48 (m, 1H), 6.16 – 6.00 (m, 2H), 4.44 – 4.15 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

(R)-2-(3,4-dimethoxyphenethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (4-121). A solution of 4-120 (23 mg, 0.0633 mmol) in EtOH/EtOAc (1:1) (2.0 mL) was added 10% Pd-C (5 mg). The reaction vessel was evacuated and refilled with hydrogen three times using vacuum pump. The reaction was stirred under hydrogen balloon at ambient temperature for 16 h. The reaction mixture was diluted with EtOAc and filtered through a celite bed. The filtrate was collected and the solvents were distilled off to afford a crude mixture which was forwarded to the next step without any further purification.

To a suspension of LAH (24 mg, 0.633 mmol) in anhydrous THF (3.0 mL) at 0 °C was added a solution of the material obtained above in THF (3.0 mL) in a dropwise fashion. The
suspension was stirred at 55 °C for three hours. The reaction mixture was cooled to 0 °C and quenched according to Fieser workup. After drying this solution with MgSO$_4$, the solvent was removed and a column run at 20% EtOAc/Hexanes gave the title compound 2-39 as a yellow oil (14 mg, 71% over to steps); $[\alpha]_D^{24} = +26.2$ (c = 1.00, CHCl$_3$) {For (-)-cuspareine: lit.$^{142} [\alpha]_D^{25} = -22.8$ (c = 1.00, CHCl$_3$)}. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.11 (dd, $J = 8.5$, 6.8 Hz, 1H), 7.01 (d, $J = 7.5$ Hz, 1H), 6.81 (d, $J = 8.1$ Hz, 1H), 6.78 – 6.71 (m, 2H), 6.62 (t, $J = 7.3$ Hz, 1H), 6.56 (d, $J = 7.8$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.31 (dt, $J = 8.7$, 4.3 Hz, 1H), 2.94 (s, 3H), 2.88 (ddd, $J = 17.5$, 12.1, 6.1 Hz, 1H), 2.77 – 2.65 (m, 2H), 2.56 (ddd, $J = 14.0$, 10.1, 6.4 Hz, 1H), 2.04 – 1.89 (m, 3H), 1.83 – 1.70 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 149.1, 147.4, 145.5, 134.8, 128.9, 127.3, 121.9, 120.3, 115.6, 111.8, 111.5, 110.8, 58.6, 56.2, 56.1, 38.3, 33.3, 32.1, 24.6, 23.8.

6.2.5 Asymmetric Alkynylation of Alkylidene Derivatives of Meldrum’s Acid

(R)-5-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4-124). Sodium (L)-ascorbate (5 mg, 0.025 mmol) was added to test tube containing a 0.3M solution of Cu(OAc)$_2$ in water (0.04 mL, 0.012 mmol). Water (0.12 mL) was added and the mixture was stirred until the mixture turned bright orange. Subsequently, 4-1 (9 mg, 0.0126 mmol) and phenylacetylene 4-50 (0.14 mL, 1.27 mmol) were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 4-123 (33 mg, 0.126 mmol). The reaction mixture was stirred vigorously at 0 °C for 18 hours, diluted with dichloromethane (2 ml) and subjected directly to flash column chromatography (30 % EtOAc/hexanes) to yield the title compound as a white foam (44 mg, 95%). Enantiomeric excess: 80%. $[\alpha]_D^{24} = +20.0$ (c = 1.00, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J = 8.6$ Hz, 2H),
7.44 – 7.37 (m, 2H), 7.23 (dd, J = 5.1, 1.9 Hz, 3H), 6.81 (d, J = 8.7 Hz, 2H), 5.04 (d, J = 2.6 Hz, 1H), 3.89 (d, J = 2.7 Hz, 1H), 3.73 (s, 3H), 1.66 (s, 3H), 1.54 (s, 3H). \(^{13}\)C NMR (125 MHz, CHCl\(_3\)) \(\delta\) 163.8, 163.4, 159.3, 131.9, 130.1, 129.1, 128.4, 128.3, 122.9, 113.9, 105.3, 86.8, 85.3, 55.4, 53.0, 36.5, 28.4, 27.9. Determination of the ee: 10 mg of 4-124 was heated in 1.1 ml of DMF/aniline (10:1) at 100 °C for 1 hour, cooled to room temperature, the reaction mixture was extracted with Et\(_2\)O and washed three times with 1 M HCl, the organic phase was filtered through a plug of silica gel, eluted with hexane/EtOAc 3:1 to give the pure anilide 4-125. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (87:13 \(n\)-hexane:isopropanol, 0.7 mL/min, 215 nm); minor \(t_r = 22.76\) min; major \(t_r = 24.54\) min. The absolute configuration was determined by analogy.\(^{105,131}\)

6.2.6 Palladium-Catalyzed Asymmetric Allylic Alkylation

Dimethyl-(R,E)-2-(1,3-diphenylallyl)malonate (4-133). Dimethylmalonate 4-127 (46 µL, 0.405 mmol) was added dropwise to another flask containing a suspension of NaH (10 mg, 0.405 mmol) in acetonitrile (0.3 mL) at 0 °C. 15-crown-5 (0.08 mL, 0.405 mmol) was then added and it was cooled to –20 °C. A solution of 1,3-diphenyl-2-propenyl acetate 4-126 (34 mg, 0.135 mmol) and 4-1 (5 mg, 0.00675 mmol) in acetonitrile (0.1 ml) was added via syringe to a flask containing \([\text{PdCl}(\eta^3-\text{C}_3\text{H}_5)]_2\) (1 mg, 0.0027 mmol) and stirred for 10 minutes at room temperature. The resulting yellow solution was added via syringe to the sodium dimethylmalonate suspension at -20 °C and the mixture was let to stir for 7 hours at this temperature. The reaction mixture was poured into water (10 ml), extracted into diethyl ether (10 ml), then washed with water (10 ml) and saturated brine (10 ml). The solution was dried over
MgSO₄, then the solvent removed under reduced pressure. The residue was purified by flash column chromatography (gradient hexanes to 5% EtOAc/hexanes) to yield the title compound as a clear oil (34 mg, 77%). Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (95:5 n-hexane:isopropanol, 0.7 mL/min, 254 nm); minor $t_r = 36.81$ min; major $t_r = 30.99$ min. The absolute stereochemistry was determined by comparison of the HPLC retention time to those reported in the literature data.¹⁵²
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BIOGRAPHICAL SKETCH

Flávio S. P. Cardoso was born in São José dos Campos, São Paulo, Brazil. He was raised in the same city and graduated from high school in the end of 2004. Subsequently, he moved to Campinas to begin his studies in chemistry at the State University of Campinas (UNICAMP). He performed undergraduate research under the supervision of Prof. Carlos Roque Duarte Correia for a period of nearly three years. His research at UNICAMP focused on the palladium-catalyzed Heck-Matsuda reaction. In the Summer of 2009, upon graduation with a B.S in Chemistry, Flavio started his graduate studies at the University of Florida. Under the guidance of Prof. Aaron Aponick, his PhD studies involved the development of a new class of atropisomers which was ultimately applied in asymmetric catalysis.