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The Preparation, Resolution and Application of
Novel 2-Furyl Phosphine Ligands
in Asymmetric Synthesis

by

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Abstract

Tertiary, C2-symmetric biaryl phosphine ligands are often fundamental components for enantioselective transition metal-mediated organic processes. This dissertation describes a novel method for the preparation of C2-symmetric biaryl compounds as well as the synthesis, resolution, and application of two novel C2-symmetric phosphines. A new resolution procedure, developed for the aforementioned ligands, was applied toward the synthesis of a variety of P-stereogenic phosphine oxides.

An *in situ* variant of the Suzuki reaction was used to prepare a number of C2-symmetric biaryl compounds. This method, which obviates the need for boronic acid isolation, was found to be tolerant to a wide variety of functional groups including esters, amides, acetals, and nitriles. The synthetic utility of this method was demonstrated through short, efficient syntheses of two fungal metabolites, 4,4'-dihydro-5,5'dimethoxy-1,1'-binaphthalene and 4,4',5,5'-tetrahydroxy-1,1'-binaphthalene.

Two atropisomeric C2-symmetric phosphine ligands were prepared. (+)-2,2'-Bis(diphenylphosphino)-3,3'binaphtho[2,1-b]furan (BINAPFu) was synthesized from 2-naphthoxyacetic acid in a five step sequence. (±)-2,2'-Bis(di-2-furylphosphino)-1,1'-binaphthalene (TetFuBINAP) was synthesized by reacting 2,2'-dibromo-1,1'-binaphthalene with chlorodi(2-furyl)phosphine.

(±)-BINAPFu and (±)-TetFuBINAP were resolved via a newly developed procedure. Staudinger reactions of the aforementioned racemates with an enantiopure organoazide provided phosphinimine mixtures that were separable by flash chromatography. Subsequent hydrolysis and trichlorosilane reduction of each phosphinimine diastereomer provided the enantiopure BINAPFu and TetFuBINAP ligands. The absolute stereochemical configurations of BINAPFu and TetFuBINAP were established by X-ray crystallography and circular dichroism spectroscopy, respectively.

BINAPFu and TetFuBINAP were compared to commercially available, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) in Pd(0)-catalyzed inter- and intramolecular Heck reactions as well as Ru(II)-catalyzed hydrogenations of α- and β-ketoesters. Investigation of the Heck arylation of 2,3-dihydrofuran showed BINAPFu to be more efficacious than BINAP and led to a new proposed mechanism for this process. The BINAPFu ligand performed poorly in
intramolecular Heck ring closure reactions and asymmetric hydrogenations. Although TetFu-BINAP provided mixed results in the arylation of 2,3-dihydrofuran, it was found to be an outstanding ligand for the intramolecular Heck cyclization of 2-bromo-N-(cyclohexen-1-carbonyl)-N-methylanaline.

The resolution of a variety of (±)-P-stereogenic phosphines was achieved by exploiting the Staudinger reaction of a phosphine racemate with enantiopure (1S,2R)-O-(t-butyldimethylsilyl)isobornyl-10-sulfonyl azide. The resulting mixtures of diastereomeric phosphinimines were generally separable by fractional crystallization or flash chromatography. Subsequent acid-catalyzed hydrolysis provided the corresponding optically pure phosphine oxides in high yield.
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in loving memory of my maternal grandfather,
Floyd Nelson of Bently, Alberta (1914-1996)
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<td>$^{13}$C-NMR</td>
<td>carbon-13 nuclear magnetic resonance</td>
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<tr>
<td>$^{1}$H-NMR</td>
<td>proton nuclear magnetic resonance</td>
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<tr>
<td>$^{31}$P-NMR</td>
<td>phosphorus-31 nuclear magnetic resonance</td>
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<td>Å</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<td>acac</td>
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<td>amu</td>
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<td>CD</td>
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</table>
CE  Cotton effect
cm⁻¹  wavenumbers
cod  cyclooctadiene
COSY  correlation spectroscopy
CSA  camphorsulfonic acid
Cy  cyclohexyl
d  doublet
dba  dibenzylideneacetone
DBTA  dibenzoyl-L-tartaric acid
dd  doublet of doublets
ddd  doublet of doublet of doublets
de  diastereomeric excess
DDQ  2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec.  decomposed
deg.  degrees
DEPT  distortionless enhancement by polarization transfer
dfpf  bis(di-2-furylphosphino)ferrocene
DIBAL  diisobutylaluminum hydride
DIC  diisopropylcarbodiimide
dioxane  1,4-dioxane
DIPEA  N,N-diisopropylethylamine
DMA  N,N-dimethylacetamide
DMAP  4-dimethylaminopyridine
DME  1,2-dimethoxyethane
DMF  N,N-dimethylformamide
DMS  methyl sulfide
DMSO  dimethyl sulfoxide
dppb  1,4-bis(diphenylphosphino)butane
dppf  bis(diphenylphosphino)ferrocene
dppp  1,3-bis(diphenylphosphino)propane
E
energy
E
general ester substituent
e.g.
exempli gratia
ee
enantiomeric excess
equiv.
equivalent
Et
ethyl
FAB-MS
fast atom bombardment mass spectrometry
FID
flame ionization detector
Fu
2-furyl
g
grams
G
general group
GC-MS
gas chromatography/mass spectrometry
h
hours
H+
acid
Hex
hexyl
hfc
3-heptafluoropropylhydroxymethylene-(+)-camphorate
HMWM
higher molecular weight material
HPLC
high-performance liquid chromatography
HRMS
high resolution mass spectrometry
HX
hydrogen halide
Hz
Hertz
hv
light
i
iso
IPA
isopropylamine
IR
infrared
J
coupling constant
kg
kilogram
kJ
kilojoules
L
ligand
L.P.
lone pair
$o$ ortho
$^\circ C$ degrees Celsius
ox. oxidation
P generalized protecting group
$p$ para
PEG poly(ethylene glycol)
Ph phenyl
PHMS polymethylhydrosiloxane
PMP pentamethylypipерidine
Pr propyl
P.S. Proton-Sponge®
pyr pyridine
R generalized alkyl group or subsituent
rt room temperature
s singlet
scCO$_2$ supercritical carbon dioxide
sec secondary
$t$ triplet
$t$ tertiary
TBDPS $t$-butyldiphenylysilyl
TBS $t$-butyldimethylsilyl
TEBA triethylbenzylammonium chloride
Temp. temperature
TES triethylsilyl
Tf trifluoromethanesulfonyl
TFA trifluoroacetic acid
TFP tri-2-furylphospine
thexyl 2-(2,3-dimethyl)butyl
THF tetrahydrofuran
THP tetrahydropyranyl
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Miscellaneous Symbols

- δ: chemical shift
- *: chiral
- θ°: cone angle
- Δ: heat
- (): polymer resin
- 🎖️: totally annoying software
- 📡: microwave
1. The Suzuki Cross-Coupling Reaction.

1.1 Introduction.

Palladium catalyzed cross-coupling between organoboron compounds and organic halides or triflates has, in recent years, been shown to be a versatile method for carbon-carbon bond formation. The original procedure developed by Suzuki\(^1\) has achieved widespread synthetic application due, in part, to the remarkable compatibility of the reaction conditions towards a large variety of functional groups. Moreover, the Suzuki cross-coupling is an attractive reaction from an industrial standpoint since the conditions employ aqueous reaction media and the relatively non-toxic inorganic byproduct of the process is easily removed from the reaction mixture. The synthetic utility of the Suzuki reaction has been demonstrated in a wide array of diverse applications ranging from small molecule preparation to complex natural product syntheses and has been the topic of recent review articles.\(^2\) After introduction to the mechanistic aspects of the Suzuki cross-coupling and discussion of recent modifications to the original procedure, this chapter describes our efforts to develop a novel in situ variant of the Suzuki reaction for the preparation of C\(_2\)-symmetric biaryl compounds.

1.1.1 Mechanistic Aspects of the Suzuki Cross-Coupling Reaction.

The general catalytic cycle for the Suzuki reaction, which involves the processes of oxidative insertion, transmetalation, and reductive elimination, is depicted in Figure 1.1. A wide variety of palladium(0) catalysts or precursors 1 have been successfully employed for the Suzuki cross-coupling reaction including Pd(PPh\(_3\))\(_4\), Pd\(_2\)dba\(_3\), Pd(OAc)\(_2\), and PdCl\(_2\)(PPh\(_3\))\(_2\). The oxidative addition precursor 2 is normally an organo-iodide, triflate or bromide. However, Buchwald,\(^4\) Fu,\(^5\) and others\(^6\) have recently extended the Suzuki methodology to include organochlorides. Oxidative addition is often found to be the rate-determining step in the catalytic cycle and the relative reactivity generally follows the order of I > OTf > Br > Cl.\(^2\) The exact details of the transmetalation step have not been fully elucidated since the mechanism of this step is thought to be highly dependant upon the nature of R\(^1\) and R\(^2\) (Figure 1.1) as well as the reaction conditions used for the coupling. For example, the nature of the base employed for the coupling has been
Inorganic bases such as Ba(OH)$_2$, NaOH, TIOH and Na$_2$CO$_3$ are most often used to achieve smooth cross-coupling. To this end, Suzuki has proposed that the base interacts with the boronic acid 4 to form a quaternary boronate anion, $R^2B(OH)_3^-$, which then proceeds in the transmetalation step with the palladium(II) halide 3. Although no direct evidence has been reported in the literature to support the role of a hydroxyboronate anion intermediate, such a hypothesis is supported by the observation that organopalladium(II) halides do not normally transmetalate with neutral organoboranes due to the low nucleophilicity of the organic group on boron. Moreover, quaternization of the boron atom to afford a negatively charged boronate anion would presumably increase the nucleophilicity of the organic group on the boron atom thus facilitating transmetalation. Alternatively, Suzuki has postulated that the base may react with the palladium(II) halide 3 to form an alkoxo- or hydroxo-palladium(II) intermediate. Such complexes are known to form upon treatment of an organopalladium(II) halide with alkoxy, hydroxy, or acetoxo anions and have in some cases been isolated and characterized. Although alkoxo- or hydroxo-palladium(II) intermediates have been postulated to be reaction
intermediates, such species have not been directly observed in the Suzuki pathway. However, both the oxidative insertion complex 3 and the reductive elimination precursor 6 have been characterized by isolation or observed by spectroscopic methods.\textsuperscript{11} The transmetalation mechanism, although not fully understood, likely takes place via either the hydroxyboronate anion or the alkoxopalladium(II) species but which route predominates is not clear. It is likely that both mechanisms are operative and that the importance of each mechanism is governed by the nature of the starting material 2, organoborane 4, base, and conditions used to effect cross-coupling.

The stereochemistry of the transmetalation adduct is thought to initially be \textit{trans} while the reductive elimination precursor must have a \textit{cis} configuration. Reductive elimination of \textit{cis}-6 to give the product 7 is known to be inhibited by excess phosphine indicating a dissociative mechanism is operative. Further, the rate of the reductive elimination step has been shown to increase as electron-withdrawing substituents are placed on R\textsubscript{1} and R\textsubscript{2} (Figure 1.1).\textsuperscript{2}

1.1.2 The Suzuki Cross-Coupling Reaction as it Applies to Biaryl Synthesis.

Biaryls are an important class of organic compounds, which are of interest in such fields as natural products chemistry, polymer chemistry, advanced materials science, asymmetric ligand design, and pharmacology. Traditionally, the synthesis of biaryl compounds has been achieved by the copper mediated Ullmann coupling\textsuperscript{12} of aryl halides. However, this reaction employs forcing conditions and often suffers from low product yields when the haloarene bears electron donating groups. In view of the tremendous importance of biaryl compounds, several catalytic methods for preparing such compounds have been developed over the past twenty years. These methods include the Kumada, Negishi, Stille, and Suzuki cross-coupling reactions and the application of these methods toward biaryl synthesis has been the topic of a recent review article.\textsuperscript{13} Of these catalytic methods, the Suzuki cross-coupling protocol is perhaps the most attractive since it is highly tolerant of a wide range of functional groups on both coupling partners, is performed under mild reaction conditions, and produces relatively non-toxic byproducts. Since the last review of biaryl synthesis,\textsuperscript{13} there have been a number of developments in the Suzuki cross-coupling method. Recent advances and modifications to the
Suzuki cross-coupling procedure are highlighted in section 1.1.3. The purpose of such a discussion is not to comprehensively detail all of the literature reports of the Suzuki biaryl synthesis since the time of Stanforth's recent review article but rather to introduce the reader to current research efforts that have resulted in significant experimental alterations of Suzuki's original procedure.

1.1.3 Recent Developments in Suzuki Biaryl Synthesis.

In light of the tremendous impact solid phase synthesis and combinatorial chemistry have had on the discovery of pharmacologically active lead compounds, in conjunction with the synthetic importance of biaryls in medicinal chemistry, it is not surprising that a tremendous amount of research has been conducted with the aim of developing solid phase versions of the Suzuki cross-coupling. Snieckus and coworkers have recently added to this effort by performing the Suzuki biaryl synthesis on a variety of bromobenzaldehydes connected to the Merrifield resin via a Leznoff acetal linker (Scheme 1.1). This method smoothly affords cross-coupled products with a wide variety of substituted boronic acids using reaction times of 24 h to 48 h. Moreover, the coupled products may easily be cleaved from the resin by mild acid hydrolysis and the solid support can subsequently be reused. In accordance with Suzuki's original findings, Snieckus has observed that the yield of cross-coupled product tends to decrease when sterically demanding boronic acids are employed. For example, reaction of para-bromide 8c with mesityl boronic acid afforded product 9c in 45% isolated yield after a 48 h reaction period. Notwithstanding the limitations of sterically encumbered boronic acids, usage of this polymer bound method could clearly be extended toward the synthesis of biaryl compound
libraries. Unfortunately, this method is limited to the production of biaryls that possess an aldehyde functional group on at least one of the aromatic rings since this moiety is employed to link the halide to the solid support. Hence, if a different functional group is required, a complementary resin employing an alternative connector group must be utilized.

The use of solid phase synthesis in organic chemistry has mainly been born from a desire to increase efficiency by making work-up and purification of reaction products easier. While the substrate bound approach is limited by the type of linker used to connect the reagent to the polymer, the use of solid supported catalysts does not suffer from this complication. Hence the development of polymer-bound palladium catalysts has been an active area of research. A reusable, polymer-supported palladium catalyst, which serves as an alternative to tetrakis(triphenylphosphine)palladium(0) in the Suzuki reaction, has recently been reported. The catalyst may easily be prepared in two steps starting with the Merrifield resin and has been shown to efficiently catalyze the Suzuki biaryl coupling of various aryl bromides with phenyl boronic acid (Scheme 1.2). While the solid supported palladium catalyst 11 gives similar results to Pd(PPh₃)₄ in a number of Suzuki biaryl forming reactions, it is known to be less heat- and air-sensitive. Whereas tetrakis(triphenylphosphine)palladium(0) generally must be stored in a freezer under an inert atmosphere, the polymer supported catalyst 11 has been shown to be stable for over a year at 20 °C in an ambient atmosphere. Moreover, the catalyst may be used

\[
\begin{align*}
\text{Scheme 1.2} \\
10 & \xrightarrow{\text{1) Ph₂PLi, THF}} 11 \\
& \xrightarrow{\text{2) Pd(PPh₃)₄}} \text{[Pd]} \\
\end{align*}
\]

\[
\begin{align*}
\text{Catalyst, Na₂CO₃} & \xrightarrow{Toluene, H₂O, reflux 24 h} \text{[Pd]} \\
\% Yield & \text{[Pd]}_4 \\
12 & \text{R = NH₂} \\
13 & \text{R = NHAc} \\
14 & \text{R = OMe} \\
15 & \text{R = Ac} \\
16 & \text{17} \\
17 & \text{R = NH₂} \quad 56 \\
18 & \text{R = NHAc} \quad 76 \\
19 & \text{R = OMe} \quad 80 \\
20 & \text{R = Ac} \quad 98 \\
\end{align*}
\]
and recycled numerous times without any noticeable decrease in activity. Quantitative analysis on the recovered catalyst resin shows that only 0.60-0.65% of the initial amount of palladium is lost per use/recovery cycle. Clearly, reusable polymer-supported palladium catalysts offer significant advantages over traditional Pd(0) catalysts from an economic point of view. The use of such catalysts in Suzuki biaryl synthesis will likely become standard practice in the near future as resin bound palladium sources become commercially available reagents.

Another intense area of research surrounding palladium catalysis centers on the endeavor to find methods of reducing reaction times. Attempts to achieve this goal by raising the reaction temperature often fail due to the collapse of the catalyst system. However, the rate of the Suzuki reaction with phosphine-free palladium sources is greatly accelerated and early recognition of this fact has allowed for the development of an aqueous phase variant of the reaction. Although aqueous phase reactions offer an environmentally friendly and economic alternative to traditional organic synthesis, the development of such methods has been greatly impeded by the sparse solubility of most organic reactants in water. Recently, a group of researchers in Hamburg, Germany have addressed this problem by cleverly applying the principles of solid phase synthesis and phase transfer catalysis. These workers found that poly(ethylene glycol) (PEG) supported aryl halides and aryl sulfonates were soluble in the aqueous phase and could be coupled with a variety of aryl boronic acids under "ligandless" palladium acetate-catalyzed conditions (Scheme 1.3). The PEG-bound cross-coupled products

Scheme 1.3

\[
\begin{align*}
21 \quad X &= \text{I} \\
22 \quad X &= \text{OTf} \\
23 \quad X &= \text{ONf} \\
24 \quad \text{PEG} - \text{O} - \text{C} - \text{S} - \text{Br} \\
25 \quad (\text{HO})_2\text{B} - \text{C} - \text{R} \\
&\quad \text{10 mol} \% \text{Pd(OAc)}_2, \text{H}_2\text{O} \\
&\quad 2.5 \text{ equiv. K}_2\text{CO}_3 \\
&\quad 70^\circ\text{C}, 2 \text{h} \\
&\quad \text{or } \bullet\bullet\bullet 2-4 \text{ min} \\
\end{align*}
\]
26 and 27 could be isolated from the reaction mixtures in 75-95\% yield. While the electron-withdrawing ester linking group served to activate the aryl halides or aryl sulfonates in the Suzuki cross-coupling reactions, the main side reaction observed in most cases was base catalyzed cleavage of the ester functionality. In order to alleviate this problem, attention was focused on increasing the rate of the cross-coupling reaction. Since microwaves are known to accelerate many organic reactions in polar solvents,\textsuperscript{22} and microwave-promoted palladium catalyzed coupling reactions had previously been reported,\textsuperscript{23} irradiation of the PEG-bound coupling reactions was investigated.\textsuperscript{21} Compared to classical heating, the microwave irradiated Suzuki cross-couplings of PEG-bound substrates 21-24 with a variety of aryl boronic acids 25 were complete within 2-4 min and the linkage to the polymer remained completely intact. The industrial benefits of performing Suzuki reactions in aqueous media with such extremely accelerated reaction times are clear, however, the necessity for highly specialized equipment to effect cross-coupling renders this method infeasible to most research laboratories.

1.2 The Development of a Novel In Situ Variant of the Suzuki Cross-Coupling Reaction.

Research efforts in the Keay laboratory have recently involved the development of new in situ methods for generating organoboronic acids and subjecting these compounds, without isolation, to Suzuki cross-coupling conditions with a wide variety of alkyl and aryl halides. The section which follows describes the reasons for developing such a variant to Suzuki's original procedure and highlights some of the original work in this area.

1.2.1 Justification for the Development of In Situ Suzuki Coupling.

During the course of developing an asymmetric total synthesis of the marine polyketide natural product (+)-xestoquinone (28), the Keay group sought to prepare furan derivative 29 as a key intermediate (Scheme 1.4). The original synthetic strategy involved a directed ortho-metalation in the C-4 position of furan 30 and subsequent trapping of the aryl anion with a suitable boron electrophile. It was envisaged that the required four carbon chain could then be introduced via a Suzuki cross-coupling reaction with iodide 31. However, isolation of the
required boronic acid proved to be very difficult presumably due to the high water solubility of the compound. In order to circumvent this problem, it was determined that the two step sequence could smoothly be performed in a single step, without the need for boronic acid isolation, by simply adding the Suzuki coupling reagents subsequent to trapping the aryl anion with trimethylborate. This approach furnished the desired coupled intermediate 29 in 96% yield after a standard work-up procedure. Although this coupling did not lead to the synthesis of xestoquinone, a similar in situ Suzuki reaction was later employed by Keay and coworkers to achieve the first asymmetric synthesis of this pentacyclic natural product (Scheme 1.5).

In general, boronic acids are quite water soluble materials and this property often complicates procedures for their isolation and purification. Due to this fact, Keay and coworkers immediately recognized that this one-pot modification of the Suzuki cross-coupling reaction was a useful synthetic achievement and the scope and limitations were studied in further detail. To this end, Dr. Shawn Maddaford was able to show that the reaction of in situ generated aryl, furyl, primary, and benzylic boronic acids with aryl, vinyl or benzylic halides was a powerful method for preparing cross-coupled products which obviated the troublesome isolation of highly water soluble materials (Table 1.1).
Table 1.1 Cross-Coupling of In Situ Generated Organoboronic Acids with Organohalides.

\[
\text{R}^1\text{Li} \xrightarrow{1) 1.3 \text{ equiv. } \text{B(OMe)}_3} \xrightarrow{2) \text{R}^2\text{X, Pd(PPh}_3)_4, \text{ base, reflux}} \text{R}^1\text{R}^2
\]

<table>
<thead>
<tr>
<th>Boronic Acid Source</th>
<th>Organo-halide</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMOM Li</td>
<td>C\text{H}_6</td>
<td>15\text{b}</td>
<td>34</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>CHO</td>
<td>THF</td>
<td>19\text{b}</td>
<td>37</td>
<td>38</td>
<td>83</td>
</tr>
<tr>
<td>N(i-Pr)</td>
<td>C\text{H}_6</td>
<td>16\text{c}</td>
<td>40</td>
<td>35</td>
<td>95</td>
</tr>
<tr>
<td>CO\text{Me}</td>
<td>THF</td>
<td>48\text{b}</td>
<td>45</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>Li</td>
<td>DME</td>
<td>2\text{c}</td>
<td>47</td>
<td>48</td>
<td>72</td>
</tr>
</tbody>
</table>

(a) Isolated yield. (b) No external base added. (c) 2 M Na\text{CO}_3 used as base.
The results listed in Table 1.1 clearly show that the palladium catalyzed in situ Suzuki reaction is of general scope. Various boronic acid precursors can be used and the reaction tolerates a wide range of functional groups including esters, aldehydes, amides, and acetals. Yields for the process were found to be moderate to excellent and the reaction times varied between 2 h and 48 h. In some cases, addition of Na₂CO₃ to the reaction mixture was not required to achieve smooth cross-coupling.

Subsequent to this study, it was conceived that the in situ Suzuki protocol could be further modified to allow for the single step preparation of C₂-symmetric biaryl compounds. The development of such a method would constitute a significant advancement in the synthesis of this important class of materials and is the topic of the following section.

1.2.2 Synthesis of C₂-Symmetric Biaryls via In Situ Suzuki Cross-Coupling.

It was envisaged that the in situ Suzuki cross-coupling reaction could be further modified in order to obtain a simple method for the preparation of C₂-symmetric biaryls. By treating a starting haloarene with only 0.5 equivalents of n-butylithium followed by an excess of trimethylborate, it was felt that it would be possible to generate the required 1:1 molar ratio of haloarene and arylboronic acid in situ, which could subsequently be coupled under the modified Suzuki conditions (Scheme 1.6). To investigate this possibility, the in situ Suzuki cross-coupling of bromobenzene (35) and iodobenzene (50) was studied under a variety of conditions (Table 1.2). Fortunately, treatment of a solution of iodobenzene in THF under the modified Suzuki coupling conditions afforded biphenyl in 73% yield (entry 1). Initial studies showed that the choice of borate, trimethoxy vs. tri(iso-propyl), had little impact on the reaction outcome and
reaction times of 12 h afforded good yields of cross-coupled product (entries 1-4). Increasing the cross-coupling reaction time past 12 h did not, in general, increase the yield of biphenyl (51).

The yield of the desired product was only slightly enhanced by the use of Ba(OH)$_2$ as base (entries 5,6). Further, subsequent to the *in situ* generation of the organoboronic acid, the reaction seemed to be tolerant of a change in solvent for the cross-coupling step (entries 7,8). Moreover, the *in situ* concept could be applied to the Suzuki-Beletskaya procedure whereby "ligandless" Pd(OAc)$_2$ is used as the catalyst in degassed ethanol (entries 10-12).$^{27}$

### Table 1.2 *In Situ* Suzuki Cross-Coupling of Iodobenzene (50) and Bromobenzene (35).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halide</th>
<th>B(OR)$_3$</th>
<th>Coupling Solvent</th>
<th>Temp. ($^\circ$C)</th>
<th>Base</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Me</td>
<td>THF</td>
<td>65</td>
<td>Na$_2$CO$_3$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>12</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>i-Pr</td>
<td>THF</td>
<td>65</td>
<td>Na$_2$CO$_3$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Me</td>
<td>THF</td>
<td>65</td>
<td>Na$_2$CO$_3$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>i-Pr</td>
<td>THF</td>
<td>65</td>
<td>Na$_2$CO$_3$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Me</td>
<td>THF</td>
<td>65</td>
<td>Ba(OH)$_2$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>12</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>i-Pr</td>
<td>THF</td>
<td>65</td>
<td>Ba(OH)$_2$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>i-Pr</td>
<td>DME</td>
<td>85</td>
<td>Ba(OH)$_2$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>i-Pr</td>
<td>C$_6$H$_6$</td>
<td>75</td>
<td>Na$_2$CO$_3$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>Me</td>
<td>THF</td>
<td>65</td>
<td>Ba(OH)$_2$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>i-Pr</td>
<td>EtOH$^b$</td>
<td>rt</td>
<td>Ba(OH)$_2$</td>
<td>Pd(OAc)$_2$</td>
<td>12</td>
<td>77</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>Me</td>
<td>EtOH$^b$</td>
<td>rt</td>
<td>Ba(OH)$_2$</td>
<td>Pd(OAc)$_2$</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>12</td>
<td>35</td>
<td>Me</td>
<td>EtOH$^c$</td>
<td>rt</td>
<td>Ba(OH)$_2$</td>
<td>Pd(OAc)$_2$</td>
<td>12</td>
<td>68</td>
</tr>
</tbody>
</table>

(a) Isolated yield.
(b) THF used for halogen-metal exchange.
(c) DME used for halogen-metal exchange.
With these results in hand, attention was next turned toward the in situ coupling of substituted aryl halides. Disappointingly, using similar conditions to those shown in Table 1.2, haloarenes bearing one or more ortho substituents failed to furnish the desired biaryls in synthetically useful yields (Table 1.3). When 1-iodo-2-methoxynaphthalene (58) was treated under our initial

**Table 1.3  In Situ Suzuki Cross-Coupling of Substituted Aryl Halides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halide</th>
<th>Coupling Solvent</th>
<th>Temp. (°C)</th>
<th>Base</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="52" /></td>
<td>PhMe</td>
<td>110</td>
<td>Na₂CO₃</td>
<td>72</td>
<td><img src="image" alt="53" /></td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="52" /></td>
<td>DME</td>
<td>85</td>
<td>Ba(OH)₂</td>
<td>12</td>
<td><img src="image" alt="53" /></td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="54" /></td>
<td>DME</td>
<td>85</td>
<td>Na₂CO₃</td>
<td>48</td>
<td><img src="image" alt="55" /></td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="54" /></td>
<td>DME</td>
<td>85</td>
<td>Ba(OH)₂</td>
<td>15</td>
<td><img src="image" alt="55" /></td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="56" /></td>
<td>THF</td>
<td>65</td>
<td>Ba(OH)₂</td>
<td>48</td>
<td><img src="image" alt="57" /></td>
<td>&lt;10</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="58" /></td>
<td>THF</td>
<td>65</td>
<td>Na₂CO₃</td>
<td>48</td>
<td><img src="image" alt="57" /></td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

(a) Isolated yield.
reaction conditions, less than 10% of the desired biaryl product 57 was isolated (entry 6). The remainder of the reaction mixture was determined to be a 2:1:1 mixture of the starting haloarene, 2-methoxy-1-naphthyl boronic acid, and 2-methoxynaphthalene, respectively. Increasing the reaction time did not significantly increase the yield of the desired binaphthyl but rather resulted in increased amounts of the hydrolytic deboration product, 2-methoxynaphthalene, being isolated from the reaction mixture. Although Suzuki and coworkers have demonstrated that the cross-coupling of sterically hindered boronic acids with haloarenes is greatly enhanced by the use of stronger bases such as Ba(OH)$_2$, NaOH and TIOH, it was found that use of a saturated Ba(OH)$_2$ solution in place of 2M Na$_2$CO$_3$ had little effect on the production of binaphthyl 57. In order to optimize the reaction for sterically hindered halides, the in situ Suzuki cross-coupling coupling of 1-bromo-2-methoxynaphthalene (56) was investigated under a variety of conditions (Table 1.4). Use of alternative catalysts such as Pd(PPh$_3$)$_2$Cl$_2$, Pd(OAc)$_2$(PPh$_3$)$_2$ and Pd$_2$dba$_3$, failed to afford higher yields of coupled product 57. Further, the in situ modified Suzuki-Beletskaya procedure also failed to furnish the desired biaryl (entry 4). In addition, the use of polar, water miscible solvents such as DMF or CH$_3$CN for the cross-coupling step did not improve the yield.

**Table 1.4 In Situ Cross-Coupling of 1-Bromo-2-methoxynaphthalene (56).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Base</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield of 57$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DME</td>
<td>85</td>
<td>Ba(OH)$_2$</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$</td>
<td>15</td>
<td>N.R.$^b$</td>
</tr>
<tr>
<td>2</td>
<td>DME</td>
<td>85</td>
<td>Ba(OH)$_2$</td>
<td>Pd(OAc)$_2$(PPh$_3$)$_2$</td>
<td>15</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>3</td>
<td>DME</td>
<td>85</td>
<td>Ba(OH)$_2$</td>
<td>Pd$_2$dba$_3$</td>
<td>15</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>rt</td>
<td>Ba(OH)$_2$</td>
<td>Pd(OAc)$_2$</td>
<td>15</td>
<td>N.R.$^b$</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>110</td>
<td>K$_3$PO$_4$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>15</td>
<td>N.R.$^b$</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>rt</td>
<td>Ag$_2$CO$_3$</td>
<td>Pd$_2$dba$_3$</td>
<td>15</td>
<td>N.R.$^b$</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>110</td>
<td>Et$_3$N</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>15</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>8</td>
<td>CH$_3$CN</td>
<td>70</td>
<td>Ba(OH)$_2$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>15</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>9</td>
<td>THF$^c$</td>
<td>rt</td>
<td>Na$_2$CO$_3$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>24</td>
<td>N.R.$^b$</td>
</tr>
<tr>
<td>10</td>
<td>PhMe/EtOH/H$_2$O$^d$</td>
<td>85</td>
<td>Na$_2$CO$_3$</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>15</td>
<td>52%</td>
</tr>
</tbody>
</table>

(a) Determined by $^1$H-NMR analysis.
(b) No cross-coupled product observed.
(c) 14 kbar pressure.
(d) 3:3:2 ratio respectively.
of cross-coupled product. Running the reaction under high pressure (14 kbar) failed to furnish the desired biaryl (entry 9). Delightfully, a 3:3:2 mixture of toluene, ethanol, and water employed by Grahn and coworkers\(^2\) afforded a 52% yield of the desired binaphthyl 57 (entry 10). This solvent mixture, which forms a homogeneous solution boiling at \textit{ca.} 85 °C, likely improves the yield of the cross-coupling due to better solvation of the inorganic base. The scope and limitations of the \textit{in situ} C\(_2\)-symmetric Suzuki cross-coupling reaction were then investigated using the optimized reaction conditions. A wide range of aryl iodides and aryl bromides (Figure 1.2) were subjected to the \textit{in situ} coupling conditions to afford a variety of cross-coupled products (Figure 1.3). In general, the optimized \textit{in situ} method affords C\(_2\)-symmetric biaryls in moderate to excellent yield and tolerates a wide range of functionalities including esters, amides, acetals and nitriles (Table 1.5). A few limitations of the procedure are however notable. Surprisingly, the reaction was limited by the presence of a phenolic TBDPS group, which was
Figure 1.3 Cross-Coupled Products for the \textit{In Situ} \textit{C}_2-Symmetric Biaryl Synthesis Scope and Limitations Study.

\begin{table}[h]
\centering
\begin{tabular}{c c}
\hline
Entry & Halide & Product & Yield ($\%$)\textsuperscript{a} \\
\hline
1 & 52 & 53 & 95 \\
2 & 54 & 55 & 73 \\
3 & 59 & 71 & 79 \\
4 & 60 & 72 & 68 \\
5 & 61 & 73 & 32 \\
6 & 62 & 74 & 79 \\
7 & 63 & 75 & 91 \\
\hline
\end{tabular}
\end{table}

Table 1.5 Results for the Preparation of \textit{C}_2-Symmetric Biaryls Using the Optimized \textit{In Situ} Suzuki Coupling Conditions.

1) 0.5 equiv \textit{n}-BuLi, THF, -78 °C
2) 1.5 equiv \textit{B}(\textit{OMe})\textsubscript{3}
3) PhMe/EtOH/H\textsubscript{2}O 3:3:1, \textit{Na}_2\textit{CO}_3, \textit{Pd}(\textit{PPh})\textsubscript{3}\textsubscript{4} 85 °C, 48 h

\begin{table}[h]
\centering
\begin{tabular}{c c c c}
\hline
Entry & Halide & Product & Yield ($\%$)\textsuperscript{a} \\
\hline
8 & 64 & 76 & 89 \\
9 & 65 & 77 & 92\textsuperscript{b} \\
10 & 66 & 78 & 0 \\
11 & 67 & 79 & 86 \\
12 & 56 & 57 & 96 \\
13 & 68 & 80 & 84 \\
14 & 69 & 81 & 73 \\
\hline
\end{tabular}
\end{table}

(a) Isolated yield.

(b) Cleavage of the TBDPS ether takes place under the reaction conditions.
cleaved under the reaction conditions (Table 1.5, entry 9). Although the cleavage of silyl ethers by palladium catalysts is a known process,\textsuperscript{30} further experimentation revealed that loss of the TBDPS protecting group was, in this case, a result of the carbonate base used for the cross-coupling step. This discovery subsequently led to the development of a general, mild set of conditions for the deprotection of phenolic silanes.\textsuperscript{31} The C\textsubscript{2}-symmetric \textit{in situ} biaryl synthesis also failed in the presence of an \textit{ortho}-oxazoline moiety (entry 10). The reasons for this limitation are not entirely clear, however, in view of the other halides successfully coupled using the \textit{in situ} method, it is unlikely that the problem is one of steric hindrance. In all cases, treatment of oxazoline 66 under the modified \textit{in situ} Suzuki conditions afforded an approximate 1:1 mixture of unreacted starting material to 4,4-dimethyl-2-phenyl-2-oxazoline. Upon completion of the scope and limitations study, an endeavor to demonstrate the synthetic utility of the \textit{in situ} Suzuki protocol in a natural product synthesis\textsuperscript{32} was undertaken. Efforts to prepare two biaryl fungal metabolites using the \textit{in situ} method are the topic of the following section. Utilization of the \textit{in situ} Suzuki biaryl synthesis for the preparation of C\textsubscript{2}-symmetric diphosphine ligands for enantioselective synthesis is discussed in Chapter Three.

1.2.3 Utilization of the \textit{In Situ} C\textsubscript{2}-Symmetric Biaryl Synthesis for the Preparation of a Natural Product.

Biaryls constitute a very large and structurally diverse subset of natural products, which often possess interesting or pharmaceutically useful biological activity. Many examples of biaryl polyketides, terpenes, lignans, coumarins,\textsuperscript{33} flavonoids, ellagitannins,\textsuperscript{34} peptides, and alkaloids have been reported in the literature and numerous methods for their preparation have been developed.\textsuperscript{35} In order to demonstrate the usefulness of the \textit{in situ} C\textsubscript{2}-symmetric Suzuki cross-coupling, a synthesis of the recently discovered 4,4'-dihydroxy-5,5'-dimethoxy-1,1'-binaphthyl (82)\textsuperscript{36} and its analogue 4,4',5,5'-tetrahydroxy-1,1'-binaphthyl (83)\textsuperscript{37} both of which have been isolated from the fungus (Ascomycetes) \textit{Daldinia concentrica},\textsuperscript{36} was initiated (Figure 1.4). Retrosynthetic analysis of the two target compounds (82 and 83) suggested that 1,8-dihydroxynaphthalene (84) would serve as a suitable starting material. Unfortunately, this required material was not commercially available and had to be prepared by minor
modification to a known literature procedure\textsuperscript{38} (Scheme 1.7). Thus, 1,8-naphthosultone (85) was fused to a NaOH/KOH mixture at 230 °C in a stainless steel beaker to afford the desired 1,8-dihydroxynaphthalene (84) in 33% yield. With this material in hand, synthesis of 4,4'-dihydroxy-5,5'-dimethoxy-1,1'-binaphthyl (82) and 4,4',5,5'-tetrahydroxy-1,1'-binaphthyl (83) was achieved according to the paths outlined in Scheme 1.8. For the former target, monomethylation of the starting diol under standard conditions gave methyl ether 86 in 95% yield. Bromination of the corresponding sodium phenoxide in CCl\textsubscript{4} afforded the desired bromide 87 along with a small amount of the undesired ortho-brominated regioisomer. The fact that the bromination had occurred in the ring bearing the hydroxyl function was evidenced by \textsuperscript{1}H-NMR spectroscopic studies. A series of one dimensional decoupling experiments were used to unambiguously assign each of the aryl proton resonances thereby identifying the two separate AX and AMX spin systems. Further ID NOE experimentation revealed that the methoxy group resided in the ring bearing the AMX spin system. Hence irradiation of the methoxy singlet at 4.08 ppm gave a 6.3% NOE enhancement of the C-7 aromatic signal at 6.86 ppm. Conversely, a reciprocal NOE of 2.6% was observed upon irradiation of the C-7 doublet. The hydroxyl
function on bromide 87 was then protected as the benzyl ether under standard conditions and subsequent in situ coupling smoothly furnished biaryl 89 in 72% yield. Hydrogenolysis of the benzyl groups using 10% Pd/C under 1 atm H₂ afforded the desired natural product 82 in an overall yield of 41% for five synthetic steps.³⁹

The synthesis of 4,4',5,5'-tetrahydroxy-1,1'-binaphthyl (83) was achieved in an analogous manner with 40% overall yield in four synthetic steps (Scheme 1.8). However, due to the highly polar nature of the tetrahydroxyl derivative 83, direct characterization of this compound was deemed infeasible. In order to solve this problem, crude 83 was subjected to exhaustive methylation and characterized as the tetramethyl ether derivative 93 (Scheme 1.9). Having achieved the goal of applying the newly developed in situ Suzuki biaryl coupling in a natural product synthesis, the synthetic utility of the new C₂-protocol had been established. Further usage of the in situ C₂-symmetric biaryl synthesis toward bidentate tertiary phosphine ligands is discussed in Chapter Three.
Subsequent to Keay’s pioneering work in the development of in situ Suzuki cross-coupling methods, workers at Merck-Frosst (Pointe-Claire-Dorval, Quebec) have recently extended the concept by employing an alternative method for generating the organoboron species (Scheme 1.10). Hence, aryl-iodides, bromides and triflates may be treated with alkoxydiboron 95 under palladium catalysis to afford aryl boronic esters 96 in situ which may subsequently be cross-coupled with a suitable Suzuki partner 97. Since this method does not require a halogen-metal exchange to incorporate the boron moiety, aryl triflates are rendered as suitable starting materials and a broader range of functional groups including aldehydes and ketones can be tolerated. However, the Merck in situ method suffers from the major disadvantage that the commercially available bis(pinacolato)diboron (95) is extremely expensive and only delivers a single boron group to the reaction pathway. Hence, from the point of view of atom economy, diboron 95 is not a very attractive reagent.

In conclusion, an efficient one step Suzuki cross-coupling protocol for the preparation of C2-symmetric biaryls has been developed. Moderate to excellent yields are obtained and the method tolerates a wide range of functional groups including esters, amides, acetals, and nitriles. The synthetic utility of the in situ C2-biaryl protocol has been demonstrated with the short, high yielding total syntheses of two fungal metabolites 82 and 83.
2. 2-Furyl Phosphines as Ligands for Transition Metal-Mediated Organic Synthesis.

2.1 Introduction.

The construction of carbon-carbon and carbon-heteroatom bonds by transition metal-mediated organic processes has become fundamental to the science of synthetic organic chemistry over the past three decades. In recent years there have been a multitude of new synthetic methods, catalysts, and reagents developed to aid in the construction of an overwhelming variety of chemical structures. In particular, the search for catalysts that exhibit higher reactivity or greater efficiency has become an extremely active area of chemical research. It has long been recognized that judicious placement of ancillary ligands in the coordination sphere of a metal can govern the steric, electronic, and physical properties of a coordinated species, thereby affecting the system's catalytic activity. Of the ligands employed for this purpose, perhaps no general classification is more ubiquitous to organic chemistry than tertiary phosphines. However, the choice of which phosphorus(III) ligand to employ for a given synthetic transformation is indeed a topic of great complexity. Several efforts have been made to classify phosphorus ligands according to steric size and electron donor ability and although these parameters have been successfully correlated to observed chemical reactivity, a priori prediction of which phosphine will be best for a given purpose is still not a reality. In order to determine which phosphine is best suited for a certain reaction, it is often necessary to rely on a trial and error type screening process. For example, in the late 1980's, Farina and coworkers reasoned that a highly dissociating ligand would be beneficial for the palladium(0)-catalyzed Stille cross-coupling reaction.43 Experimental screening of a variety of poor donor ligands subsequently revealed that the hypothesis was correct and tri-2-furylphosphine (TFP) was thus identified as an exceptional Stille ligand. Based on this landmark discovery, numerous other workers have since screened TFP in a variety of transition metal-catalyzed reactions. This chapter begins with a brief look at the steric and electronic properties of phosphorus(III) ligands with special attention being paid to phosphines bearing the 2-furyl group. Following this discussion, the use of TFP as a ligand for transition metal-mediated synthesis is exhaustively reviewed.44 The development of new 2-furyl phosphorus ligands is the topic of the final section.
2.1.1 Quantification of the Steric and Electronic Properties of Phosphorus Ligands.

Clearly, the steric and electronic properties of a tertiary phosphine can dramatically influence the reactivity of a metal center and lead to marked changes in chemical reactivity. The steric bulk and electron donor ability of a ligand are difficult properties to quantify and indeed the two properties are closely related. For example, as the steric bulk of the R groups in a tertiary phosphine of type PR₃ is increased, it is expected that the intervalence angles about the phosphorus atom will increase (Figure 2.1). Such a structural change would thereby reduce the s-character of the phosphorus lone pair orbital making the ligand more Lewis basic. Therefore, it is often difficult to separate steric and electronic effects with respect to phosphorus donor ligands since the two factors are so intimately related.

Tolman has suggested using a geometrical parameter known as the cone angle⁴⁵ to classify phosphorus ligands according to size. For phosphines of type PR₃, the cone angle is defined as the apex of a cylindrical cone, centered 2.28 Å from the center of the phosphorus atom, which radiates out towards the R groups and just touches the van der Waals radii of the outermost atoms⁴⁶ (Figure 2.2). In cases where the R groups contain internal degrees of freedom, the Tolman cone is taken to be the minimum angle which satisfies the condition that all of the

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**Figure 2.1** Effect of Steric Bulk on the Intervalance Angles of Monophosphines.

![Figure 2.1](image)

R¹ larger than R causes $\theta^1 > \theta$

---

**Figure 2.2** The Tolman Cone Angle for Monophosphines.

![Figure 2.2](image)
R groups are completely contained within the geometrical construct. For unsymmetrical phosphines or chelating diphosphines, the concept of cone angle is not as clear, however, and Tolman has proposed how an effective cone angle for such ligands could be defined.\textsuperscript{45} Although the cone angle definition seems to be rather arbitrary, the values obtained by Tolman (Table 2.1) have been successfully correlated to the physical and spectroscopic properties as well as the chemical reactivity of a variety of coordination compounds.\textsuperscript{45} However, based on Tolman’s definition, it is hard to justify the large discrepancy between the PPh\textsubscript{3} cone angle (145°) and the P(C\textsubscript{6}F\textsubscript{5})\textsubscript{3} cone angle (184°) given that the H and F atoms are similar in size.\textsuperscript{47} As would be expected from the size of a 2-furyl group relative to a phenyl substituent, the cone angle of 133° measured for TFP\textsuperscript{48} is slightly smaller than the triphenylphosphine cone angle.

In order to quantify the electron donor ability of phosphine ligands, Strohmeier\textsuperscript{49} and Tolman\textsuperscript{50} have proposed that the CO stretching frequencies of monosubstituted transition metal carbonyls could be used as a measure (Table 2.2). Ligands of high donor ability cause a greater degree of backbonding from the metal center into the CO \(\pi^*\) orbitals and hence give rise to a decreased CO bond order. Conversely, weakly donating ligands result in decreased M-CO backbonding, which in turn gives rise to higher CO stretching frequencies. As a standard measure, the \(A_1\) carbonyl mode of Ni(CO)\textsubscript{3}L complexes, where L is the monodentate phosphine ligand, can readily be determined with an accuracy of \(\pm 0.3\) cm\textsuperscript{-1}. Such complexes are conveniently prepared upon mixing Ni(CO)\textsubscript{4} and the phosphine ligand in a 1:1 molar ratio at

### Table 2.1 Tolman Cone Angle (\(\theta^e\)) for a Variety of Phosphines and Phosphinites.\textsuperscript{45}

<table>
<thead>
<tr>
<th>ligand</th>
<th>Cone angle ((\theta^e)) in deg</th>
<th>ligand</th>
<th>Cone angle ((\theta^e)) in deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH\textsubscript{3}</td>
<td>87</td>
<td>P(p-Tol)\textsubscript{3}</td>
<td>145</td>
</tr>
<tr>
<td>P(OMe)\textsubscript{3}</td>
<td>107</td>
<td>P(m-Tol)\textsubscript{3}</td>
<td>165</td>
</tr>
<tr>
<td>PMe\textsubscript{3}</td>
<td>118</td>
<td>PCy\textsubscript{3}</td>
<td>170</td>
</tr>
<tr>
<td>P(OPh)\textsubscript{3}</td>
<td>128</td>
<td>P(O-t-Bu)\textsubscript{3}</td>
<td>172</td>
</tr>
<tr>
<td>PET\textsubscript{3}</td>
<td>132</td>
<td>P(t-Bu)\textsubscript{3}</td>
<td>182</td>
</tr>
<tr>
<td>TFP</td>
<td>133</td>
<td>P(C\textsubscript{6}F\textsubscript{5})\textsubscript{3}</td>
<td>184</td>
</tr>
<tr>
<td>P(C\textsubscript{3}F\textsubscript{3})\textsubscript{3}</td>
<td>137</td>
<td>P((\alpha)-Tol)\textsubscript{3}</td>
<td>194</td>
</tr>
<tr>
<td>PPh\textsubscript{3}</td>
<td>145</td>
<td>P(mesityl)\textsubscript{3}</td>
<td>212</td>
</tr>
</tbody>
</table>
Table 2.2: Electronic Parameter $v$ for a Variety of Phosphines and Phosphinites.¹⁰

<table>
<thead>
<tr>
<th>ligand</th>
<th>$v$ (cm⁻¹)</th>
<th>ligand</th>
<th>$v$ (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF₃</td>
<td>2110.8</td>
<td>P(p-Tol)₃</td>
<td>2066.7</td>
</tr>
<tr>
<td>P(C₆F₅)₃</td>
<td>2090.9</td>
<td>P(o-Tol)₃</td>
<td>2066.6</td>
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<tr>
<td>P(OPh)₃</td>
<td>2085.3</td>
<td>PMe₃</td>
<td>2064.1</td>
</tr>
<tr>
<td>PH₃</td>
<td>2083.2</td>
<td>PEt₃</td>
<td>2061.7</td>
</tr>
<tr>
<td>P(OMe)₃</td>
<td>2079.5</td>
<td>PBu₃</td>
<td>2060.3</td>
</tr>
<tr>
<td>PPh₃</td>
<td>2068.9</td>
<td>PCy₃</td>
<td>2056.4</td>
</tr>
<tr>
<td>P(m-Tol)₃</td>
<td>2067.2</td>
<td>P(t-Bu)₃</td>
<td>2056.1</td>
</tr>
</tbody>
</table>

Room temperature. Unfortunately, the electronic parameter $v$ for tri-2-furylphosphine (TFP) has not been reported in the literature.

Alternatively, Allen and Taylor have shown that the $^1J(^{31}P-^{77}Se)$ coupling constant of phosphorus selenides may be used as a measure of the parent phosphine basicity.⁵¹ An increase in the magnitude of $^{31}P-^{77}Se$ coupling constant in these compounds has been shown experimentally and theoretically to correspond to an increase in s-character of the phosphorus lone pair. In other words, the phosphorus selenides of poorly donating phosphines exhibit larger $^1J(^{31}P-^{77}Se)$ coupling constants than the corresponding phosphorus selenides of electron rich phosphines (Table 2.3). In light of the close relationship which exists between the steric bulk of the phosphine R groups and the s-character of the phosphorus lone pair (Figure 2.1), the $^{31}P-^{77}Se$ coupling constant method gives a remarkably reliable measure of phosphine basicity.

Table 2.3: $^{31}P$ NMR Data for Various Phosphine Selenides.⁵¹

<table>
<thead>
<tr>
<th>PR₃</th>
<th>$^1J(^{31}P-^{77}Se)$ in PR₃Se (Hz)</th>
<th>PR₃</th>
<th>$^1J(^{31}P-^{77}Se)$ in PR₃Se (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh₃</td>
<td>732</td>
<td>PPh(2-thienyl)₂</td>
<td>752</td>
</tr>
<tr>
<td>PPh₂(o-Tol)</td>
<td>730</td>
<td>P(2-thienyl)₃</td>
<td>757</td>
</tr>
<tr>
<td>P(p-MeOC₆H₄)₃</td>
<td>708</td>
<td>PPh₂(2-furyl)</td>
<td>754</td>
</tr>
<tr>
<td>PPh₂(m-CF₃C₆H₄)</td>
<td>766</td>
<td>PPh(2-furyl)₂</td>
<td>774</td>
</tr>
<tr>
<td>PPh₂(2-thienyl)</td>
<td>743</td>
<td>P(2-furyl)₃</td>
<td>793</td>
</tr>
</tbody>
</table>
Fortunately, the magnitude of the $J(P-^{77}\text{Se})$ coupling constant seems to be predominantly controlled by the electronic properties of the R groups rather than the overall steric size of the phosphine. For example, the $J(P-^{77}\text{Se})$ coupling constants for Ph$_3$P-Se and Ph$_2$(o-Tol)P-Se shown in Table 2.3 are very similar even though the Tolman cone angles for these two phosphines are 145° and 161°, respectively. From the data in Table 2.3, it can be seen that an additive effect is observed in the $^{31}P-^{77}\text{Se}$ coupling constant upon the systematic replacement of phenyl groups in PPh$_3$ with 2-furyl or 2-thienyl groups. Moreover, these two heteroaryl groups are electron withdrawing relative to the phenyl substituent. As a result, 2-furyl and 2-thienyl phosphines are poorer σ-donor ligands. In the absence of synergic bonding, these ligands would then be expected to more easily dissociate from a metal center. However, the σ withdrawal of electrons away from the phosphorus atom by the heteroaryl groups causes the system to compensate by transferring electron density from the filled metal d orbitals into the $\pi^*$-antibonding orbitals of the ligand. In other words, 2-furyl$^{52}$ and 2-thienyl$^{53}$ phosphines can act as π-acids. Clearly, this effect would be more pronounced for late transition metals in low oxidation states.$^{54}$ In 1988, several years after the first synthesis$^{55,56}$ and characterization$^{57}$ of the TFP ligand, Farina and coworkers tested this phosphine in a Stille cross-coupling$^{43}$ with the hope that TFP’s low donicity toward palladium(II) would accelerate the rate of reaction. This pioneering study, which constituted the first time TFP had been used in a metal-catalyzed reaction, subsequently led to the widespread use of tri-2-furylphosphine as a Stille ligand and further investigations in other metal-catalyzed processes.

2.2 The Use of Tri-2-furylphosphine (TFP) as a Ligand in Metal-Catalyzed Reactions.

2.2.1 The Discovery of TFP as an Exceptional Ligand for the Stille Reaction.

In 1988, during a research program directed towards the preparation of 3-substituted cephalosporin derivatives for antibiotic screening, workers at Bristol-Myers sought to couple 3-chloromethylcephem 99 with various organostannanes using the Stille protocol$^{58}$ (Scheme 2.1). Using the standard Pd(PPh$_3$)$_4$ catalyst system in refluxing THF gave poor yields of the desired cross-coupled products and very slow reaction rates.$^{43}$ Changing the cross-coupling conditions
to include higher boiling, more polar solvents or additives failed to improve the reaction yield. Faced with these results, Farina postulated that the use of less coordinating, poorer donating phosphine ligands should render the Pd(II)-allyl intermediate more electrophilic and hence more reactive in the rate-determining transmetalation step. Based on Allen's study of tri-2-furylphosphine, Farina and coworkers decided to test the TFP ligand in the Stille reaction. To their delight, use of a Pd₂(dba)₃/TFP catalyst system in refluxing THF efficiently afforded the desired cross-coupled products (Scheme 2.2). Moreover, a forty-five fold rate enhancement was observed when lactam 101 was coupled with vinyltributylstannane in the presence of the tri-2-furylphosphine catalyst system.

In a related study, aimed at developing an efficient synthesis of antibiotic BMY-28100, Farina showed that the beneficial effects observed upon substitution of TFP for PPh₃ in the Stille reaction may be of general scope. Treatment of vinyl triflate 107 with a variety of organostannanes at room temperature in NMP using ZnCl₂ and the TFP catalyst system smoothly
afforded the desired cross-coupled products 108-110 in moderate to excellent yields\(^{64}\) (Scheme 2.3). Performing the reaction with triphenylphosphine required elevated reaction temperatures and resulted in extensive decomposition of the starting triflate. Using TFP as the palladium ligand afforded a ca. 17 fold rate enhancement and allowed for a much milder set of conditions to be employed. The synthetic power of the Stille cross-coupling reaction, in conjunction with the TFP rate enhancement, makes this methodology the first general, economically viable route to 3-substituted cephalosporin antibiotics.

The favorable effects of using TFP in the Stille coupling of organoiodides was later demonstrated by Farina in a project aimed at the synthesis of thymidylate synthetase inhibitors for cancer chemotherapy.\(^{65,66}\) Treatment of 5-iodouracil (111) with a variety of stannanes and the TFP catalyst system at room temperature smoothly furnished the desired coupled products in moderate to excellent yields (Scheme 2.4). Literature conditions for coupling vinyl iodides and stannanes\(^{67}\) were found to be unsatisfactory in the present case. Farina subsequently determined that the TFP catalyst system could be effectively employed for the derivatization of 5-iodouridine and deoxyuridine precursors (Scheme 2.5). The coupling conditions were tolerant
toward ester and silyl ether protecting groups on the sugar moiety as well as an unprotected hydroxyl group. Use of mild reaction conditions in conjunction with the TFP catalyst system proved crucial to the obtainment of coupled products 118-120 in synthetically useful yields.

Subsequent to these findings, Farina systematically studied the use of poor donating ligands such as TFP and triphenylarsine in a diverse range of Stille cross-coupling reactions. This rigorous kinetic study conclusively showed that large rate enhancements, typically $10^2-10^3$ over triphenylphosphine based catalysts, are observed with TFP and Ph$_3$As (Table 2.4). While observed ligand effects in the Stille reaction had previously been attributed to steric origin, Farina’s results clearly demonstrate that no correlation exists between the relative rates of coupling and the Tolman cone angle. In addition, the results confirm that ligands of low donor

Table 2.4 Relative Rates of Stille Coupling Between Iodobenzene and Vinyltributyltin with Various Pd$_2$(dba)$_3$/Ligand Catalysts at 50 °C in THF.52

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand$^a$</th>
<th>Cone Angle (deg)</th>
<th>Relative Rate$^b$</th>
<th>Inhibition Factor$^c$</th>
<th>Yield (%)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>145</td>
<td>1</td>
<td>19</td>
<td>15.2</td>
</tr>
<tr>
<td>2</td>
<td>(4-MeOC$_6$H$_4$)$_3$P</td>
<td>145</td>
<td>&lt;0.07</td>
<td>&gt;100</td>
<td>&lt;2</td>
</tr>
<tr>
<td>3</td>
<td>(o-Tol)$_3$P</td>
<td>194</td>
<td>35.2</td>
<td>3.4</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>TFP</td>
<td>133</td>
<td>105</td>
<td>3.7</td>
<td>&gt;95</td>
</tr>
<tr>
<td>5</td>
<td>P(C$_6$F$_5$)$_3$</td>
<td>184</td>
<td>e</td>
<td>--</td>
<td>13.2</td>
</tr>
<tr>
<td>6</td>
<td>Ph$_3$As</td>
<td>142</td>
<td>1100</td>
<td>1.3</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

(a) Pd:L ratio= 1:4; (b) For PPh$_3$ $k=4.6 \times 10^{-5}$ min$^{-1}$; (c) ratio of PdL$_2$ catalyst rate to PdL$_4$ catalyst rate; (d) HPLC yield after 72 h; (e) Catalyst decomposition was instantaneous (<2 min).
ability generally afford less stable catalyst systems. For example, the P(C₆F₅)₃ ligand (entry 5) gives a catalyst of high reactivity which completely decomposes under the conditions of the reaction within 2 minutes. Although triphenylarsine (entry 6) generally yielded the fastest coupling rates, Farina noted that the Ph₃As catalyst was found to be less stable than the TFP derived species. Hence ligands of intermediate donicity, which strike a compromise between increased reactivity and decreased stability, are likely to serve as the best cross-coupling catalysts. Farina further showed that free ligand inhibits the Stille reaction and the degree of inhibition was greater for ligands of high donor ability (Table 2.4). To account for this observation, it was postulated that a pre-equilibrium exists between the fully coordinated species 121 and a coordinatively unsaturated intermediate 122 (Scheme 2.6). Ligands of high donicity therefore impede the reaction by lowering the concentration of the reactive species 122. As can be seen from the data in Table 2.4, ligands which give high rates of coupling are generally associated with low inhibition factors while sluggish catalysts are comprised of ligands with large inhibition factors.

The utilization of tri-2-furylphosphine in the Stille cross-coupling, which often allows the reaction to proceed at ambient temperature, may be extremely advantageous when unwanted thermally controlled side reactions are possible. Under classical Stille conditions, aryl triflate 123 and allyltributyltin give a mixture of double bond isomers, compounds 124 and 125 (Scheme 2.7). The major product of the reaction is a result of double bond migration into conjugation.
with the aromatic ring. Using TFP as the Stille ligand at room temperature furnishes the desired olefin 124 in 78.5% yield, free from any traces of the conjugated isomer. Similarly, the palladium-catalyzed coupling of acyl chlorides with vinyltins often results in products with a significant amount of E/Z double bond isomerism even under relatively mild conditions (Scheme 2.8). However, the coupling of benzylic chloride (126) with (Z)-1-propenyltributyltin (127) using TFP as the palladium ligand affords the desired product 128 with remarkable stereospecificity (97%). Clearly, ligands of poor Lewis basicity offer a major synthetic advantage when the starting materials and/or products of a process contain sensitive or labile functional groups. As a result, TFP and Ph₃As have become the ligands of choice for the Stille reaction.

Farina’s recent review has comprehensively detailed the Stille cross-coupling reaction through 1994 and the section which follows supplements this review by covering the recent use of tri-2-furylphosphine as a Stille ligand. In some cases, authors have reported the use of TFP in the Stille reaction without comparison to either PPh₃ or Ph₃As catalyst systems. These accounts are included for completeness, however, special attention will be paid to the literature reports, which either demonstrate a clear advantage to using the TFP catalyst system or compare the use of different ligands under otherwise identical conditions.

2.2.2 Use of TFP in the Stille Reaction Since 1994.

2.2.2.1 Investigations of Stille Byproduct Formation Using TFP.

A number of unwanted side reactions have been observed in the Stille coupling including homocoupling, alkyl group transfer, protodestannylation, phosphorus to palladium aryl migration, and Cine substitution. Many of these processes may be attenuated through the use of
additives\textsuperscript{73} or by lowering the reaction temperature.\textsuperscript{72} Since TFP often allows the Stille reaction to proceed at room temperature, use of this ligand can be advantageous for limiting these undesired side reactions.\textsuperscript{74} The Cine substitution (Scheme 2.9) has, however, traditionally been attributed to steric hindrance at the $\alpha$ carbon of the migratory group on tin.\textsuperscript{75} While initial studies on the TFP catalyst system, relative to the PPh\textsubscript{3} catalyst, have shown small increases in the amount of Cine product obtained,\textsuperscript{76} Flohr has recently demonstrated that judicious choice of electrophile, ligand, and coupling conditions may be used to control the ratio of Stille/Cine products.\textsuperscript{77} Treatment of vinyl stannane 134 with $p$-methoxyiodobenzene 135 under the modified TFP Stille conditions afforded a 4:1 mixture of the Stille and Cine products respectively (Scheme 2.10). Although the yield was increased upon using the weaker donating ligand Ph\textsubscript{3}As, the relative proportion of Cine substituted product was also found to increase. Clearly, electronic effects in the electrophile may influence the product distribution and hence the choice of catalyst ligand is an important factor governing the reaction outcome.

As noted previously, double bond isomerism is often a significant side reaction to the Stille cross-coupling.\textsuperscript{72} When substituted allylic stannanes are employed in the Stille reaction, extensive allylic rearrangement has been observed.\textsuperscript{78} The less desirable $\gamma$-product, which results from allylic rearrangement, is normally the major component of the reaction mixture. Recently,
Tsuji has shown that the use of highly dissociating ligands such as TFP and Ph₃As favor the formation of the more synthetically useful α-product 139 (Scheme 2.11). Hence treatment of tributyl[(E)-4-(trimethylsilyl)-2-butenyl]stannane (138) with phenyl triflate and a Ph₃As derived catalyst afforded the highest yield and regioselectivity. Moreover, the double bond stereochemistry of the α-product was found to increase in favor of the trans isomer as the ligand donicity was decreased.

Homocoupling of stannanes is one of the most common side reactions observed in Stille coupling and in some instances has been shown to be synthetically useful. Tamao and coworkers have recently developed a catalytic homocoupling of arylstannanes using an acrylate dibromide derivative 142 as the stoichiometric oxidant (Scheme 2.12). In this study, the highest yields of homocoupled product 51 were obtained when using highly basic, bidentate ligands such as 1,3-bis(diphenylphosphino)propane (dppp). However, since the catalytic cycle
involves an oxidative addition step, it is unclear from this study whether the efficacy of homocoupling decreases with the use of more poorly donating phosphine ligands.

2.2.2.2 Small Molecule Synthesis Using TFP Modified Stille Reactions.

2.2.2.2.1 Alkenyl Iodide Precursors.

Since Farina's review of the Stille reaction, several workers have applied the TFP modified Stille conditions in a wide range of small molecule syntheses. For example, Müllen and coworkers have prepared a variety of linear polyenes such as 146 via cross-coupling of bis-stannane 145 with two equivalents of vinyl iodide 144 (Scheme 2.13). Although a PdCl₂(MeCN)₂ catalyst system was found to afford the desired polyene 146 in comparable yield, the TFP catalyst was more stable under the reaction conditions. Pancrazi and coworkers have also utilized the modified Stille protocol for the synthesis of polyene systems (Scheme 2.14). Treatment of vinyl iodide 147 and stannane 148 with a Pd₂(dba)₃/PPh₃ catalyst system furnished triene 149 in 34% isolated yield while the TFP derived catalyst afforded only 26% of the desired product. Employment of a triphenylarsine catalyst for this coupling improved the yield to 44% but unfortunately led to the production of unwanted side products.
Vedejs and Monahan\textsuperscript{83} have recently reported the derivatization of 5-(tributylstannyI)-2-phenyloxazole (151) with methyl (Z)-3-iodocrotonate (150) (Scheme 2.15). Using the TFP catalyst system in place of PdCl\(_2\)(MeCN)\(_2\) was found to increase the cross-coupling yield albeit with decreased retention of double bond geometry. Mathey and coworkers\textsuperscript{84} have reported the functionalization of vinyl iodide 153 using various alkynyl-, vinyl-, and aryl tributylstannanes (Scheme 2.15). The resulting substituted phosphanorbornadienes can be obtained in excellent yields giving access to a wide variety of new ligands for homogeneous catalysis.

2.2.2.2 Alkenyl Bromide Precursors.

Numerous examples of Stille cross-coupling between vinyl bromides and organotin species, using the TFP modified protocol, have recently been reported in the literature. For example, treatment of geminal dibromide 156 and tributylphenyltin (157) with a Pd\(_2\)(dba)\(_3\)/TFP catalyst in toluene at 100 °C for 20 h gives predominantly the trans functionalized product 158 (Scheme 2.16).\textsuperscript{85} Moreover, the high yield and regioselectivity observed using the tri-2-furylphosphine catalyst system was found to be general for a wide variety of 1,1-dibromo-1-alkenes and stannanes. Interestingly, performing the reaction at 80 °C in DMF with 1.5 equivalents of...
DIPEA gives the alkynyl product 160 exclusively in 91% isolated yield. This reaction was found to be of general scope with the desired substituted acetylenes being formed in good yields from a wide variety of geminal dibromides and organostannanes.\(^8\)

Lehn and coworkers\(^8\) have recently used TFP modified Stille conditions to functionalize geminal dibromide 161 with two equivalents of stannane 162 (Scheme 2.17). The desired cycloalkylidene product 163 was obtained in only 5% yield after three days when Pd(PPh\(_3\))\(_4\) was used as the catalyst. Utilization of Pd\(_2\)(dba)\(_3\) in conjunction with the TFP ligand led to a dramatic increase in the rate of coupling providing compound 163 in 72% isolated yield.

Lipshutz and coworkers\(^8\) recently prepared polyene 166 via a TFP-mediated Stille cross-coupling of vinyl bromide 164 and stannylated dienyne 165 (Scheme 2.18). It has been
demonstrated that subsequent hydrozirconation of terminal acetylene 166 with Schwartz's reagent provides a powerful method for the bidirectional construction of all-\(E\) polyenes. Meyers\(^8\) has recently shown that 2-bromooxazoline derivative 167 can be functionalized with a variety of vinyl-, alkynyl-, and aryl tributylstananes under mild TFP-mediated Stille conditions. In this study, both TFP and PPh\(_3\) derived catalysts were found to provide the desired substituted oxazolines 169 in moderate to excellent yield.

2.2.2.2.3 Alkynyl Halide Precursors.

Alkynyl halides have been used far less frequently in the TFP modified Stille reaction. Zapata and Rondón\(^8\) have recently reported the room temperature cross-coupling of acetylenic bromides with alkenyltins to furnish highly conjugated enynes (Scheme 2.19). Treatment of
bromide 170 with functionalized alkenyl stannane 171 with a \( \text{PdCl}_2(\text{MeCN})_2/\text{TFP} \) catalyst system in NMP at room temperature for 8 h afforded coupled product 172 in 95% yield. Moderate to excellent yields have been obtained using this procedure with a variety of coupling partners although the reaction does seem to be limited by the presence of an electron withdrawing group in the cis position of the alkenyltin species (Scheme 2.19).

2.2.2.2.4 Aryl Halide and Sulfonate Precursors.

The TFP modified Stille coupling reaction has been used extensively in recent years on aryl-iodide, bromide, chloride, and triflate starting materials (Scheme 2.20). For example, the arylation of vinyl stannane 176\(^90\) and alkynyl stannane 179\(^91\) in the presence of the TFP catalyst system has been reported by Shirakawa. In the latter case, performing the reaction with the PPh\(_3\) ligand under otherwise identical conditions gave only 1% of the desired aryl acetylene 180. Workers at Los Alamos National Laboratories have recently reported the Stille cross-coupling of iodobenzene (50) and vinyltributyltin (181)\(^92\) with tri-2-furylphosphine in supercritical carbon dioxide (Scheme 2.20). The only phosphine ligand to out perform TFP in this study was tris[3,5-bis(trifluoromethyl)phenyl]phosphine which gave styrene (182) in near quantitative yield. While the latter phosphine does constitute a poorly donating ligand, Tumas and coworkers\(^92\) noted that the increase in yield is likely due to the enhanced solubility of the catalyst in scCO\(_2\).\(^93\) Arylation of stannylated dienyne 165 with \( p \)-methoxyiodobenzene (135) in NMP at 50 °C using a Pd\(_2(\text{dba})_3/\text{TFP} \) catalyst furnished arene 183 in 81% yield after removal of the TMS protecting group\(^87\) (Scheme 2.20). Mathey and coworkers\(^94\) have reported a regioselective functionalization of dibromoarene 184 with alkynyl stannane 185 under TFP modified Stille conditions. The resulting substituted phosphabenzene 186 was thus obtained in 60% isolated yield as a single regioisomer (Scheme 2.20). Treatment of 2,6-dichloropurine derivative 187 with 2-(tributylstannyl)furan (188) under classical Stille conditions afforded a 5:2 mixture of 6-substituted and 2-substituted products, respectively, in moderate yield. However, use of a TFP based catalyst system allowed the reaction to be performed at a lower temperature providing the desired 6-substituted product 189 exclusively in 88% isolated yield.\(^95\)
Scheme 2.20

175 + 176 $\xrightarrow{\text{Pd}_{2}(\text{dba})_3, \text{TFP}}$ toluene, 90 °C, 13 h → 177

ref. 90

178 + 179 $\xrightarrow{[\text{PdCl(\pi-C_6H_5)]_2, \text{TFP}}$ THF, rt, 24 h → 180

ref. 91

50 + 181 $\xrightarrow{\text{Pd}_{2}(\text{dba})_3, \text{TFP}}$ scCO$_2$, 90 °C, 5 h → 182

ref. 92

135 + 165 $\xrightarrow{1) \text{Pd}_{2}(\text{dba})_3, \text{TFP, NMP 50 °C}}$ 2) K$_2$CO$_3$, EtOH → 183

ref. 87

184 + 185 $\xrightarrow{\text{Pd}_{2}(\text{dba})_3, \text{TFP}}$ THF, 55 °C, 18 h → 186

ref. 94

187 + 188 $\xrightarrow{\text{Pd(TFP)}_4}$ DMF, 50 °C, 22 h → 189

ref. 95
Finally, treatment of aryl triflate 190 and tetravinyltin (191) with a variety of palladium(0) catalysts was found to give 7-vinylflavone 192 in moderate yield\(^6\) (Scheme 2.20). In this study, the best yield of the desired vinylated product 192 was realized using the traditional Pd(PPh\(_3\))\(_4\) catalyst system.

### 2.2.2.2.5 Acyl Chloride Precursors.

A remarkable example of the synthetic versatility gained through the use of TFP in the Stille reaction was recently reported by Dussault whereby benzoyl chloride (193) was coupled with peroxide 194 to furnish enone 195 in excellent yield\(^7\) (Scheme 2.21). Clearly, the advantageous use of a poorly donating ligand, which allows the reaction to be performed at ambient temperature, is essential for the successful coupling of such a thermally labile functional group.
Hodgson and coworkers\(^98\) have recently reported that enantiopure (S)-MTPA-Cl (196) may be cross-coupled with chiral stannane 197 under TFP modified conditions to furnish enone 198. Subsequent stereochemical analysis of product 198 serves as a method for determining the enantiomeric purity of the starting organostannane 197.

### 2.2.2.3 Approaches Toward and Total Syntheses of Natural Products Involving TFP Modified Stille Reactions.

The TFP modified Stille conditions have recently been used in a variety of contexts for the total syntheses of complex natural products and advanced intermediates. In a particularly striking example, Amos B. Smith III and coworkers\(^99\) successfully prepared (-)-rapamycin (201) and its naturally occurring congener (-)-27-demethoxyrapamycin (202), using a TFP modified Stille macrocyclization as the key synthetic transformation (Scheme 2.22). Hence treatment of vinyl iodide 199 with a PdCl\(_2\)(TFP)\(_2\) catalyst in a mixture of DIPEA, DMF, and THF at room temperature, under conditions of high dilution, furnished the desired macrocycle in 74\% isolated yield. Subsequent removal of the silyl protecting groups gave the desired natural product 201 identical in all respects to the natural material. Fürstner and coworkers\(^100\) have reported the total synthesis of (R)-(−)-lasiodiplodin (205) and its de-O-methyl congener 206 using a TFP modified Stille allylation procedure (Scheme 2.22). Treatment of aryl triflate 203 and allyltributyltin with a Pd\(_2\)(dba)\(_3\)/TFP catalyst in NMP at 40 °C smoothly provided terminal diene 204 in 93\% yield. Molander and coworkers\(^101\) have recently synthesized (±)-steganone (210) using a TFP modified Stille coupling between benzyl bromide 207 and 3-tributylstannyl-(5H)-furan-2-one (208) (Scheme 2.22). Treatment of vinylstannane 211 and iodide 212 with a TFP catalyst system at 50 °C for 4.5 d was found to give diene 213 in 86\% isolated yield. Subsequent Sharpless asymmetric dihydroxylation of diene 213 has been shown by Armstrong and Barsanti\(^102\) to be an efficient strategy for the synthesis of the 2,8-dioxabicyclo[3.2.1]octane ring system found in the zaragozic acid family (Scheme 2.22). A mild, convergent approach to the vitamin D skeleton has recently been reported by Mancareñas and Mouriño\(^103\) using TFP modified Pd(0) catalysis. Thus, treatment of iododiene 215 and vinylstannane 216 with a Pd\(_2\)(dba)\(_3\)/TFP catalyst system in DMF at room temperature for 4 days gave a 33\% yield of conjugated triene 217 (Scheme 2.22).
Scheme 2.22

Conditions: (a) (TFP)_2PdCl_2, DIPEA, DMF, THF, rt, 74% R=OMe; 65% R=H. (b) allyltributylstannane, LiCl, Pd_3(dba)_2, TFP, NMP, 40 °C, 93%. (c) Pd_3(dba)_2, TFP, DMA, 80 °C, 83%. (d) Pd_3(dba)_2, TFP, ZnCl, DMF, 50 °C, 4.5 d, 86%. (e) Pd_3(dba)_2, TFP, Cul, DMF, 25 °C, 4 d, 33%.
Snieckus and coworkers\textsuperscript{104} have recently reported the synthesis of defucogilvocarcin V (220) using a TFP modified Stille coupling between aryl triflate 218 and tributylvinyltin (181) (Scheme 2.23). The total synthesis of \((\pm)-\text{licarin B}\)\textsuperscript{105} (223) has been achieved via Stille coupling of aryl iodide 221 with \((E)-\text{propenyltributyltin}\) (222). Eupomatenoids-1 and -12, two closely

\textbf{Scheme 2.23}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme223.png}
\caption{Synthesis of defucogilvocarcin V (220) and \((\pm)-\text{licarin B}\) (223).}
\end{figure}

Conditions: (a) Pd\textsubscript{2}(dba)	extsubscript{3}, TFP, NMP, rt, 5 h, 69\%. (b) Pd\textsubscript{2}(dba)	extsubscript{3}, TFP, LiCl, DMF, 120-130 °C, 84-86\%. (c) Pd\textsubscript{2}(dba)	extsubscript{3}·CHCl\textsubscript{3}, TFP, NMP, rt, 6 d, 34\%. (d) Pd\textsubscript{2}(dba)	extsubscript{3}, TFP, NMP, 25 °C, 27\% (57\% based on recovered starting material). (e) Pd\textsubscript{2}(dba)	extsubscript{3}, TFP, LiCl, NMP, rt, 1.5 d, 93\%.
related natural products (not shown), have also been synthesized by Engler\textsuperscript{105} using the same Stille functionalization as the final step. Hirama and coworkers\textsuperscript{106} have recently synthesized the marine antibiotic korormicin (227) using a Stille cross-coupling (Scheme 2.23). Treatment of vinyl iodide 224 and epoxy stannane 225 with a TFP derived Pd(0) catalyst in NMP at room temperature for 6 d furnished key intermediate 226 in 34\% yield. A total synthesis of (-)-pateamine A (231) has recently been developed\textsuperscript{107} whereby macrocyclic bromide 228 is coupled with stannyl diene 229 under TFP modified conditions. In this study, stopping the Stille reaction prior to completion and recycling the unreacted bromide 228 proved beneficial due to competitive formation of a palladium $\pi$-allyl species. Overman and coworkers\textsuperscript{108} have recently succeeded in the total synthesis of the C\textsubscript{15} alkaloid (+)-aloperine (235) using Diels-Alder chemistry. In an initial approach, which later had to be abandoned, diene 234 was prepared in 93\% isolated yield using a TFP-mediated Stille reaction between functionalized stannane 232 and enol triflate 233 (Scheme 2.23). Subsequent [4+2] cycloaddition of diene 234 with methyl acrylate unfortunately failed to provide the required cycloadduct.

2.2.2.4 TFP Modified Stille Reactions Involving Organometallic Substrates.

The Stille cross-coupling of various organometallic species using tri-2-furylphosphine based catalysts has recently been studied. For example, treatment of cyclohexadienyl triflate iron $\pi$-complex 236 and vinyltributyltin (181) with Pd(PPh\textsubscript{3})\textsubscript{4} in NMP at room temperature for 16 h gave coupled product 237 in 38\% yield\textsuperscript{109} (Scheme 2.24). However, utilization of the TFP derived catalyst system for this coupling increases the yield of the reaction to 50\%. In either

\begin{center}
\textbf{Scheme 2.24}
\end{center}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme224.png}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Ligand} & \textbf{Yield (\%)} \\
\hline
PPh\textsubscript{3} & 38 \\
TFP & 50 \\
\hline
\end{tabular}
\end{table}
case, the $\eta^4$ bound tricarbonyliron moiety is cleanly retained under the cross-coupling conditions. In contrast to this finding, Johansson and coworkers$^{110}$ have reported that the Stille coupling of ($\eta^6$-arene)Cr(CO)$_3$ complex 238 with iodobenzene affords a mixture of products (Scheme 2.25). Photolysis of the reaction mixture and subsequent analysis of the products conclusively showed that CO transfer had taken place under the reaction conditions. Moreover, unwanted methyl group transfer had competed with the desired arylation process. Using a TFP based catalyst gave lower overall conversion but an increased ratio of carbonylated products. In either case, the desired Stille product, biphenyl (51), was the minor component of the reaction mixture.

### Scheme 2.25

\[
\begin{align*}
238 & \xrightarrow{1) \text{PhI, Pd}_2(\text{dba})_3, \text{Ligand, DMF, LiCl, 100 °C, 24 h}} \quad 239 \quad 240 \quad 51 \\
& \xrightarrow{2) \text{hv, 24 h}} \quad \text{Ligand} \quad \text{Yield (\%)} \\
\text{PPh}_3 & \quad 44 \quad 24 \quad 13 \\
\text{TFP} & \quad 36 \quad 25 \quad 2
\end{align*}
\]

2.2.2.5 New Frontiers In Stille Coupling Using TFP Modified Conditions.

Until recently, the Stille reaction has been limited to the coupling of organostannanes with organohalides and sulfonates. Liebeskind and coworkers$^{111}$ have reported the efficient cross-coupling of organotins with various aryl-, heteroaryl-, alkenyl-, benzyl-, and heterobenzylic$^{112}$ sulfonium salts using the TFP derived catalyst system (Scheme 2.26). In this study, very low levels of palladium catalyst (0.01-0.5 mol%) could be employed to obtain a variety of cross-coupled products 243 in moderate to excellent yield. Recent advances in the Stille coupling procedure have not been limited, however, to the use of novel oxidative insertion precursors. Herrmann$^{113}$ has reported a new $N$-heterocyclic carbene catalyst system 244 for the Stille process (Scheme 2.26). In contrast to Farina’s findings,$^{52}$ the use of dissociative ligands such as TFP in conjunction with the imidazolin-2-ylidene catalyst system did not lead to increased yields or
reaction rates. Unfortunately, palladium catalyst 244 was not compared to either the Pd(PPh₃)₄ or Pd₂(dba)₃/TFP catalyst systems. While the N-heterocyclic carbene moiety presumably imparts increased thermal stability to the Pd species, the overall efficiency of catalyst 244 relative to traditional bis(phosphine) Stille catalysts remains to be studied.

2.2.2.6 TFP Modified Stille Reactions for the Preparation of Oligomers and Polymers.

Tri-2-furylphosphine has recently been employed as a Stille ligand for the preparation of various polymers and oligomers. Cyclopentadiene derivative 248 was synthesized by Tamao and coworkers through the cross-coupling of diiodide 246 with two equivalents of 2-(tributylstannyl)thiophene (247) (Scheme 2.27). The interesting physical and electronic properties of conjugated thienyl systems such as compound 248, has generated considerable interest in polythiophene materials. Functionalized sexithiophene 250 has recently been prepared via Stille coupling of dibromide 249 with 2-(tributylstannyl)thiophene (247) (Scheme 2.27). Use of poorly coordinating ligands was found to be highly beneficial to the obtention of oligomer 250 in high yield. Poly(phenylenethiophene) polymers such as 253 have been prepared
through Stille cross-coupling reactions. For example, polymerization of 2,5-dioctyl-1,4-diiodobenzene (251) with 1,4-bis(tributylstannyl)-thiophene (252) has been reported with the TFP modified catalyst system \(^{116}\) (Scheme 2.27) giving a 47% yield of the desired polymer 253 with moderate molecular weight (40 000 amu). When the polymerization was carried out with PPh\(_3\) as the ligand, the yield and molecular weight of the polymer decreased to 34% and 24 000 amu respectively. Conversely, using a ligand of lower donicity such as Ph\(_3\)As gave 253 in 57% yield with an average molecular weight of 56 000 amu. Although the triphenylarsine catalyst was found to increase the yield and molecular weight of the desired polymer, the catalyst lifetime was found to be significantly shorter than the corresponding TFP derived system.

Silole-acetylene polymers such as 256 exhibit interesting physical properties such as narrow bandgaps and have been applied as efficient electron-transporting emissive materials in organic electroluminescent devices \(^{117}\) (Scheme 2.28). TFP-mediated Stille coupling of dibromosilole
derivative 254 with bis(stannylethynyl)arene 255 in refluxing THF smoothly furnished the desired polymer 256 in excellent yield\textsuperscript{118} (Scheme 2.28).

The Stille coupling of enantiopure spirosilane monomers 257 and 258 to give the corresponding oligomers 259 has been reported\textsuperscript{119} (Scheme 2.29). Using high dilution techniques, Tamao and coworkers have successfully prepared the cyclic tetramer 260 in 8% yield.\textsuperscript{119} This compound, which has an estimated pore size of 9.4 Å, should prove very interesting in the construction of self-assemblies having chiral network structures.
2.2.2.7 Resin Bound TFP-Mediated Stille Cross-Coupling.

Carbon-carbon bond forming reactions on solid support\textsuperscript{120} can be a powerful, automatable tool for combinatorial drug discovery efforts. The solid phase synthesis of biaryls via the Stille reaction has been investigated by Sucholeiki and coworkers\textsuperscript{121} (Scheme 2.30). Treatment of the

\begin{scheme}
\text{Scheme 2.30}
\end{scheme}

\begin{align*}
\text{Conditions A: } & \text{i) 3 equiv. iodobenzene (50), 10 mol\% Pd}_3(\text{dba})_2, 10 \text{ mol\% TFP, 2 equiv. LiCl, NMP, 25 °C, 12 h; ii) 5\% TFA-CH}_2\text{Cl}_2, 15\% \text{ yield (2 steps).} \\
\text{Conditions B: } & \text{i) 3 equiv. trimethylphenyltin, 10 mol\% Pd}_3(\text{dba})_2, 10 \text{ mol\% TFP, 2 equiv. LiCl, NMP, 25 °C, 12 h; ii) 5\% TFA-CH}_2\text{Cl}_2, 33\% \text{ yield (2 steps).}
\end{align*}

Rink amide resin \textit{261} and 4-tributylstannylphenylacetic acid (\textit{262}) with diisopropylcarbodiimide (DIC) in CH\textsubscript{2}Cl\textsubscript{2} cleanly furnished resin bound stannane \textit{264}. Subsequent palladium-catalyzed Stille cross-coupling of amide \textit{264} with iodobenzene (\textit{50}) using the classic triphenylphosphine based catalysts failed to produce the desired biaryl under a variety of conditions. However, usage of the tri-2-furylphosphine derived catalyst system provided amide \textit{266} in 15\% yield after cleavage from the solid support (Scheme 2.30). Alternatively, aryl iodide \textit{265} could be coupled with trimethylphenyl tin under TFP modified conditions to give compound \textit{266} in 33\% overall yield. This methodology has also been studied with other polymer supports but the yields of cross-coupled products are generally quite low.\textsuperscript{121}
Since the Stille methodology is a powerful tool for carbon-carbon bond formation, which tolerates a wide range of functionalities, a variety of multistep transformations have been reported which include this cross-coupling reaction. Liebeskind and coworkers have reported a number of interesting methods for the construction of substituted aromatics based on the ring opening of cyclobutenones. This methodology has recently been applied towards the synthesis of highly oxygenated, angularly-fused polycyclic aromatic compounds. The functionalized cyclobutenones required for thermal rearrangement may conveniently be prepared via Stille cross-coupling. For example, treatment of naphthyl stannane and chlorocyclobutenone under the TFP modified Stille protocol affords the desired 4-arylcyclobutenone intermediate (not shown) which subsequently undergoes electrocyclic ring opening/closure \textit{in situ} to give substituted phenanthrene (Scheme 2.31). Many biologically important polyketide natural products including pradimicin A, cervinomycin A, and simaomicin \( \alpha \) contain a core phenanthrene structure similar to compound 269.

The preparation of isocoumarins via a two step Stille coupling/palladium annulation procedure has recently been reported by Shen and coworkers (Scheme 2.32). In this sequence, dibromide is regioselectively functionalized at the \textit{trans} position using a TFP modified Stille reaction. Subsequent palladium-catalyzed annulation onto the ester function with loss of MeBr furnishes the desired isocoumarin in moderate to excellent yield. Interestingly, these workers found that the TFP ligand performed very well when the migratory group on tin was an aryl
group. However, if a vinylstannane was employed, better results were obtained using the traditional Pd(PPh₃)₄ catalyst system.

In an effort to develop therapeutic agents for neurodegenerative disorders such as Alzheimer’s and Huntington’s diseases, Nagata and Hume have sought to cross-couple substituted quinoline 273 with 2-propenyl(tributyl)tin (274) (Scheme 2.33). Unexpectedly, the product of the Stille coupling underwent a palladium-catalyzed oxidative cyclization under the reaction conditions to provide sulfonamide 275. Using a Pd₂(dba)₃/TFP catalyst system, cyclized product 275 was obtained in higher yield along with 15% of the uncyclized adduct 276. In both cases, cross-coupling was found to occur exclusively at the 5 position giving the corresponding 7-chloro derivatives 275 and 276.

A one-pot palladium-catalyzed hydrostannylation/Stille coupling has recently been developed by Maleczka (Scheme 2.34). A variety of acetylenes 277, including propargyl-alcohols and amines, may be treated with either Bu₃SnH or (Bu₃Sn)₂O and polymethylhydrosiloxane (PMHS) to give an (E)-vinylstannane which subsequently undergoes
2.2.3 Tri-2-furylphosphine as a Ligand in Other Palladium-Catalyzed Organic Reactions.

2.2.3.1 Palladium-Catalyzed Cross-Coupling of Organozinc Compounds.

The palladium-catalyzed Negishi\textsuperscript{128} cross-coupling reaction between aryl iodides and aryl zinc compounds is a powerful method for the formation of biaryl bonds which tolerates a wide variety of functionalities and employs quite mild reaction conditions. Knochel and coworkers have recently applied the tri-2-furylphosphine ligand in a wide variety of Negishi cross-coupling reactions (Scheme 2.35). Treatment of aryl zinc\textsuperscript{280} and methyl 2-iodobenzoate (281) with a \( \text{Pd(dba)}_2/\text{PPh}_3 \) catalyst in THF for 4 hours smoothly furnished biaryl\textsuperscript{282} in 79% isolated yield. Similar to Farina's findings,\textsuperscript{52} Knochel and coworkers observed a significant increase in cross-coupling rate upon employment of the TFP ligand and product 282 was thus obtained in 83% yield after a 1.5 h reaction period. Knochel and Rottländer\textsuperscript{130} have subsequently applied the TFP modified Negishi coupling to the solid phase synthesis of polyfunctional biaryls, diphenylmethanes and terphenyls. These workers have elegantly shown that a variety of resin bound aryl- and heteroaryl halides 283 can be efficiently coupled under mild TFP-mediated conditions with functionalized aryl- and benzylic zinc bromides 284 (Scheme 2.35). Cleavage of the cross-coupled products from the solid support using TFA in \( \text{CH}_2\text{Cl}_2 \) generally furnished the desired materials in high yield and purity. The same workers have also shown that aryl iodides which bear triflate\textsuperscript{131} or nonaflate\textsuperscript{132} moieties selectively couple through the halide functionality with aryl- and benzylic\textsuperscript{133} zinc reagents using TFP based catalysts (Scheme 2.36).
Hence, bifunctional iodides of type 286 were found to smoothly couple with substituted organozincs 287 to afford biaryl sulphonates 288 in excellent yield under mild reaction conditions. Moreover, subsequent palladium-catalyzed cross-coupling chemistry on biaryl products 288 with a variety of electrophiles provides a general, efficient synthesis of polyfunctional terphenyls.

Knochel and coworkers have demonstrated the tremendous versatility of the palladium-catalyzed Negishi cross-coupling reactions using a wide variety of zincated nitrogen containing heterocycles including substituted imidazoles, thiazoles, quinolines, pyridines, purines,
pyrimidines, and nucleosides (Scheme 2.37). For these studies, in situ generation of the Pd catalyst from bis(dibenzylideneacetone)palladium(0) (1-2 mol%) and TFP (4-8 mol%) generally gave the best results affording the desired cross-coupled products in moderate to excellent yields.
Knochel and coworkers\textsuperscript{135} have recently shown that zincated thymine derivatives may be coupled with aryl- and vinyl iodides under TFP modified conditions (Scheme 2.38). This methodology, which is amenable to solid phase synthesis, constitutes the first report of a heterocyclic benzylic zinc reagent used in a cross-coupling reaction. Using the TFP based catalyst system, organozinc 303 was cross-coupled with a variety of substituted aryl iodides 304 at room temperature for 12 h to furnish the desired coupled products 305 in 62-95\% isolated yield. Using Rink- or Wang-resin bound aryl iodides with organozinc 303 gave, after cleavage from the solid support, the expected cross-coupled products in 89-93\% purity as indicated by HPLC analysis.

The antitumor drug Z-tamoxifen (310) has recently been prepared by Knochel and coworkers through a TFP-mediated Negishi coupling of vinyl iodide 309 and aryl zinc 308 (Scheme 2.39).\textsuperscript{136} The required iodide 309, which can be obtained in high stereochemical purity via
carbonickelation of a suitably functionalized alkyne and subsequent iodolysis, couples with the organozinc reagent 308 with complete retention of the double bond geometry giving the desired product in 77% isolated yield.

Kagan has recently employed the TFP modified Negishi reaction in the diastereoselective ortho functionalization of enantiopure ferrocenyl sulfoxides\(^\text{137}\) (Scheme 2.40). Directed ortho lithiation of S-sulfoxide 311 with LDA in THF at \(-78^\circ\text{C}\) and subsequent transmetalation of the resulting lithio ferrocene with ZnCl\(_2\) afforded \((R_{\text{Fc}}, S_s)-312\) with 98% diastereoselectivity. TFP modified Negishi cross-coupling of 312 with \(p\)-(dimethylamino)iodobenzene (313) according to Knochel’s conditions\(^\text{121}\) afforded \(\alpha\)-aryl sulfoxide \((S_{\text{Fc}}, S_s)-314\) in 37% isolated yield.

The palladium-catalyzed cross-coupling of organozinc reagents with \(\alpha,\beta\)-unsaturated carbonyl derivatives bearing an \(\alpha\)-iodide function has been studied by Negishi and coworkers. For example, treatment of iodide 315 with alkynyl zinc reagent 316 in DMF with a Pd(dba)\(_2\)/TFP catalyst furnished enyne 317 in excellent yield (Scheme 2.41).\(^\text{138}\) Similarly, \(\alpha\)-iodoeneone 318 was found to cross-couple with vinyl zinc 319 under TFP modified conditions to afford diene 320 in 72% yield (Scheme 2.42).\(^\text{139}\) Unfortunately, this coupling procedure could not successfully be extended to the functionalized \(\alpha\)-iodoeneone 321 (Scheme 2.42). All attempts to
couple this halide with alkenyl zinc reagent 319 failed to provide >5% yield of the desired diene 322. In order to alleviate this problem, Negishi and coworkers sought to couple TMS protected allylic alcohol 323 with zincated olefin 319 (Scheme 2.43). The desired diene 324, which was required for a formal synthesis of (±)-carbacyclin, was thus obtained in 84% isolated yield after selective cleavage of the TMS ether functionality.\textsuperscript{139}

Negishi’s conditions for the cross-coupling of α-iodoenones with zinc reagents have recently been employed by Molander and coworkers in a synthetic approach toward the alkaloid natural product cephalotaxine.\textsuperscript{140} Treatment of azido halide 325 with aryl zinc 326 in DMF at room temperature with a Pd\textsubscript{2}(dba)\textsubscript{3}/TFP catalyst system furnished coupled product 327 in 48% yield (Scheme 2.44). Under otherwise identical conditions, α-iodoenone 325 could be coupled with aryl zinc 328 in 72% yield after a 12 h reaction period. In both cases, thermal decomposition of the azide functionality was avoided by use of the mild TFP-mediated cross-coupling conditions. Moreover, as noted by Carboni and coworkers,\textsuperscript{141} use of the less nucleophilic TFP ligand in place of PPh\textsubscript{3} with azido substrates may serve to eliminate competitive phosphinimine formation.
The total synthesis of nakienone A, a polyene natural product of marine origin, has recently been reported by Negishi and coworkers.\textsuperscript{138,142} The key synthetic step, which was performed using a TFP derived catalyst, involved the palladium(0) cross-coupling of vinyl zinc 330 with iodo diene 331 (Scheme 2.45). After selective cleavage of the TMS protecting group, the desired product 332 was obtained in 90% yield with full control of the alkene geometry.

The synthesis of purinecarbonitriles via palladium(0)-catalyzed cross-coupling of halopurines with zinc cyanide has been reported by Gundersen.\textsuperscript{143} In this study, Pd(TFP)_4 was found to be the catalyst of choice giving high yields of the desired nitriles. For example, treatment of chloropurine 333 and Zn(CN)_2 (334) with Pd(PPh)_3 in NMP at 90 °C gave cyanopurine 335 in 52% isolated yield (Scheme 2.46). Alternatively, use of the Pd(TFP)_4 catalyst gave the desired product in 75% yield while the Pd(AsPh)_3 completely failed to catalyze the reaction. Moreover, Gundersen has shown this trend to be quite general for a variety of 2-, 6-, and 8-halopurines as well as 8-haloadenosine nucleoside derivatives.
Morin and Malan\textsuperscript{144} have recently described a method for the preparation of boronic acid substituted amino acids using TFP modified palladium catalysis (Scheme 2.47). Treatment of boronate ester 336 and enantiopure organozinc reagent 337 with a Pd(OAc)\textsubscript{2}/TFP catalyst system in benzene afforded a 50-55\% yield of the desired product without evidence of competitive Suzuki type coupling. Subsequent hydrogenolysis and removal of the Boc protecting group provided enantiopure 4-borono-L-phenylalanine in high yield.

The palladium-catalyzed functionalization of bis(iodozincio)methane (339) has been reported by Utimoto and coworkers\textsuperscript{145} (Scheme 2.48). Coupling of 339 with cinnamyl chloride (340) in
the presence of the TFP derived catalyst system and subsequent quenching of the mixture with DCI/D₂O smoothly afforded product 341 in 97% yield. Under otherwise identical conditions, use of the PPh₃ palladium(0) catalyst gave only 16% of the desired product. Clearly, a ligand of low donicity is highly beneficial to the present cross-coupling reaction. Utimoto has used the described cross-coupling of bis(iodozincio)methane (339) with a large variety of electrophiles in a stepwise fashion to efficiently synthesize numerous difunctionalized methylene compounds.¹⁴⁵

It has recently been demonstrated that the palladium(0)-catalyzed allylic alkylation of various allylic acetates with functionalized alkyl- and alkenyl zinc reagents proceeds smoothly with the TFP catalyst system¹⁴⁶ (Scheme 2.49). Cross-coupling of cyclohex-2-enyl acetate (342) with Reformatsky reagent 343 at room temperature using a Pd(OAc)₂/TFP catalyst gave product 344 in 56% isolated yield. In all cases, employment of PPh₃ or P(o-Tol)₃ derived catalysts resulted in less than 25% yield of the desired ester 344. Treatment of E-cinnamyl acetate (345) with alkenylzinc 346 at 40 °C for 20 h with the TFP catalyst gave product 347 in good yield via a regiospecific attack of the nucleophile on the less substituted terminus of the Pd π-allyl intermediate.

2.2.3.2 TFP-Mediated Arylation and Alkylation of Olefins by Organopalladium Compounds: The Heck Reaction and Related Processes.

The palladium(0)-catalyzed Heck reaction¹⁴⁷ is a powerful method for the functionalization of a large variety of unsaturated substrates. Countless intermolecular, intramolecular and asymmetric¹⁴⁸ versions of the Heck reaction have been reported in the literature¹⁴⁹ and perhaps...
the only major limitation of the reaction is that the oxidative addition precursor may not contain β-hydrogen atoms. The Heck reaction between n-butyl acrylate (350) and aryl chlorides has recently been studied in considerable detail by Herrmann and coworkers\(^{150}\) (Scheme 2.50). Treatment of activated aryl chloride 348 and acrylate 350 with \(\text{Pd(OAc)}_2/\text{PPh}_3\) in DMA at 150 °C for 24 h afforded the desired Heck product 351 in 69% yield along with 6.4% n-butyl E-cinnamate (353). The latter product results from an unwanted phosphorus to palladium aryl migration process which occurs in the oxidative addition complex. Performing the reaction with TFP as the Pd ligand, under otherwise identical circumstances, gave the desired Heck product in 64% yield along with 4.1% of the furyl transfer byproduct 354. Treatment of deactivated chloride 349 and acrylate 350 with the PPH\(_3\) derived catalyst system at 160 °C for 24 h furnished 41% of the desired Heck product 352 again containing 6.4% of compound 353. However, employment of the TFP catalyst for this reaction completely failed to produce either product 352 or byproduct 354. This result suggests that the TFP modified Pd(0) species is not able to oxidatively add to \(p\)-chloroanisole (349).

Recently, Tumas\(^{92}\) and Rayner\(^{151}\) have independently studied the Heck coupling of iodobenzene (50) with simple olefins using a variety of phosphine catalysts in supercritical carbon dioxide. Tumas found that methyl acrylate (355) was efficiently arylated in scCO\(_2\) at 90 °C after 12 h using a \(\text{Pd(OAc)}_2/\text{TFP}\) catalyst system (Scheme 2.51). In this study, tri-2-
furylphosphine was found to be the best ligand in terms of both conversion and turn over number\(^{152}\) (TON/h\(^{-1}\)). Moreover, TFP was the only non-fluorinated phosphine to provide methyl E-cinnamate (356) in synthetically useful yield. Rayner and coworkers\(^{151}\) have found that the use of fluorinated palladium sources can be beneficial for scCO\(_2\) Heck reactions (Scheme 2.51). Employment of commercially available Pd(OCOCF\(_3\))\(_2\) as the precatalyst allowed for the use of lower reaction temperatures and catalyst loadings. Hence treatment of methyl acrylate (355) and

<table>
<thead>
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<th>Ligand</th>
<th>Conversion (%)</th>
<th>TON/h(^{-1})</th>
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<tr>
<td>P(o-Tol)(_3)</td>
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<td>1</td>
</tr>
<tr>
<td>TFP</td>
<td>&gt;95</td>
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iodobenzene (50) at 80 °C for 15 h in scCO\(_2\) with a Pd(OCOCF\(_3\))\(_2\)/TFP catalyst system afforded coupled product 356 in excellent yield. Similarly, styrene (182) could be regioselectively arylated with iodobenzene (50) in scCO\(_2\) to give \(\text{trans}\)-stilbene (357) in 76% isolated yield (Scheme 2.51). In either case, TFP was found to be the ligand of choice.

The Heck coupling of various organopalladium species with enol ethers\(^{153}\) and other olefins, which contain an \(\alpha\)-heteroatom,\(^{154}\) has been studied in considerable detail. Unlike olefins that carry an electron withdrawing functionality, unsaturated substrates carrying an \(\alpha\)-heteroatom
often exhibit poor regioselectivity in the Heck reaction.\textsuperscript{155} Hallberg and coworkers\textsuperscript{156} have recently studied the Heck arylation of acyclic enol ether 358 with phenyl triflate (359) using a variety of catalyst systems (Scheme 2.52). In this study, both the PPh\textsubscript{3} and TFP derived catalyst systems were found to give coupled product 360 in high yield as a mixture of \(\alpha\)- and \(\beta\)-regioisomers. While none of the phosphines tested were able to impart exclusive \(\alpha\)-selectivity to the reaction, it is interesting to note the observed trend in the \(\beta\)-product double bond geometry as the ligand becomes less coordinating. A reversal of selectivity can be seen in favor of the cis isomer upon changing the ligand from PPh\textsubscript{3} to AsPh\textsubscript{3} (Scheme 2.52).

Hallberg and coworkers\textsuperscript{157} have also studied the Heck arylation of various \(N\)-substituted 2,5-dihydropyrroles using the TFP catalyst system (Scheme 2.53). In this study, treatment of 1-(methoxycarbonyl)-2,5-dihydropyrrole (361) and iodobenzene with a Pd(OAc)\textsubscript{2}/dppp catalyst
system in DMF at 100 °C afforded a mixture of products 362-365. By using a large excess of the starting olefin, formation of the diarylated product 364 could efficiently be attenuated. In addition, changing the catalyst ligand to P(o-Tol)_3 and adding a silver salt suppressed the double bond isomerization such that the desired product 362 could be obtained in >95% purity as evidenced by GCMS analysis. However, when triflates were employed as arylating agents, addition of lithium chloride and changing the catalyst ligand to TFP resulted in the formation of the desired product 366 and byproduct 367 in >96/4 ratio. This observation was found to be quite general for a variety of aryl triflates giving the desired 3-substituted-2,3-dihydropyrroles 366 in moderate yield and high isomeric purity.\textsuperscript{157}

Kosugi and coworkers\textsuperscript{158} have reported using the TFP catalyst system in a ternary coupling reaction between chloride 368, stannane 369, and norbornadiene (370) to give adduct 371 in 89% yield as a single stereoisomer (Scheme 2.54). Subsequent retro Diels-Alder chemistry with product 371 provides an expedient, high yielding route to fatty acid derivatives.

![Scheme 2.54](image)

A powerful, stereodefined cyclization of tosyl carbamate 372 with various electrophiles 373 to furnish 4-arylidenene-3-tosyloxazolidin-2-ones 374 has been described by Balme and coworkers\textsuperscript{159} (Scheme 2.55). Use of Pd(OAc)_2 as the palladium source in conjunction with the
weakly coordinating TFP ligand in acetonitrile at room temperature was found to be optimal providing the desired cyclized products in 56-76% yield. In all cases, ring closure occurred in a 5-exo-dig fashion giving the trans arylated products 374 stereospecifically.

Sinou and coworkers\textsuperscript{160} have recently reported an unusual palladium-catalyzed annulation of vinyl bromide functionalized carbohydrates to provide bicyclic glycals (Scheme 2.56). Treatment of bromoalkene 375 with a Pd(OAc)$_2$/PPh$_3$ catalyst system resulted in an intramolecular Heck cyclization with concomitant β-dealkoxypalladation giving pyran 377 in 72% isolated yield. While few examples of such β-eliminations have been reported in the literature, these authors postulate that the anomeric oxygen facilitates the process by complexation to the metal center (Scheme 2.56). Consistent with this hypothesis, use of a readily dissociating ligand such as TFP resulted in an increased rate of reaction giving compound 377 in 77% yield. Conversely, employment of a highly basic, chelating phosphine such as bis(diphenylphosphino)propane (dppp) furnished 377 in 10% yield after a 24 h reaction period.

The palladium-catalyzed cyclization of dienes and enynes to produce five and six membered rings has been explored extensively by Trost and coworkers.\textsuperscript{161} In an interesting study related to this chemistry, Gore\textsuperscript{162} proposed that functionalized diquinanes such as 381 could be prepared by palladium-catalyzed annulation of propargylic ester 378 via a σ-allenylpalladium intermediate 379 (Scheme 2.57). Subsequent oxidation of the allenic product 380 according to literature precedent\textsuperscript{163} would then furnish the desired enone 381. Unfortunately, treatment of acetate 378 with a variety of Pd$_2$(dba)$_3$/phosphine catalysts only led to slow decomposition of the starting
material. However, utilization of the TFP ligand afforded diene 382 in 36% isolated yield (Scheme 2.58). Changing the solvent to acetic acid and heating the reaction to 110 °C resulted in the formation of diene 383 and enone 384 in 20% and 13% yield, respectively. The formation of these two products can be explained by a mechanism involving the expected σ-allenylpalladium intermediate 379 closing onto the double bond in an unusual 6-endo-trig fashion. Subsequent acid catalyzed addition of AcOH or H₂O to the resulting cyclized product would then furnish acetate 383 and enone 384, respectively. Use of the TFP catalyst system afforded the highest yield of enol acetate 383 and further attempts to improve this process have unfortunately been unsuccessful.

The palladium(0)-catalyzed cyclization-carbonylation of allylic acetate 385 has recently been studied by Takahashi and coworkers¹⁶⁴ (Scheme 2.59). Treatment of 385 in acetic acid under an atmosphere of carbon monoxide with a Pd₂(dba)₃/PPh₃ catalyst system furnished a mixture of three stereoisomeric products 386-388 in 19% isolated yield. Utilization of a TFP derived
catalyst was found to significantly improve the yield of the reaction but also resulted in reduced stereoselectivity. The major stereoisomer 386, which contained the correct relative stereochemistry for a variety of natural products, and its epimer 387 were subsequently converted to (±)-isoiridomyrmecin via a three step synthetic sequence in 47% yield.\textsuperscript{164}

The palladium-catalyzed intramolecular cyclization of olefinic propargylic carbonates using the TFP catalyst system has been reported by Pimm and coworkers\textsuperscript{165} (Scheme 2.60). Heating tosyl sulfonamide 389 or 390 under an atmosphere of CO with a Pd\textsubscript{2}(dba)\textsubscript{3}/PPh\textsubscript{3} catalyst in AcOH at 45 °C and subsequent esterification of the product with CH\textsubscript{2}N\textsubscript{2} furnished cyclopropane derivatives 391 and 392 in 10% and 65% yields, respectively. However, use of the corresponding TFP catalyst afforded the desired products 391 and 392 in 93% isolated yield.
Cyclization of carbonates 389 and 390 with trapping agents other than carbon monoxide, including organoboranes, dialkylzincs, and hydride sources, has been shown to be quite efficient using the TFP derived catalyst. Treatment of enantiopure gem-bis-sulfone 393 under the described conditions afforded cyclized product 394 in 91% yield (Scheme 2.61). Subsequent hydrogenation and reductive cleavage of a single sulfone group followed by MoOPh oxidation afforded the monoterpane natural product (-)-α-thujone (395) in high yield.

Palladium(0)-catalyzed intramolecular cyclization followed by anion capture can be an extremely powerful synthetic sequence for the preparation of fused-, spiro-, carbo-, and heterocyclic systems. Such processes have been studied in considerable detail by Grigg and coworkers for a large variety of substrates and anion transfer agents. For example, treatment of aryl iodide 396 with a Pd\textsubscript{2}(dba)\textsubscript{3}/TFP catalyst in anisole at 110 °C along with a tetraphenylborate anion transfer agent afforded ether 397 in 60% isolated yield (Scheme 2.62). Similarly, the palladium-catalyzed polyene cyclization of sulfonamide 398 and
subsequent anion capture with NaBPh₄ gave spiro product 399 as a single diastereomer in 63% yield. Unfortunately, no comparisons have been presented for these two reactions using the standard PPh₃ catalyst system.

2.2.3.3 Palladium-Catalyzed Cycloisomerization of Dienes, Diynes, and Enynes.

The palladium-catalyzed cycloisomerization of bisdienes to give carbocyclic five- and six-membered rings has recently been studied by Takacs and coworkers using various ligands (Scheme 2.63). Treatment of unsymmetrical tetraene 400 with either a PPh₃ or TFP derived catalyst system at 65 °C for 24 h was found to afford trans-cyclohexane derivative 401 in quantitative yield as a E,E:E,Z isomeric mixture. However, the cycloisomerization of bisdiene 402, using a different catalyst precursor, gave compound 403 in near quantitative conversion with the PPh₃ ligand while the TFP and AsPh₃ catalyst systems resulted in only 40% of the desired cyclized product. Hence, catalysts that are comprised of highly dissociating ligands seem to be less general for palladium-catalyzed cycloisomerization reactions. Trost and coworkers, upon studying the cycloisomerization of α,ω-diynes using various phosphine ligands, also found the TFP ligand to be less effective (Scheme 2.64). Bisacetylene 404, when
treated with a Pd(OAc)$_2$/PPh$_3$ catalyst under high dilution conditions, could be cyclized to give macrocycle 405 in 55% yield a single double bond isomer. Utilization of the TFP ligand, however, provided only 7.2% of the desired 15-membered ring 405. Optimal conditions for this macrocyclization involved the use of the bulky, electron rich ligands such as tris(o-methoxyphenyl)phosphine.

Trost and coworkers$^{169}$ have reported an elegant palladium-catalyzed cycloisomerization of diyne 406 to give tricycle 408 in a single operation (Scheme 2.65). Using PPh$_3$ as the palladium ligand, reaction of acetate 406 gave a complex mixture of products while use of the weakly coordinating TFP ligand afforded cycloisomer 408 in 61% yield as a single diastereomer. Interestingly, only the trans isomer of the starting olefin was found to undergo the subsequent 6π-electrocyclic ring closure giving the desired tricyclic diene 408.

The cycloisomerization of enyne 409 and subsequent cross-coupling of α-alkylpalladium intermediate 410 with various organostannanes has recently been studied by Kibayashi and coworkers$^{170}$ (Scheme 2.66). Heating 1,6-ene 409 and vinytributylstannane with a PPh$_3$ based
catalyst system in THF/HOAc produced a 28% yield of the desired cross-coupled product 411 along with mixture of double bond isomers, 412 and 413, resulting from β-hydride elimination. Use of the TFP ligand resulted in a 69% yield of the unwanted elimination products with only a trace of the desired product being formed. Interestingly, a “ligandless” Pd-catalyst provided the desired cross-coupled product 411 exclusively in 45% yield.

2.2.3.4 Palladium-Catalyzed Etherification and Lactonization Reactions Using TFP.

The tri-2-furylphosphine ligand has recently been used in a number of palladium-catalyzed etherification and lactonization reactions. For example, Sinou and coworkers have studied the relationship between phosphine donor ability and regioselectivity of etherification using allyl carbonate 414 and phenol (415) (Scheme 2.67). The findings suggested that both steric and electronic effects govern which end of the π-allyl complex is attacked by the nucleophile. Specifically, ligands of low donicity were found increase the regioselectivity in favor of the unbranched product 416. Conversely, highly basic phosphines generally gave sluggish catalysts, which favored formation of the branched regioisomer 417. In a subsequent study, the same workers investigated an intramolecular etherification of allylic carbonate 418 for the preparation of cis- and trans-linalyl oxides 419 and 420, respectively (Scheme 2.67). While both PPh₃ and TFP derived catalysts smoothly furnished the desired cyclized products in good yield, the
diastereomeric ratio was found to be independent of phosphine basicity. Furthermore, it was determined that the double bond geometry of the starting diol had no effect on either the yield or diastereoselectivity of the reaction.

The palladium(0)-mediated lactonization of pentyloic acids has been investigated using the TFP derived catalyst system. Treatment of acid \(\text{421}\) and acetylenic bromide \(\text{422}\) with potassium \(t\)-butoxide in DMSO and a palladium catalyst was found to give lactone \(\text{423}\) in moderate to excellent yield\(^{173}\) (Scheme 2.68). The reaction proceeds by nucleophilic attack of the carboxylate anion onto the triple bond, which is presumably activated by the \(\sigma\)-ethynylpalladium complex, in an 5-exo-dig fashion. In this study, TFP was found to work remarkably well giving the desired cyclized product \(\text{423}\) in 90% isolated yield. Similarly, treatment of 3-pentyloic acid (424) and iodobenzene (50) with \(t\)-BuOK in DMSO and a palladium catalyst afforded lactone \(\text{425}\) in moderate yield\(^{174}\) (Scheme 2.68). In this case, cyclization proceeds in a 5-endo-dig manner giving initially the 3\(H\)-furan-2-one product. Subsequent base catalyzed isomerization of the double bond furnishes enone \(\text{425}\). For this process, TFP was found to be the ligand of choice and consistently outperformed \(\text{Ph}_3\text{As}\) in terms of both yield and rate of reaction.
2.2.3.5 Palladium-Catalyzed Cross-Coupling of Acetylenes.

The palladium-catalyzed Sonogashira coupling\(^\text{175}\) of terminal acetylenes with organohalides is a powerful method for the preparation of conjugated alkynes. Schreiber and coworkers\(^\text{176}\) have used TFP derived catalysts to cross-couple a variety of alkynes for the preparation of enetetracynes (Scheme 2.69). Treatment of thexyldimethylsilyl acetylene 426 and alkynyl iodide
with a Pd₂(dba)₃/TFP catalyst in benzene afforded the desired product 428 in 77% isolated yield. Schreiber and coworkers have employed these optimized conditions for a variety of alkyne-alkyne coupling reactions obtaining the desired products in 59-77% yield.¹⁷⁶

The cross-coupling of alkynes with haloalkynes has also been studied by Vasella and coworkers.¹⁷⁷ Treatment of THP protected propargylic alcohol 429 and iodo alkyne 430 with a PPh₃ based catalyst system in DMSO at room temperature afforded the desired heterocoupled product 431 in 63% yield along with the corresponding homocoupled products 432 and 433 in 21% and 14% yields, respectively (Scheme 2.70). However, use the TFP ligand led to the highest rate of coupling and the best selectivity for the desired heterocoupled product 431. Vasella and coworkers¹⁷⁸ have successfully employed the TFP modified catalyst system for the synthesis of a wide variety of bis-acetylene linked carbohydrate compounds 436 starting with suitably protected haloalkynes 434 and terminal acetylenes 435 (Scheme 2.71).

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**Scheme 2.70**

![Scheme 2.70](image.png)

<table>
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<th>Ligand</th>
<th>Yield (%)</th>
<th>Ratio (%)</th>
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<tr>
<td>TFP</td>
<td>88</td>
<td>65 19 4</td>
</tr>
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**Scheme 2.71**

![Scheme 2.71](image.png)

Conditions: a) PdCl₂(PhCN)₂, TFP, DIPEA, DMSO, 50 °C. b)Pd₂(dba)₃, TFP, Cul, DMSO, rt.
The attempted Sonogashira coupling of alkyne 437 and α-bromo enone 438 has been reported by Buszek and Jeong\textsuperscript{179} (Scheme 2.72). Using catalytic Pd(PPh\textsubscript{3})\textsubscript{4} failed to furnish the desired cross-coupled product so recourse was taken in a stoichiometric quantity of palladium. Under these conditions, the major product was determined to be phenyl derivative 439 resulting from an aryl migration from the phosphine ligand. Employing a catalytic quantity of Pd(PPh\textsubscript{3})\textsubscript{4} in conjunction with three equivalents of added triphenylphosphine resulted in a 95% yield of 439. Similarly, adding an excess of TFP to the mixture gave the corresponding furyl adduct in 95% yield contaminated with a small amount of the phenyl derivative 439. In contrast, tribenzylphosphine, tributylphosphine and tricyclohexylphosphine did not result in the transfer of benzyl, butyl or cyclohexyl groups, respectively.\textsuperscript{179}

The palladium-catalyzed oxidative dimerization of terminal acetylene 440 using different catalyst ligands has been studied by Lindsey and coworkers\textsuperscript{180} (Scheme 2.73). Employing a Pd\textsubscript{2}(dba)\textsubscript{3}/PPh\textsubscript{3} catalyst system in toluene at 50 °C afforded porphyrin dimer 441 in 37% yield
along with a significant amount of higher molecular weight material (HMWM). However, utilization of a TFP derived catalyst was found to increase the yield and purity of the desired diyne 441. Although AsPh$_3$ catalysts have worked well in similar coupling reactions, use of this catalyst with porphyrin acetylene 440 furnished dimer 441 in 56% isolated yield with a 0.80:1 HMWM:product ratio.

2.2.3.6 TFP Modified Palladium(0)-Catalyzed Cross-Coupling of Organoboron Compounds: The Suzuki Reaction and Related Processes.

The effect of ligand donicity on ambient temperature Suzuki coupling has recently been studied by Anderson and coworkers$^{181}$ (Scheme 2.74). Treatment of mesitylboronic acid (442) and iodobenzene (50) with tetrakis(triphenylphosphine)palladium(0) in DMA at room temperature using 10% aqueous TIOH as the base furnished biaryl 443 in near quantitative yield. Utilization of TFP and AsPh$_3$ as ligands, under otherwise identical conditions, resulted in diminished yields of the desired biaryl 443. Moreover, these workers noted that the rate of Suzuki cross-coupling between mesityl boronic acid (442) and iodobenzene (50) did not increase upon using ligands of reduced donor ability.

The Suzuki cross-coupling of phenylboronic acid (16) and iodobenzene (50) in supercritical carbon dioxide has been reported by Rayner and coworkers$^{151}$ (Scheme 2.75). Using a fluorinated palladium source in conjunction with the TFP ligand gave biphenyl (51) in 79% isolated yield after a 24 hour reaction period. Again, the favorable solubility of TFP in scCO$_2$ proved to be highly advantageous making this the ligand of choice for the described conditions.
Palladium-catalyzed homocoupling of arylboronic acids to give symmetrical biaryls has recently been studied by Moreno-Mañas and coworkers\textsuperscript{182} (Scheme 2.76). In this study, treatment of 4-(trifluoromethyl)phenylboronic acid (444) with a Pd\textsubscript{2}(dba)\textsubscript{3}/PPh\textsubscript{3} catalyst system under an ambient atmosphere furnished biaryl 445 in 40\% yield after a 73 hour reaction time. Alternatively, employment of a TFP derived catalyst system was found to accelerate the reaction giving the desired homocoupled product 445 in 93\% yield after a 15 hour reaction period.

### 2.2.3.7 Palladium-Catalyzed Amination, Phosphonylation, and Sulfenylation of Aryl Halides.

Early efforts by Buchwald and coworkers\textsuperscript{183} to develop a palladium-catalyzed amination of aryl bromides resulted in conditions which require a stochiometric equivalent of (N,N-diethylamino)tributyltin (447) (Scheme 2.77). Treatment of benzylamine 446 with aminostannane 447 and a Pd(PPh\textsubscript{3})\textsubscript{4} catalyst at 80 °C furnished the desired dihydroindole 448 in 75\% isolated yield. Utilization of a Pd\textsubscript{2}(dba)\textsubscript{3}•CHCl\textsubscript{3}/TFP catalyst system was slightly less efficient providing the desired heterocycle in 67\% yield. Under main group-free conditions,\textsuperscript{183a}
optimal results for the intramolecular amidation of bromide 449 or 450 were achieved with Pd$_2$(dba)$_3$/TFP as the catalyst and CsCO$_3$ as the base. Hence the desired cyclized products 451 and 452 were obtained in 99% and 87% isolated yields, respectively. Employment of PPh$_3$ based catalysts either required longer reaction times or provided lower yields.

Palladium-catalyzed phase-transfer phosphonylation of aryl-iodides and bromides using the TFP ligand has recently been reported by Beletskaya and coworkers\(^{184}\) (Scheme 2.78). In this study, both the PPh$_3$ and TFP derived catalyst systems provided the desired arylphosphonates in high yield although significantly reduced reaction times were observed using latter catalyst.
These workers have shown that dimethyl, diethyl, and diisopropyl phosphonates may be cross-coupled with a variety of aryl halides, bearing electron donating or withdrawing functionalities, in high yield using the TFP catalyst system.

In an effort to prepare unnatural amino acid derivatives, Tomich and coworkers\textsuperscript{185} have sought to cross-couple \textit{N}-protected \textit{p}-iodophenylalanine 456 with \textit{t}-butylthiol (457) under palladium catalysis (Scheme 2.79). Although the dppf ligand furnished the desired thiophenylalanine derivative 458 in near quantitative yield, utilization of PPh\textsubscript{3} or TFP for the coupling resulted in poor yields. In the latter case, only a trace of the desired cross-coupled product was detected by HPLC analysis. Hence, ligands of low donicity appear to have an adverse effect on the present cross-coupling reaction.

\subsection{2.2.3.8 \textbf{Palladium-Catalyzed Silylstannylation Using TFP.}}

Kocienski and coworkers\textsuperscript{186} have reported the use of TFP in the palladium-catalyzed silylstannylation of \textit{1}-phenylthio-\textit{1}-alkynes (Scheme 2.80). Treatment of a variety of thioalkynes
and Me₃SiSnMe₃ (460) in THF at room temperature for 2 hours with a Pd₂(dba)₃/TFP catalyst system furnished the desired olefins 461 in good yields. Using a Pd(PPh₃)₄ catalyst required heating and extended reaction times to provide the same set of silylstannanes 461 in only 11-58% yield. In either case, the regioselectivity of the reaction highly favored formation of the desired α-stannylated isomer 461.

2.2.4 Nickel-Catalyzed Reactions Using Tri-2-furylphosphine.

Shirakawa and coworkers¹⁸⁷ have recently reported the nickel-catalyzed cross-coupling of aryl halides and sulfonates with organostannanes. Although this process is analogous to the palladium catalyzed Stille reaction, the TFP catalyst system has proven to be less effective than the corresponding PPh₃ catalyst for the cross-coupling of 2-chloronaphthalene (462) and tributylvinyltin (181) (Scheme 2.81). Unfortunately, in these studies usage of the TFP catalyst has been limited to aryl chloride precursors and it is therefore unclear whether Farina’s observations regarding TFP in the Stille process⁵² apply to the present cross-coupling reaction.

Trost and coworkers¹⁸⁸ have studied the nickel-catalyzed coupling of allylamines with boronic acids using a variety of phosphine ligands. Treatment of allylamine 464 and phenylboronic acid (16) with a [Ni(cod)₂]/PPh₃ catalyst system in refluxing benzene furnished a mixture of coupled products 465 and 466 in 72% yield (Scheme 2.82). Under otherwise identical conditions, the corresponding TFP catalyst provided compounds 465 and 466 in the same relative ratio but in reduced yield. Although the isomeric ratio of products remained
constant using the PPh$_3$ and TFP derived catalysts, Trost and coworkers have shown that strongly donating and sterically demanding ligands such as triisopropylphosphine tend to favor bond formation at the less substituted $\gamma$-position of allylamine 464.

Nickel-catalyzed asymmetric addition of Grignard reagents to unsaturated cyclic acetals has recently been studied by Hoveyda and coworkers$^{189}$ (Scheme 2.83). Interestingly, treatment of dimethyl acetal 467 and $n$-BuMgCl with 5 mol% of nickel complex 468 in THF at room temperature afforded ketone 469 in 10% ee (80% yield) after an acidic workup. However, using a 10 mol% PPh$_3$ additive, under otherwise identical conditions, provided the desired cross-coupled product 469 in 82% ee with 61% conversion. The reasons for the observed enhancement in stereoselectivity upon the addition of excess achiral phosphine have not yet been established although it has been shown that PPh$_3$ affords optimal results. Treatment of acetal 467 and $n$-BuMgCl with 5 mol% catalyst 468 and 5 mol% TFP gave product 469 in 40 % ee (60% conversion). Although highly basic phosphines generally increased the yield of the desired product, these ligands also proved to be detrimental to enantioselectivity.
2.2.5 Rhodium-Catalyzed Conjugate Addition Using the TFP Ligand.

The rhodium(I)-catalyzed conjugate addition of phenyl boronic acid (16) with methyl vinyl ketone (470) using various phosphine ligands has been reported by Miyaura and coworkers\textsuperscript{190} (Scheme 2.84). Heating a mixture of MVK (470) and boronic acid 16 in aqueous DMF solution with a $[\text{Rh(acac}(CO)_{2}]$/PPh$_3$ catalyst system furnished the desired product 471 in 83\% yield. Under otherwise identical conditions, utilization of the TFP ligand afforded ketone 471 in 94 \% yield. Although the TFP ligand performs well in this process, optimal conditions for the desired conjugate addition have been shown to include the use of 7-membered chelate ligands such as bis(diphenylphosphino)butane (dpdb).\textsuperscript{190}

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh$_3$</td>
<td>83</td>
</tr>
<tr>
<td>TFP</td>
<td>94</td>
</tr>
</tbody>
</table>

2.3 Other 2-Furyl Phosphines in Metal-Mediated Organic Synthesis.

Although there are numerous examples of 2-furyl phosphine containing structures reported in the literature, very few of these materials have been employed as ligands in metal-catalyzed organic reactions. The sections which follow comprehensively detail the use of novel 2-furyl phosphine ligands in synthetic processes.\textsuperscript{191,192} Where possible, the results obtained with these ligands are compared to those attained with structurally similar phosphine analogues.
2.3.1 Reactions Using $2,2'$-Bis[1-(di-2-furylphosphino)ethyl]-1,1'-biferrocene.

A series of trans-chelating chiral phosphine ligands, abbreviated as TRAPs, containing a biferrocene core structure have been introduced by Ito and coworkers$^{193}$ (Figure 2.3). These ligands have been shown to be effective in a variety of rhodium(I)-catalyzed asymmetric reactions including hydrogenation of prochiral olefins, Michael addition to $\alpha$-cyanocarboxylates, and hydrosilylation of ketones. The 2-furyl substituted TRAP $472b$ (FuTRAP)$^{194}$ has recently been employed in the asymmetric hydrogenation of various $\alpha,\beta$-unsaturated esters. For example, heating a solution of ester $473$ under a hydrogen atmosphere in the presence of a Rh(I)-PhTRAP catalyst furnished the desired product $474$ in 90% ee having the $S$-configuration$^{195}$ (Scheme 2.85). Although the corresponding FuTRAP catalyst also provided product $474$ in high yield, a significant reduction in enantioselectivity was observed. Ito and coworkers have obtained similar results in the rhodium(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate ($475$)$^{196}$ (Scheme 2.86). Using a $[\text{Rh(cod)}]_2\text{BF}_4$/PhTRAP catalyst under an atmosphere of $\text{H}_2$ provided (S)-dimethyl 2-methylsuccinate ($476$) in 26% ee while the FuTRAP based catalyst only resulted in a 7% enantiomeric excess. Ligands of higher donicity, such as ethyl analogue $472d$,
proved to be highly efficient catalysts giving the desired diester 476 in 96% ee. Interestingly, hydrogenation of dimethyl 2-isopropylidenedisuccinate 477 with various TRAP ligands resulted in similar findings, however, the sense of enantioselection was opposite to that obtained with olefin 475. In either case, incorporation of the electron withdrawing 2-furyl moiety into the TRAP ligand clearly results in diminished stereoselectivity.

Ito and coworkers\textsuperscript{197} have also applied the FuTRAP ligand 472b in the palladium-catalyzed enantioselective cycloisomerization of 1,6 enynes (Scheme 2.87). Treatment of sulfonamide 479

$$\text{PhSO}_2 \backslash \text{N} \backslash \text{TMS}$$

479

$$\text{Ph}_2 \text{N} \backslash \text{TMS}$$

480

<table>
<thead>
<tr>
<th>TRAP Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,S)-(R,R)-472c</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>(S,S)-(R,R)-PhTRAP (472a)</td>
<td>77</td>
<td>36</td>
</tr>
<tr>
<td>(S,S)-(R,R)-FuTRAP (472b)</td>
<td>76</td>
<td>4</td>
</tr>
</tbody>
</table>
with a Pd$_2$(dba)$_3$/PhTRAP catalyst system furnished cyclopentane derivative 480 in 77% yield and 36% ee. The corresponding FuTRAP catalyst afforded nearly racemic product in comparable yield. However, utilization of the p-CF$_3$C$_6$H$_4$ derived TRAP ligand 472e provided the desired cyclized product 480 in 76% yield and 48% ee. Further improvement of the enantioselectivity using ligand 472e was achieved (76% ee) by performing the reaction at 0 °C albeit at the expense of product yield (24%).

### 2.3.2 Reactions Using 1,1'-Bis(di-2-furylphosphino)ferrocene.

Steric and electronic effects in the palladium-catalyzed amination of aryl bromides have recently been studied in considerable detail by Hartwig and coworkers. Using dppf ligand (482), aryl bromide 481 and n-butylamine reacted to give the desired secondary amine 484 in 52% yield along with 21.6% diaryl amine 485 and 4.4% n-butylbenzene (486) (Scheme 2.88). Changing the catalyst ligand to bis(di-2-furylphosphino)ferrocene (483) resulted in an increased selectivity for the desired monoarylated amine 484 albeit with a diminished overall yield. In addition, the amount of protodehalogenated material 486 increased to 16% upon employing the furyl phosphine ligand. While the proportion of this byproduct was found to increase, Hartwig has shown in a related study that electron poor phosphines such as 483 generally give less byproduct resulting from phosphorus to palladium aryl migration.
2.3.3 Reactions Using 1'-[2-(Di-2-furylphosphino)-1-naphthyl]isoquinoline as Ligand.

The rhodium-catalyzed asymmetric hydroboration/oxidation of various substituted styrenes has recently been investigated by Brown and coworkers using furyl phosphine catalyst 489 (Scheme 2.89). A series of five styrenes 487 bearing electron donating groups (EDG) smoothly provided the desired secondary alcohols 490 in high yields (75-82%) and enantioselectivities (86-94%) with phenyl catalyst 488. Employment of the furyl catalyst 489 on the same series of starting materials 487 generally led to slightly lower product yields and enantioselectivities. However, the furyl phosphine catalyst 489 provided superior results, in terms of both yield and stereoselectivity, to catalyst 488 in the hydroboration/oxidation of electron poor styrenes 491. Based on these results, Brown and coworkers have postulated that the smaller molar volume of the P(Fu)₂ group relative to PPh₂ may be responsible for the diminished ee's in the electron rich
series. Moreover, these workers have suggested, based on models of olefin complexation to the metal center, that a bulkier ligand with the electronic properties of the furyl moiety should provide the best results.\textsuperscript{199}

2.3.4 Reactions Using Biphenyl Derived Furyl Phosphines.

The ruthenium-catalyzed asymmetric hydrogenation of acrylic acid derivative \textsuperscript{493} has recently been reported by Scalone and coworkers\textsuperscript{200} using a variety of bidentate phosphine ligands (Scheme 2.90). The desired product \textsuperscript{496}, a key building block for the calcium antagonist mibefradil, was obtained in 88\% ee with the S-configuration using the (R)-BIPHEMP ligand (\textsuperscript{494}). Alternatively, utilization of furyl ligand \textsuperscript{495}\textsuperscript{201} furnished acid \textsuperscript{496} in 90\% ee. Optimal results for this hydrogenation reaction included using chiral bis(diphenylphosphino)ferrocene derived catalysts whereby compound \textsuperscript{496} could be obtained in >99\% conversion and 98\% optical purity.\textsuperscript{200}

Genêt and coworkers\textsuperscript{202} have reported using furyl phosphine ligand \textsuperscript{499}\textsuperscript{201} in the ruthenium-catalyzed asymmetric hydrogenation of phenylthio ketone \textsuperscript{497} (Scheme 2.91). Treatment of a methanolic solution of compound \textsuperscript{497} under an atmosphere of \textsuperscript{H}_{2} (30 bar) at room temperature for 24 hours with a (R)-MeOBIPHEP (\textsuperscript{498}) derived catalyst furnished the desired product \textsuperscript{500} in 90\% ee having the \textit{R}-configuration. Using the analogous 2-furyl ligand \textsuperscript{499} under conditions of higher pressure and longer reaction time provided the desired alcohol \textsuperscript{500} in comparable enantioselectivity (88\% ee). Superior results have been obtained using furyl catalyst \textsuperscript{499} for the
ruthenium-catalyzed asymmetric hydrogenation of dihydrogeranylacetone (501) \(^{203}\) (Scheme 2.92). Treatment of ketone 501 with a MeOBIPHEP (498) derived catalyst at room temperature under a \(H_2\) atmosphere (35 bar) furnished a 97:3 mixture of compounds 502 (77% ee) and 503, respectively. Employment of the corresponding furyl phosphine catalyst resulted in a significant enantioselectivity enhancement with the desired product 502 being isolated in 91% optical purity. Similar results have been obtained for a variety of other terpenoid starting materials.\(^{203}\)

2.4 Conclusions.

Although tri-2-furylphosphine (TFP) is similar in size to triphenylphosphine, the electronic properties of TFP relative to PPh3 are very different. The former phosphine is substantially less Lewis basic and is therefore a poorer \(\sigma\)-donor ligand in transition metal-mediated organic reactions. Pioneering work by Farina has shown the use of TFP derived palladium catalysts to
be highly advantageous in the Stille cross-coupling reaction with significant rate accelerations being observed over traditional PPh₃ based catalysts. These findings have led numerous workers to employ TFP derived catalysts in a wide variety of Stille cross-coupling reactions for the preparation of small molecules, complex natural products, and polymers. In many cases, Stille coupling with the TFP ligand allows for milder reaction conditions and hence the attenuation of many unwanted side reactions.

The superior results obtained with TFP in the Stille cross-coupling reaction have prompted many researchers to investigate the effects of using this ligand in other metal-catalyzed processes. In many cases, clear advantages to using TFP have been identified while in other cases this ligand performs poorly when compared to bulky or electron rich phosphines. Based on the investigations summarized herein, several research groups have sought to develop novel phosphine ligands that incorporate the 2-furyl moiety. While these efforts are still in their infancy, some promising results have been obtained and further research should prove to be very interesting.

2.5 Project Objectives.

As illustrated in the above review, the use of phosphines bearing the 2-furyl moiety can be advantageous in some transition metal-catalyzed processes and detrimental to others. In 1995, at the onset of this project, the tri-2-furyl phosphine ligand had been well established as an exceptional ligand for the Stille cross-coupling reaction and subsequently applied toward a variety of other processes with mixed results. While it was well established that 2-furyl phosphines act as poorer σ-donors than the corresponding phenyl phosphines, the relationship between ligand donicity and reaction efficiency had not been fully established for most processes. Moreover, even less was known about how 2-furyl phosphine ligands might effect the enantioselectivity of various asymmetric reactions. Of particular interest to the Keay laboratory was how an axially stereogenic 2-furyl phosphine analogue of BINAP would affect the asymmetric polyene cyclization and intermolecular Heck reaction. Hence a project was initiated to design and synthesize a bidentate 2-furyl phosphine ligand for asymmetric catalysis. The synthetic approach would have to be high yielding and start with relatively inexpensive starting
materials. Ideally, such a synthesis would be amenable to large scale preparation and provide the desired material in high purity with as few synthetic operations as possible. Moreover, the ligand must be obtainable in optically pure form and be configurationally stable at elevated temperatures (<150 °C). With such a phosphine in hand, studies of various asymmetric processes could be conducted to gain an understanding of how ligand donicity affects enantioselectivity. Clearly, structural changes to the BINAP ligand would be required to incorporate a 2-furyl moiety and hence observed differences in ligand reactivity relative to BINAP may be somewhat attributable to structural modifications rather than solely to electronic effects. For this reason, the ligand design must strive to mimic key structural characteristics of the BINAP ligand, such as bite angle and chiral pocket rigidity, as closely as possible. Chapter 3 discusses the structural design process and development of a highly efficient synthetic route to the 2,2'-bis(diphenylphosphino)-3,3'-binaphtho[6]furan (BINAPFu) ligand. Optical resolution of BINAPFu and assignment of the absolute stereochemistry are presented in Chapter 4. Applications of the BINAPFu ligand in asymmetric synthesis, including the ruthenium-catalyzed hydrogenations of α- and β-ketoesters as well as the palladium-catalyzed Heck reactions, are examined in Chapter 5.

3.1 Introduction.

Since Noyori's introduction of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as chiral ligand for asymmetric catalysis, numerous workers have shown that remarkably high degrees of enantioselectivity can be obtained using this phosphine in a wide variety of transition metal-mediated organic reactions. Based on the superior results often realized using BINAP in asymmetric transformations, coupled with the recent interest in 2-furyl phosphine ligands, a project was undertaken to develop an axially stereogenic diphosphine ligand which incorporates the 2-furyl group. At the onset of this endeavor, a literature search revealed that no such structure had ever been reported. Moreover, it was clear that very little was known about how phosphine σ-donor ability affected the course of enantioselective reactions. However, many workers have now sought to develop chiral 2-furyl phosphine ligands for asymmetric synthesis and several reports of asymmetric reactions using these ligands have recently been disclosed (vide supra). These investigations have been prompted, in part, by recent evidence to suggest that less electron-rich ligands are or should be advantageous in some metal-mediated organic processes. For example, Shibasaki and coworkers have recently developed 2,2'-bis(diphenylarsino)-1,1'-binaphthyl (506) (BINAs) and shown this poorly donating ligand to be more effective than BINAP (505) for an intramolecular asymmetric Heck reaction (Scheme 3.1). In addition, Amatore and coworkers have studied the oxidative addition of iodobenzene with in situ generated palladium(0) complexes of triphenylphosphine and TFP showing that in 

![Scheme 3.1](image-url)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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</thead>
<tbody>
<tr>
<td>(R)-BINAP</td>
<td>55</td>
<td>32</td>
</tr>
<tr>
<td>(R)-BINAs</td>
<td>90</td>
<td>82</td>
</tr>
</tbody>
</table>
DMF, \( \{\text{Pd(dba)}_2 + n\text{TFP}\} \) is always more reactive than \( \{\text{Pd(dba)}_2 + n\text{PPh}_3\} \) for \( n \geq 2 \). These reports, in conjunction with Keay's interests in the asymmetric polyene cyclization, led to the development of two novel 3,3'-'bifuryl derived diphosphine analogues of BINAP (Figure 3.1). It was envisioned that the reduced \( \sigma \)-donor ability of BIBENFu (508) and BINAPFu (509) relative to BINAP (505) may allow for more facile oxidative addition in the palladium-catalyzed Heck reaction when using aryl iodide precursors. Since oxidative insertion is often thought to be the rate determining step for many Heck reactions, using a ligand of reduced donicity should result in an overall rate enhancement for the process. Moreover, increasing the rate of oxidative addition may allow the reaction to be performed at lower temperatures thereby providing better kinetic control and increased degrees of enantioselection.

The sections which follow describe the design aspects and syntheses of the BIBENFu (508) and BINAPFu (509) ligands. Unfortunately, the former phosphine 508 proved not to be configurationally stable at ambient temperature and as a result, its synthesis led to the incorporation of the binaphtho[b]furan framework into the ligand design. Optical resolution of the BINAPFu ligand and assignment of the biaryl axis absolute stereochemistry are presented in Chapter 4. Applications of the BINAPFu ligand in ruthenium-catalyzed hydrogenations and palladium-catalyzed Heck reactions are described in Chapter 5.

### 3.2 The Design of Novel Axially Stereogenic 2-Furyl Phosphine Ligands.

The axially stereogenic diphosphine ligand BINAP, originally developed by Noyori and coworkers, has become one of the most useful chiral ligands in synthetic organic chemistry. It has been postulated that the high degree of enantioselection often observed when using BINAP is
a result of the rigid chiral pocket that is formed when this ligand binds to a metal center. For example, the solid state structure of [(R)-BINAP]PdCl$_2$ (510) obtained by Hayashi, shows a highly skewed seven-membered metallacycle whereby two of the phosphine phenyl groups (A and B) π-stack with the binaphthyl framework while the other two phenyl groups (C and D) protrude toward the chloride ligands (Figure 3.2). This “quasi-graphitic” interaction between the binaphthalene framework and the phosphine aryl groups (A and B), which has been observed in a variety of BINAP structures, is thought to be required for achieving efficient asymmetric induction with this ligand.

In order to develop a C$_2$-symmetric furyl phosphine analogue of BINAP, it was conceived that a prudent design would retain the bis(diphenylphosphino) moieties and incorporate the furyl functionality into the biaryl framework. In this way, it was felt that the electronic properties of the phosphine ligand could be altered with minimal perturbation of the chiral pocket structure. Since previous work in the Keay laboratory with 3,3′-bifuran systems had been unsuccessful, it was decided that perhaps a 3,3′-bibenzo[b]furan structure would constitute a suitable biaryl framework. Unfortunately, it could not be ascertained from computer aided molecular modeling of BIBENFu (508), whether or not the bibenzo[b]furan system would be configurationally stable over the desired temperature range (<150 °C).
A synthesis of BIBENFu (508) was undertaken starting with commercially available and relatively inexpensive 2,3-benzofuran (511). Although it has been reported that treatment of compound 511 with 1 equivalent of Br₂ followed by an excess of t-BuOK in t-BuOH gives exclusively the desired 3-bromo isomer 512, such conditions were found to afford a 9:1 mixture of regioisomers 512 and 513, respectively (Scheme 3.2). The ratio of bromobenzo[b]furans 512 and 513 was determined by integration of the singlets at δ 7.57 ppm (H-2 for 512) and δ 6.73 ppm (H-3 for 513). This mixture, which was inseparable by distillation or chromatography, was subjected to modified in situ Suzuki conditions to furnish the desired 3,3'-bibenzo[b]furan (514) in 74% yield along with a small amount of the 2,3'-isomer 515. Compound 514 gave a satisfactory elemental analysis and the low resolution mass spectrum was consistent with the structure. The symmetrical nature of the product was clearly evident from the $^{13}$C-NMR spectrum, which only showed eight unique carbon signals. In contrast, the $^{13}$C-NMR spectrum of the unsymmetrical 2,3'-isomer 515 had sixteen different carbon signals. Although the isomers could not be separated by column chromatography, the desired biaryl 514 could be obtained in high purity after crystallization from a CH₂Cl₂/hexanes mixture. Treatment of bisbenzo[b]furan 514 with 3 equivalents of n-BuLi in diethyl ether smoothly afforded the

**Scheme 3.2**

Conditions: (a) Br₂, CCl₄. (b) t-BuOK, t-BuOH, 81% 9:1 mixture of 512 and 513. (c) n-BuLi, Et₂O, -78 °C then B(OMe)₃. (d) Pd(PPh₃)₄, Na₂CO₃, toluene, EtOH, H₂O, reflux, 74% 514; 6% 515.
desired diliitho species after 1 hour at 0 °C, as evidenced by deuterium quenching studies. Treatment of the dianion thus obtained with freshly distilled diphenylphosphinic chloride provided the desired phosphine oxide 516 in 88% isolated yield (Scheme 3.3). Trichlorosilane reduction\(^{216}\) of BIBENFu oxide 516 in refluxing xylene smoothly furnished the desired diphosphine 508 in quantitative yield. \(^{31}\)P-NMR analysis of the BIBENFu ligand in \(\text{CDCl}_3\) solution showed a sharp singlet at -31.1 ppm, relative to \(\text{H}_3\text{PO}_4\) in \(\text{D}_2\text{O}\), which was completely free from contamination by the corresponding phosphine oxide (+16.7 ppm). Moreover, unlike BINAP,\(^{217}\) no evidence of air oxidation was observed upon extended exposure of BIBENFu to an ambient atmosphere.

**Scheme 3.3**

\[
\text{Scheme 3.3}
\]

514 \(\rightarrow\) a,b \(\rightarrow\) 516 \(\rightarrow\) c \(\rightarrow\) 508, (+/-)-BIBENFu

Conditions: (a) 3.0 equiv. \(n\)-BuLi, Et\(_2\)O, -78 °C. (b) 3.0 equiv. PPh\(_3\)Cl, 88%. (c) 20 equiv. SiCl\(_3\)H, 24 equiv. Et\(_3\)N, xylene, 165 °C, 5 h, >95%.

With racemic ligand 508 and phosphine oxide 516 in hand, attention was now focused on the separation of the two optical isomers. Following the reported literature resolution for the bisphosphine oxide of BINAP (BINAPO),\(^{218}\) compound 516 was heated with an equimolar amount of (1S)-(+)10-camphorsulfonic acid (517) in a mixture of acetic acid and ethyl acetate (Scheme 3.4). Unfortunately, subsequent cooling of the resulting mixture failed to produce the desired hydrogen-bonded complex 518 in crystalline form. Removal of the volatile materials under high vacuum and \(^1\)H-NMR analysis of the residue thus obtained showed only unreacted phosphine oxide 516 and CSA (517). Moreover, performing the procedure under conditions of
higher concentration only resulted in the precipitation of unreacted resolving agent. These observations led to the conclusion that the desired complex 518 was not being formed under the present reaction conditions. Prolonged reflux periods and changes to the solvent composition were met with similar results.

Heating oxide 516 with 1 equivalent of (-)-DBTA (519), another known resolving agent for (±)-BINAP, in a mixture of CHCl₃ and EtOAc gave a clear solution which upon cooling afforded a white precipitate. ¹H-NMR analysis of the solid material thus obtained showed only unreacted resolving agent. Changing the concentration of reactants, solvent composition, or reaction time led, in all cases, to the isolation of unreacted starting materials (Table 3.1).

**Table 3.1 Attempted Optical Resolution of Phosphine Oxide 516 Using (-)-DBTA.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. 516</th>
<th>Equiv. 519</th>
<th>Solvents</th>
<th>Concentration (M)ᵃ</th>
<th>Reflux Time (h)</th>
<th>Resultᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CHCl₃/EtOAc (1:1)</td>
<td>0.044</td>
<td>0.5</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>CHCl₃/EtOAc (1:1)</td>
<td>0.085</td>
<td>1.0</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>CHCl₃/EtOAc (1:1)</td>
<td>0.038</td>
<td>4</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>CHCl₃/EtOAc (1:1)</td>
<td>0.038</td>
<td>48</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2</td>
<td>CHCl₃/EtOAc (1:1)</td>
<td>0.063</td>
<td>8</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>CHCl₃/EtOAc (9:1)</td>
<td>0.039</td>
<td>4</td>
<td>N.R.</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>CHCl₃/EtOAc (1:9)</td>
<td>0.044</td>
<td>4</td>
<td>N.R.</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1</td>
<td>CHCl₃/C₆H₆ (1:1)</td>
<td>0.054</td>
<td>6</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

(a) refers to the concentration of compound 516; (b) N.R.=no reaction.

In addition to the CSA and DBTA resolution techniques, the separation of optical isomers by chiral phase HPLC methods was also investigated. Analyzing samples of phosphine oxide 516 or BIBENFu (508) with either a Chiralcel® OJ or OB column, under a wide variety of flow rates and solvent systems, gave single peak spectra at 254 nm UV-detection. Cooling the HPLC column in an ice bath during analysis only resulted in signal broadening. These observations, in
conjunction with the difficulties experienced with the CSA and DBTA resolution procedures, indicated that the BIBENFu chiral axis was probably not configurationally stable at ambient temperature. Subsequent to reaching this conclusion, an alternative synthesis of BIBENFu (508) was reported by Benincori and coworkers$^{219,220}$ along with two novel biheteroaryl phosphine ligands 526 and 532 (Scheme 3.5). Treatment of 2,3-benzofuran (511) with 2 equivalents of Br$_2$ in CHCl$_3$ in the presence of KOAc provided dibromide 521 in 60% yield. Regioselective debromination was achieved through halogen-metal exchange with n-BuLi at -70 °C giving the desired 3-bromobenzo[b]furan 512 in 86% yield. Subsequent oxidative coupling of the 3-lithio species using CuCl$_2$ gave biaryl 514 in 26% yield. Finally treatment of compound 514 with 2 equivalents of n-BuLi followed by reaction with diphenylphosphoric chloride or

![Scheme 3.5](image)

Conditions: (a) 2 equiv. Br$_2$, CHCl$_3$, KOAc. (b) 1 equiv. n-BuLi, -70 °C then H$_2$O. (c) 1 equiv. n-BuLi, THF, CuCl$_2$, 0 °C, 6 h. (d) 2 equiv n-BuLi, THF, TMEDA, -50 °C. (e) 2 equiv. PPh$_3$(O)Cl. (f) 2 equiv. PPh$_3$Cl. (g) 1 equiv. Br$_2$, CHCl$_3$, NaOAc. (h) H$_2$O$_2$, CH$_2$Cl$_2$, 0 °C. (i) SiCl$_3$, Et$_3$N, xylenes, 100 °C, 10 h.
chlorodiphenylphosphine provided phosphine oxide 516 or phosphine 508, respectively. Benincori and coworkers have also concluded that the BIBENFu ligand is not configurationally stable at room temperature. Although these workers have claimed in a patent to prepare the 4,4',6,6'-tetramethyl derivative of BIBENFu in optically pure form, usage of this ligand in a transition-metal catalyzed reaction has yet to be reported. Interestingly, the bis-benzothiophene ligand 526 (BITIANP) and its tetramethyl analogue 532 were both found to be configurationally stable at 100 °C in DMF solution. Moreover, Benincori et al. have employed optically pure BITIANP (526) and Me₄-BITIANP (532) ligands in the ruthenium(II)-catalyzed enantioselective hydrogenation of prochiral ketones and olefins. In addition, Tietze and coworkers have applied these benzothiophene ligands in asymmetric palladium-catalyzed Heck reactions. Recently, Benincori and coworkers have prepared two new atropisomeric 2-furyl phosphine ligands, 533 and 534, and claimed in a patent that they are superior ligands for enantioselective hydrogenation, hydroformylation, hydrosilylation, and hydrocyanation reactions (Figure 3.3). However, neither phosphine has been specifically reported in any transition-metal catalyzed process to date.

**Figure 3.3** Recently Patented Atropisomeric 2-Furyl Phosphine Ligands.

3.4 Synthesis of 2,2'-bis(diphenylphosphino)-3,3'-binaphtho[b]furan (BINAPFu).

3.4.1 *In Situ* Suzuki Coupling Approach.

In order to apply the modified *in situ* Suzuki biaryl synthesis toward the preparation of BINAPFu (509), a short and efficient synthesis of the required halide, 3-bromonaphtho[b]furan (535), needed to be developed (Scheme 3.6). It was conceived that this compound could be
obtained from the parent heterocycle 536 by addition of Br₂ followed by a regioselective elimination of HBr. Since this approach was successful for the preparation of 3-bromobenzo[b]furan (512) (vide supra), a synthesis of the required heterocycle 536 was conducted with minor modifications to an established literature procedure.²²² Hence heating 2-hydroxy-1-naphthaldehyde (537) and ethyl chloroacetate (538) in DMF with K₂CO₃ at 130 °C for 18 hours gave ester 539 in 89% yield (Scheme 3.7). Base saponification of compound 539 in aqueous methanol at 65 °C furnished acid 540 in quantitative yield. Subsequent copper-mediated decarboxylation in refluxing quinoline afforded the desired naphtho[b]furan (536) in 80% overall yield (3 steps) which displayed properties consistent with those reported in the literature.²²²

With naphtho[b]furan (536) in hand, attention was turned toward finding regioselective bromination conditions for the preparation of the desired 3-bromo isomer 535. Treatment of compound 536 with 1 equivalent of Br₂ in CCl₄ at ambient temperature followed by potassium t-butoxide in t-butanol afforded a 41:59 mixture of the desired halide 535 and the unwanted 2-bromo isomer 541 (Table 3.2, entry 1). The ratio of the isomeric bromides was determined by integration of the ¹H-NMR spectrum. By analogy to the bromobenzo[b]furan isomers (vide supra), the more deshielded singlet at δ 7.75 ppm was assigned to the α furan proton of 3-isomer
and the less deshielded singlet at $\delta$ 7.20 ppm was assigned to the $\beta$ furan proton of the undesired 2-isomer 541. Unfortunately, these two compounds were not separable by flash chromatography or reverse phase HPLC methods. Performing the reaction at 0 $^\circ$C resulted in a slight increase in the 2-bromoisomer 541 (entry 2) suggesting that this compound is kinetically favored. Changing the base from $t$-BuOK to potassium acetate resulted in the exclusive formation of the unwanted regioisomer 541 (entry 3). Interestingly, applying Benincori's bromination conditions to the present system resulted in the formation of dibromide 542 as the sole reaction product regardless of the base used (entries 4 & 5). Mass spectral analysis of compound 542 indicated the presence of two bromine atoms and $^1$H-NMR analysis clearly showed two singlets at $\delta$ 7.91 and 7.13 ppm.

Table 3.2 Bromination of naphtho[b]furan (536).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product Ratio$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>535</td>
</tr>
<tr>
<td>1</td>
<td>1) Br$_2$/CCl$_4$, rt 2) $t$-BuOK/$t$-BuOH</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>1) Br$_2$/CCl$_4$, 0 $^\circ$C 2) $t$-BuOK/$t$-BuOH</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>1) Br$_2$/CCl$_4$, rt 2) KOAc, 45 $^\circ$C</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1) 2 equiv. Br$_2$/CHCl$_3$ 2) KOAc, 50 $^\circ$C</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1) 2 equiv. Br$_2$/CHCl$_3$ 2) $t$-BuOK/$t$-BuOH</td>
<td>0</td>
</tr>
</tbody>
</table>

(a) As measured by $^1$H-NMR analysis.

Since the bromination of naphtho[b]furan (536) could not be controlled to give the required 3-bromoisomer selectively, recourse was sought in the free radical bromination of 2,3-dihydronaphtho[b]furan (543) (Scheme 3.8). It was conceived that under such conditions,
Scheme 3.8

Scheme 3.9

Bromination would occur in the benzylic position to give monobromide 544 and ultimately geminal dibromide 545. Subsequent elimination of HBr would then furnish the desired 3-bromonaphtho[b]furan (535) in a regioselective fashion. The required dihydrofuran starting material 543 was prepared in a two step synthetic sequence in 71% overall yield beginning with the parent heterocycle 536 (Scheme 3.9). Treatment of compound 536 with a molar equivalent of Br₂ in benzene furnished trans-dibromide 546 in 91% yield which was subsequently reduced with LiAlH₄ in refluxing THF to furnish the desired dihydronaphtho[b]furan 543. The ¹H-NMR spectrum was in close agreement to the literature spectrum of compound 543 prepared by an alternative route.²²³ Under a variety of conditions, subjection of compound 543 to NBS and benzoyl peroxide followed by treatment with base (t-BuOK or KOAc) furnished mixtures of 2-bromonaphtho[b]furan (541) and naphtho[b]furan (536). Using photochemical bromination conditions, complex mixtures of multiply halogenated products were obtained as evidenced by GC-MS analysis. Faced with these results, the synthetic route toward BINAPFu, which required 3-bromonaphtho[b]furan as a key intermediate, was abandoned.
3.4.2 *In Situ* Stille Coupling Approach.

A second generation approach toward the BINAPFu ligand was conceived whereby aryl tin could be cross-coupled with triflate under Stille conditions. The required stannane could potentially be generated *in situ* from triflate via palladium catalyzed coupling with hexamethylditin. Enol triflate could be prepared in a straightforward manner from 3-ketonaphtho[b]furan (549) by treatment with a suitable base and triflating agent. Although ketone had been previously prepared, established syntheses of this compound were characterized by low product yields (<35%) and difficult isolation procedures. It was therefore decided that a new, efficient synthesis of the required ketone would have to be developed. Since 1-acetyl-2-hydroxynaphthalene (550) was readily available, it was reasoned that α-chlorination of the ketone function followed by 5-*exo-trig* ring closure would provide an expedient route to the desired ketone (Scheme 3.11). Unfortunately, several chlorination reagents including sulfuryl chloride and hexachloro-2,4-cyclohexadienone failed to provide α-chloroketone in synthetically useful yields. Recourse was sought in the three step α-bromination of ketone via TMS enol ether (Scheme 3.11). Treatment of hydroxy-ketone with 1.1 equivalents of tert-butyldimethylsilyl chloride in CH₂Cl₂ and Et₃N furnished TBS ether in 89% yield. Although the TMS enol ether could be formed using LHMDS and TMSCl in an ethereal solvent, much more consistent results were obtained when ketone was treated with TMSOTf in a mixture of methylene chloride and triethylamine. Bromination of enol silyl ether with 1 equivalent of Br₂ in CCl₄ proceeded with loss of TMSBr to furnish α-bromo ketone in modest yield. Cleavage of the TBS ether under standard conditions occurred with concomitant ring closure to provide the desired naphthoketone in 61% overall yield. Although this four step synthetic sequence provided the desired ketone in moderate yield, without the need for
costly purification routines, the use of expensive protecting groups and reagents rendered this method somewhat infeasible for large scale preparation. In order to address these concerns, an alternative synthesis of compound 549 was conceived whereby readily available 2-naphthoxyacetic acid (555) could be subjected to Friedel-Crafts acylation conditions to provide the desired compound directly (Scheme 3.12). Treatment of acid 555 with Eaton’s reagent at ambient temperature for 18 h afforded the desired ketone 549 in 68% yield. Alternatively, preparation of the corresponding acyl chloride, under standard conditions, and subsequent
reaction with AlCl₃ gave naphthoketone 549 in 95% yield. Interestingly, in both cases, acylation occurred regiospecifically in the 1-position to give the desired product 549 with remarkable purity (Figure 3.4). This procedure, which does not require any purification steps, can easily be performed on a 50 gram scale to provide ketone 549 in excellent yield.

As expected, formation of enol triflate 548 was facile using 1 equivalent of LHMDS and N-phenyltrifluoromethanesulfonimide (PhNTf₂) in THF (Scheme 3.13). However, subjecting this compound to *in situ* Stille cross-coupling conditions was met with mixed results. Treatment of triflate 548 with 0.5 equivalents of hexamethylditin and a Pd(PPh₃)₄ catalyst in dioxane afforded the best results, providing the desired biaryl 556 in 63% isolated yield. The structure of 556 was confirmed by the following (*inter alia*) evidence. Low resolution mass spectral analysis exhibited a molecular ion of 334 m/z and ¹H-NMR analysis showed a singlet at δ 7.89 ppm for
the furan α-proton. Unfortunately, attempts to scale this reaction up resulted in the increased formation of unwanted byproducts including protodestannylated material 536, unreacted stannane 557, and the product of methyl transfer 558. In addition, these contaminants greatly complicated the purification of the desired biaryl by flash chromatography. Using different cross-coupling solvents, catalysts, and additives failed to attenuate the formation of unwanted byproducts and typically afforded biaryl 556 in less than 30% isolated yield. Faced with these results, in conjunction with the undesirable use of a highly toxic and expensive tin reagent, it was decided that an alternative method for forming the biaryl bond would have to be developed.

### 3.4.3 McMurry Coupling Approach.

The low-valent titanium homocoupling of aldehydes and ketones developed independently by Mukaiyama,\(^{229}\) Tyrlik,\(^{230}\) and McMurry\(^{231}\) has been applied in a wide variety of contexts to prepare symmetrical olefins.\(^{232}\) It was conceived that the BINAPFu biaryl bond could be constructed via a McMurry coupling of readily available ketone 549 followed by DDQ oxidation of the resultant olefin 559 (Scheme 3.14). Hence, reductive coupling of compound 549 with TiCl\(_4\) and zinc-copper couple\(^{233}\) in refluxing DME smoothly provided olefin 559 in good yield. Activated zinc dust\(^{234}\) worked equally as well for this purpose giving biaryl 556 in 78% isolated yield after DDQ oxidation.\(^{235}\) \(^{1}H\)-NMR analysis of compound 559 showed that the product had been formed essentially as a single isomer (>95%) which was assigned as the \(E\) configuration on the basis of steric arguments. Due to facile carbon-carbon double bond migration, olefin 559
could not be fully characterized. Upon oxidation with DDQ, the broad singlet ($\delta$ 5.25 ppm) integrating as four protons in the $^1$H-NMR spectrum of 559 was replaced by a sharp singlet ($\delta$ 7.87 ppm) representing the two furan $\alpha$-protons in biaryl 556.

Installation of the bis(diphenylphosphino) moieties was accomplished in an analogous manner to that previously described for the BIBENFu ligand. Lithiation of the biaryl scaffold 556 with 2.5 equivalents of $t$-BuLi and subsequent treatment of the resulting dianion with freshly distilled diphenylphosphinic chloride provided phosphine oxide 560 in 88% yield (Scheme 3.15). Reduction of the oxide 560 with trichlorosilane in a mixture of xylenes and triethylamine furnished racemic BINAPFu (509) in near quantitative yield as a white crystalline solid. Alternatively, lithiation of biaryl 556 followed by treatment of the resultant dianion with 2.0 equivalents of chlorodiphenylphosphine gave the desired diphosphine 509 directly in 91% yield. Analytically pure ligand may be readily obtained from the crude reaction mixture by simple recrystallization from a CH$_2$Cl$_2$/hexanes solvent system.
3.5 Structural Characterization of the BINAPFu Ligand.

As stated previously, a fundamental aspect of the ligand design required that the 2-furyl
groups be incorporated in such a way that the electronic properties of the phosphorus atoms may
be altered with as little perturbation of the chiral pocket structure as possible. In order to
investigate the success of the ligand design with respect to this requirement, the palladium(II)
chloride complex of BINAPFu was prepared (Scheme 3.16) and analyzed by single crystal

\[ \text{Scheme 3.16} \]

Conditions: (a) 1.0 equiv. \((\text{CH}_3\text{CN})_2\text{PdCl}_2\), \(\text{CH}_2\text{Cl}_2\), rt, 28 h, 93%.

\[ 509 \text{ (+/-)-BINAPFu} \]
\[ 561 \]

X-ray diffraction (Figure 3.5). Crystals of compound 561 were obtained by slow diffusion of
\(\text{Et}_2\text{O}\) into an acetone saturated solution of the complex under an argon atmosphere. Comparing
the projections of \([(\pm)-\text{BINAPFu}]\text{PdCl}_2\) (561) with Hayashi’s \([(R)-\text{BINAP}]\text{PdCl}_2\) structure, a
few structural differences are immediately apparent. Whereas two of the phenyl rings (A and B)
in the \([(R)-\text{BINAP}]\text{PdCl}_2\) complex \(\pi\)-stack with the binaphthalene framework, the corresponding
phenyl groups in compound 561 (A and B) do not show perpendicular relationships with the
binaphtho[b]furan system. Also noteworthy in the \([(\pm)-\text{BINAPFu}]\text{PdCl}_2\) structure is that the
square planar geometry about the palladium atom seems to be less distorted than in the
corresponding \((R)-\text{BINAP}\) complex 510. These observations suggest that the chiral pocket
formed in the \([\text{BINAPFu}]\text{PdCl}_2\) complex is somewhat less rigid than that obtained with the
BINAP ligand. However, several similarities are also observed upon comparing the
\([\text{BINAP}]\text{PdCl}_2\) and \([\text{BINAPFu}]\text{PdCl}_2\) structures. In both structures, two of the phenyl rings (C
and D) project outward toward the coordination sites occupied by the chloride ligands. The
\([\text{BINAP}]\text{PdCl}_2\) bite angle, defined by the P1-Pd-P2 vertex, of 92.7° compares well to that
measured for the \([\text{BINAPFu}]\text{PdCl}_2\) structure (93.4°). Values for the Pd-P and Pd-Cl bond
lengths compare quite favorably although slight differences can be seen due to the reduced electron donor ability of the BINAPFu ligand (Table 3.3). As expected, the mean Pd-P bond length is slightly longer in the [BINAPFu]PdCl₂ complex owing to the reduced σ-donor ability of the phosphorus atoms relative to BINAP. As a result, the Pd-Cl bond lengths are
Table 3.3 Comparison of Selected Bond Lengths in the [(R)-BINAP]PdCl$_2$ (510) and [(±)-BINAPFu]PdCl$_2$ (561) X-ray Structures.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Average Bond Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pd-P</td>
</tr>
<tr>
<td>[(R)-BINAP]PdCl$_2$ (510)</td>
<td>2.245</td>
</tr>
<tr>
<td>[(±)-BINAPFu]PdCl$_2$ (561)</td>
<td>2.264</td>
</tr>
</tbody>
</table>

slightly shorter in compound 561. Given the structural changes that had to be made in order to incorporate the 2-furyl moieties, it was felt that the structural homology between the two organometallic complexes was great enough to warrant further investigation with the BINAPFu ligand. The optical resolution of (±)-BINAPFu is presented in Chapter 4 and applications of this ligand in asymmetric synthesis are presented in Chapter 5.
4. Resolution of the (±)-BINAPFu Ligand.

4.1 Resolution on an Analytical Scale Using Chiral Stationary Phase HPLC.

Subsequent to developing a simple, highly efficient synthesis of racemic BINAPFu (509), attention was focused on finding a method for obtaining the two pure optical antipodes. In order to achieve this goal, it was first necessary to find a convenient method for determining the enantiopurity of diphosphine 509. Fortunately, (±)-BINAPFu could be readily separated by analytical HPLC using a Chiralcel® OJ column (Figure 4.1) indicating that the rotational barrier of the biaryl axis was of sufficient magnitude to impart configurational stability at room temperature. Although preparative HPLC columns employing similar chiral stationary phases are commercially available, optical resolution of the BINAPFu ligand in large quantities using this method was deemed to be infeasible. Based on manufacturer’s guidelines for column loading capacities, it would have taken over 200 injections to obtain a gram of each pure optical antipode making the HPLC method both time consuming and prohibitively expensive. However, the analytical protocol devised for the resolution of (±)-BINAPFu, shown in Figure 4.1, served as a convenient method for optical purity determination. Unfortunately, conditions for the analytical HPLC resolution of phosphine oxide 560 could not be devised using either a Chiralcel® OJ or OB column under a wide variety of eluent systems and flow rates.
4.2 Attempted Resolution of Phosphine Oxide 560 via Co-crystallization with Enantiopure Acids.

Although several methods for achieving optical resolution of stereogenic organophosphorus compounds are known, efforts were initially focused on procedures which have been applied to BINAP and related C2-symmetric diphosphines. Perhaps the most efficient and direct method for resolving BINAP involves the co-crystallization of the corresponding bis-phosphine oxide, BINAP, with relatively inexpensive enantiopure acids. This method, which relies on protonation of the weakly basic phosphoryl oxygen atoms, is typically performed by treating the racemic diphosphine with 0.5 molar equivalents of (-)-dibenzoyltartaric acid (DBTA, 519). In this manner, a 1:1 complex can be selectively formed between the resolving agent and a single enantiomer of the diphosphine, which is obtained in high purity by crystallization. The material remaining in the mother liquor, now highly enriched in the opposite enantiomer, can be obtained in optically pure form via treatment with (+)-DBTA.

Heating (±)-phosphine oxide 560 with an excess of (-)-DBTA (519) in a mixture of chloroform and ethyl acetate, according to the conditions employed for (±)-BINAPO, resulted only in the precipitation of unreacted starting material 560 (Table 4.1, entry 1). In addition, concentration of the mother liquor and subsequent 1H-NMR analysis of the resulting residue showed only unreacted oxide 560 and resolving agent 519 thus indicating that complex formation had not taken place. Systematic alteration of the reaction conditions including solute concentration, heating period, solvent composition, and molar equivalence of resolving agent resulted only in the isolation of unreacted (±)-oxide 560 (entries 2-5). Utilization of (-)-DBTA monohydrate in place of the corresponding anhydrous resolving agent gave similar results (entries 6-9). In all cases, evidence supporting the formation of hydrogen bonded complex 562 could not be found suggesting that protonation the BINAPF phosphoryl oxygen atoms with tartaric acid derivatives may not be feasible. Based on this conclusion, recourse was sought in using a more acidic, enantiopure resolving agent such as the commercially available and relatively inexpensive (1S)-(+)10-camphorsulfonic acid (CSA•H2O, 517).
Table 4.1 Attempted Resolution of Racemic Phosphine Oxide 560 via Complexation with (-)-DBTA (519).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Resolving Agent (Equiv.)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvents (Ratio)</th>
<th>Concentration (M)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reflux Time(h)</th>
<th>Result&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-)-DBTA (1)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/EtOAc (1.5:1)</td>
<td>0.034</td>
<td>0.25</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>(-)-DBTA (1)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/EtOAc (1.5:1)</td>
<td>0.091</td>
<td>0.25</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>(-)-DBTA (1)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/EtOAc (1.5:1)</td>
<td>0.036</td>
<td>3.0</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>(-)-DBTA (2)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/EtOAc (7.5:1)</td>
<td>0.047</td>
<td>6.0</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>(-)-DBTA (1)</td>
<td>THF</td>
<td>0.096</td>
<td>0.50</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>(-)-DBTA•H&lt;sub&gt;2&lt;/sub&gt;O (1)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/EtOAc (2.0:1)</td>
<td>0.037</td>
<td>3.0</td>
<td>N.R.</td>
</tr>
<tr>
<td>7</td>
<td>(-)-DBTA•H&lt;sub&gt;2&lt;/sub&gt;O (2)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/EtOAc (2.0:1)</td>
<td>0.046</td>
<td>3.0</td>
<td>N.R.</td>
</tr>
<tr>
<td>8</td>
<td>(-)-DBTA•H&lt;sub&gt;2&lt;/sub&gt;O (5)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;/EtOAc (1.3:1)</td>
<td>0.023</td>
<td>0.50</td>
<td>N.R.</td>
</tr>
<tr>
<td>9</td>
<td>(-)-DBTA•H&lt;sub&gt;2&lt;/sub&gt;O (1)</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>0.054</td>
<td>6</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

(a) Relative to 1 equiv. of phosphine oxide 560; (b) Refers to concentration of compound 560; (c) N.R. = no reaction.

Noyori and coworkers have shown that (±)-BINAP can be resolved upon treatment with a molar equivalent (1S)-(+)-CSA•H<sub>2</sub>O (517) in a 3:1 mixture of ethyl acetate and acetic acid.\(^{218}\) Although this stoichiometry allows for a 2:1 complex formation between the resolving agent and a single enantiomer of the phosphine oxide, these workers obtained a crystalline adduct consisting of (R)-(+)BINAP, (1S)-(+)CSA, ethyl acetate, and acetic acid in a 1:1:1:1 ratio as evidenced by X-ray crystallographic analysis. The mother liquor contained unreacted resolving agent 517 and enantioenriched (S)-(+)BINAP indicating that complexation occurred in an enantioselective fashion. Following this procedure, heating racemic phosphine oxide 560 with an equivalent of (1S)-(+)CSA monohydrate (517) in a 3:1 mixture of EtOAc and AcOH only furnished crystals of unreacted resolving agent. However, increasing the relative amount of (+)-CSA•H<sub>2</sub>O to 5 equivalents clearly resulted in the quantitative formation of a hydrogen bonded adduct as evidenced by proton NMR spectroscopy (Figure 4.2). Interestingly, this large excess
of resolving agent was found to be absolutely essential for the formation of the desired hydrogen bonded complex. Since the formation of CSA bound complex 563 was found to be quantitative, it follows that the adduct should exist as two distinct stereochemical isomers. Although shifting of the aromatic resonances was evident in the $^1$H-NMR spectrum of the bound adduct relative to phosphine oxide 560, splitting of the signals to reveal two separate diastereomeric forms of the complex was not observed. Moreover, $^{31}$P-NMR analysis of the hydrogen bound complex showed a sharp singlet at +19.7 ppm. Attempts to selectively recrystallize CSA adduct 563 from a variety of solvents as a single diastereomer led, in all cases, to eventual decomposition and precipitation of pure resolving agent 517. Further attempts to resolve the BINAPFu ligand via phosphine oxide 560 were abandoned in light of these unfortunate observations.

4.3 Attempted Resolution of (±)-BINAPFu Using Palladium(II) Amine Complexes.

The direct resolution of optically active phosphines using enantiopure palladium(II) complexes 564 and 565 (Figure 4.3), originally developed by Otsuka and coworkers, has been shown to be remarkably well suited for bidentate systems. Resolving agents 564 and 565 may be conveniently prepared via ortho-palladation of optically pure (S)-N,N-dimethyl-α-phenylethylamine or (S)-N,N-dimethyl-α-(1-naphthyl)ethylamine, respectively. According to
a procedure employed by Noyori and coworkers, $^{204}$ (±)-BINAP (505) may treated with 0.5 equivalents of palladium(II) dimer 564 to give a 1:1 mixture of diastereomeric chloride salts 566a and 566b (Scheme 4.1). Subsequent anion exchange with NaBPh$_4$ furnishes compounds 567a and 567b, which are readily separable by fractional crystallization from a ternary solvent system of dichloromethane, ethyl acetate, and benzene. Using this procedure as a general guide, (±)-BINAPF$_6$ (509) was treated with 0.5 equivalents of resolving agent 564 followed by anion exchange with 1.0 molar equivalents of KPF$_6$ (Scheme 4.1). The hexafluorophosphate anion was

Conditions: (a) 0.5 equiv. dimer 564, C$_6$H$_6$, rt, 12 h. (b) 1.0 equiv. NaBPh$_4$, rt, 0.5 h. (c) 1.0 equiv. KPF$_6$, rt, 0.5 h.
substituted for tetraphenylborate used by Noyori since the majority of resolutions using reagent 463, including biaryl systems, employ the former counter ion. Under these conditions, a 1:1 mixture of diastereomeric PF$_6$ salts 569a and 569b was obtained as evidenced by $^{31}$P-NMR analysis (Figure 4.4). In addition to a septet positioned at +177.3 ppm ($^1J_{P,P}$=711 Hz), corresponding to the PF$_6$ anion (not shown), four equal intensity doublets were observed at 3.1, 3.4, 21.6 and 22.6 ppm, respectively. In each Pd diastereomer, the two phosphorus atoms are heterotopic and thus couple with each other ($^3J_{P,P}$=35 Hz) to give a characteristic four line pattern. By application of the trans effect, the higher field doublets at 3.4 and 3.1 ppm can be assigned to the more labile phosphorus atoms opposite to the nitrogen donor ligand (P2 for each diastereomer, Figure 4.4). Disappointingly, attempts to separate the diastereomeric palladium(II) adducts 569a and 569b by recrystallization from a wide variety of solvent systems proved fruitless. Utilization of the 1-naphthylethylamine derived resolving agent 565 in place of the corresponding 1-phenylethylamine reagent 564 furnished similar results and in both cases, the highly polar nature of the Pd(II) adducts formed rendered chromatographic techniques infeasible.
4.4 Attempted Resolution of (±)-BINAPFu via Formation of Phosphonium Salts with Enantiopure Organohalides.

Since the formation of phosphonium salts from phosphines and organohalides is a facile process, it was conceived that such a reaction could be exploited in order to append an enantiopure moiety to the BINAPFu ligand. It was postulated that the mixture of diasteromers thus obtained may be separable via fractional crystallization if a suitable halide could be identified. As an initial approach, racemic BINAPFu was treated with 2 equivalents of

Table 4.2 Attempted Formation of BINAPFu Phosphonium Salts Using Enantiopure Organohalides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organohalide</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="571" alt="Chemical Structure" /></td>
<td>CCl₄</td>
<td>77</td>
<td>20</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td><img src="571" alt="Chemical Structure" /></td>
<td>xylenes</td>
<td>144</td>
<td>18</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td><img src="571" alt="Chemical Structure" /></td>
<td>DMF</td>
<td>153</td>
<td>3</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td><img src="572" alt="Chemical Structure" /></td>
<td>xylenes</td>
<td>144</td>
<td>18</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td><img src="573" alt="Chemical Structure" /></td>
<td>xylenes</td>
<td>144</td>
<td>18</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td><img src="573" alt="Chemical Structure" /></td>
<td>dioxane</td>
<td>102</td>
<td>24</td>
<td>N.R.</td>
</tr>
<tr>
<td>7</td>
<td><img src="573" alt="Chemical Structure" /></td>
<td>pyridine</td>
<td>115</td>
<td>18</td>
<td><img src="574" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>8</td>
<td><img src="574" alt="Chemical Structure" /></td>
<td>xylenes</td>
<td>144</td>
<td>48</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

(a) based on ¹H-NMR analysis; N.R.=no reaction.
(S)-(+) -citronellyl bromide (571) in refluxing CCl₄ for 20 hours (Table 4.2, entry 1). Surprisingly, under these conditions only unreacted starting materials were obtained from the reaction mixture. Increasing the reaction temperature and using more polar solvents failed to improve this result (entries 2-3). Employing a more reactive halide such as (S)-(+) -citronellyl iodide (572), also failed to furnish the desired phosphonium salt. Commercially available (S)-(+) -1 -iodo -2-methylbutane (573) gave similar results when treated with (+)-BINAPFu in refluxing xylenes for 18 hours (entry 5). Solvents capable of facilitating the reaction by nucleophilic assistance, such as dioxane and pyridine, also failed to furnish the desired phosphonium salt (entries 6-7). In the latter case, pyridinium salt 574 could be efficiently isolated from the reaction mixture in near quantitative yield as a bright orange solid material. Employing compound 574 as the electrophile in refluxing xylenes for 48 hours furnished only unreacted starting materials. The unexpected failure of primary halides 571-573 and pyridinium salt 574 to react with the BINAPFu ligand may be attributed, in part, to the steric bulk of the phosphine nucleophile. In order to determine whether or not electronic effects were partially responsible, (+)-BINAPFu was treated with excess iodomethane in refluxing CCl₄ for 6 hours (Scheme 4.2). This experiment furnished the desired bis-phosphonium salt 575 in 93% yield thus indicating that the BINAPFu ligand possesses sufficient nucleophilicity to react with primary organohalides. ³¹P-NMR analysis of phosphonium salt 575 showed a sharp singlet at +12.9 ppm while proton NMR analysis revealed a doublet at 2.98 ppm (²Jₚ,H=13.4 Hz) integrating to 6 protons thereby indicating that the desired product was isolated. Attempts to resolve bis-phosphonium salt 575 by reaction with enantiopure silver salts, including silver hydrogen dibenzoyl-L-tartrate (Ag-DBHT) and silver (1S)-(+) -10-camphorsulfonate, led only to the formation of complex mixtures as evidenced by ³¹P-NMR analysis (Scheme 4.2).
4.5 Attempted Resolution via Synthetic Routes: Redesign of the BINAPFu Synthesis to Allow for Resolution at an Earlier Stage.

Although the synthesis developed for the BINAPFu ligand (*vide supra*) is short and efficient, failure to identify a suitable method for obtaining the optically pure material via known resolution methods led to the consideration of alternative synthetic routes. It was postulated that an enantiopure electrophile of type 577 could potentially be reacted with lithiated biaryl 576 to give bis-phosphonamide 578 as a 1:1 mixture of diastereomers\(^{246}\) (Scheme 4.3). Such an approach would thus install the required 2,2'-phosphorus atoms while appending a chiral auxiliary for optical resolution. Separation of the resulting diastereomer mixture and subsequent synthetic manipulation of each pure isomer, 578a and 578b, would then provide routes to the optically pure BINAPFu antipodes. Following this general scheme, commercially available trans-1,2-cyclohexane diamine was resolved\(^{247}\) and the \((R,R)\)-isomer\(^{248}\) 579 was converted to the corresponding \(N,N'\)-dimethyl derivative 580 according to a literature procedure\(^{249}\) (Scheme 4.4). Diamine 580, thus obtained, was treated with 1 molar equivalent of phosphorus trichloride according to a standard procedure\(^{250}\) to furnish chlorophosphine 581 in 72% isolated yield. This

---

**Scheme 4.3**

\[
\begin{align*}
576 & \quad 577 \text{ R=alkyl, aryl} \\
578a \text{ and } 578b & \text{ (1:1 ratio of axial isomers)} \\
509 & \text{ enantiopure}
\end{align*}
\]

**Scheme 4.4**

\[
\begin{align*}
\text{(R,R)-579 \text{ R=H}} & \quad \text{580 \text{ R=Me}} \\
\text{581} & \quad \text{582a and 582b (1:1 ratio of axial isomers)}
\end{align*}
\]

Conditions: (a) 2.1 equiv. ethyl chloroacetate, 4.6 equiv. NaOH, H\(_2\)O, 0 °C, 2 h, 82%. (b) 8.5 equiv. LiAlH\(_4\), THF, rt, 1 h, 92%. (c) 1.0 equiv. PCl\(_3\), 2 equiv. NEt\(_3\), Et\(_2\)O, -40 °C, 72%. (d) 0.5 equiv. compound 576, Et\(_2\)O, rt, 1.5 h. (e) 2 equiv. BH\(_3\)•DMS, rt, 24 h, 74% (2 steps).
highly moisture and oxygen sensitive\textsuperscript{250} compound was prepared using Schlenk techniques under an atmosphere of argon and used without purification. Trapping dianion 576, prepared as previously described, with 1,3-diazaphoholidine derivative 581 and subsequent reaction with BH\textsubscript{3}•DMS provided a 1:1 mixture of diastereomers 582\texttextit{a} and 582\texttextit{b}, respectively (Scheme 4.4). Bis-borane complex 582 was prepared \textit{in situ} in order to prevent potential complications due to air oxidation of the phosphine precursor.\textsuperscript{250} \textsuperscript{1}H-NMR analysis of the crude phosphine-borane mixture, 582\texttextit{a} and 582\texttextit{b}, clearly showed four doublets of equal intensity corresponding to the N-methyl groups (Figure 4.5). In each diastereomer, the two diastereotopic N-methyl signals exhibit $^{3}J_{P-H}$ coupling with the phosphorus atom to give a pair of doublets. Evidence supporting the formation of the desired bis-borane complex was found in both IR and FAB-MS analysis. A strong absorption in the IR spectrum was observed at 2390 cm$^{-1}$ corresponding to the B-H stretching frequency\textsuperscript{251} while FAB-MS analysis confirmed a molecular weight of 702 (calculated for C\texttextit{40}H\texttextit{50}B\texttextit{2}N\texttextit{4}O\texttextit{2}P\texttextit{2}) showing a M+Na\textsuperscript{+} signal at 725 amu. Although separation of compounds

\begin{center}
\textbf{Figure 4.5} 400 MHz \textsuperscript{1}H-NMR Spectrum of Compounds 582\texttextit{a} and 582\texttextit{b} Obtained as a 1:1 Mixture of Axial Stereoisomers.
\end{center}
582a and 582b could not be achieved using standard recrystallization or flash chromatographic techniques, a small sample (~3 mg) of each pure diastereomer was obtained by preparative HPLC using a reversed phase C_{18} column. While this labor intensive and costly separation technique clearly does not provide a route towards large quantities of resolved material, the obtainment of diastereomERICALLY pure borane adducts 582a and 582b was highly encouraging. Moreover, it was postulated that by simply changing the diamine used to prepare phosphoramidous chloride 577 (Scheme 4.3), it may be possible to prepare a more readily separable mixture of axial diastereomers. Driven by this hypothesis, diamine 584 was prepared and resolved according to standard literature procedures (Scheme 4.5). Diazaphospholidine 585, a reagent which has been used to derivatize hydroxy biaryls for enantiopurity determination, was subsequently prepared upon treatment of (S,S)-(−)-diamine 584 with 1 equivalent of phosphorus trichloride in Et_{3}N/Et_{2}O solution. Further reaction with 2,2′-dilithiated binaphthofuran 576 and BH_{3}•DMS as previously described furnished a 1:1 mixture of axially isomeric borane adducts 586a and 586b in 71% yield. Infrared spectral analysis of compounds 586a and 586b clearly showed a B-H stretching band at 2391 cm\(^{-1}\) and FAB-MS exhibited a M+H\(^{+}\) peak at 899 amu. Fortunately, separation of stereoisomers 586a and 586b was facile by fractional crystallization from a CHCl_{3}/hexanes solvent system. Under these conditions, compound 586a selectively crystallized leaving highly enriched (>95%) isomer 586b in the mother liquor. The latter compound could be further purified by flash chromatography. The isomeric purity of borane adducts 586a and 586b was easily determined by \(^1\)H-NMR spectroscopy. The AX pattern of doublets, corresponding to protons H-1 and H-2 (Figure 4.6),
Figure 4.6 200 MHz $^1$H-NMR Spectrum of Compounds 586a and 586b Obtained as a 1:1 Mixture of Axial Stereoisomers.

for each diastereomer provided a convenient spectroscopic means for determining isomeric purity. With pure borane adducts 586a and 586b in hand, attention was focused on removing the diamine moiety and installing the required phenyl substituents.

Supported by literature precedent,$^{246,255}$ it was envisioned that the diamine chiral auxiliary could be cleaved from borane adduct 586a upon treatment with anhydrous HCl, providing enantiopure chloride 587 (Scheme 4.6). Subsequent reaction with four equivalents of phenyllithium or phenyl Grignard and removal of the BH$_3$ protecting group would then furnish the desired diphosphine 509 in optically pure form. Following this approach, isomerically pure compound 586a was treated with 8 molar equivalents of HCl (1.0 M solution in Et$_2$O) at 0 °C for 1 hour. The mixture thus obtained was filtered under argon to remove (1S,2S)-N,N'-dimethyl-1,2-diphenylethylenediamine dihydrochloride and the filtrate was treated with 5 equivalents of
phenyllithium at -40 °C (Table 4.3, entry 1). Under these conditions, a complex mixture of products was obtained as evidenced by $^{31}$P-NMR analysis. Lowering the reaction temperature to -40 °C for the acid addition or using phenyl Grignard in place of phenyllithium failed to improve this result (entries 2-3). Employing anhydrous HCl(g) instead of the 1.0 M ethereal solution also afforded a complex mixture of products. In all cases, isolation of the unwanted amine hydrochloride salt confirmed that cleavage of the P-N bonds was occurring under the reaction conditions. Low temperature $^{31}$P-NMR analysis indicated that complex mixture formation was occurring previous to the addition of the organometallic reagent. Other Bronstead acids, including MsOH and TFA in methanolic solution, afforded similar results. Although the

Table 4.3 Attempted Acid Promoted Cleavage of the Diamine Chiral Auxiliary from Isomerically Pure Borane Adduct 586a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions for Cleavage</th>
<th>Substitution Conditions</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.0 equiv HCl (1.0 M in Et$_2$O), 0 °C</td>
<td>5.0 equiv. PhLi, -40 °C</td>
<td>C.M.</td>
</tr>
<tr>
<td>2</td>
<td>8.0 equiv HCl (1.0 M in Et$_2$O), -40 °C</td>
<td>5.0 equiv. PhLi, -78 °C</td>
<td>C.M.</td>
</tr>
<tr>
<td>3</td>
<td>8.0 equiv HCl (1.0 M in Et$_2$O), -40 °C</td>
<td>5.0 equiv. PhMgBr, -40 °C</td>
<td>C.M.</td>
</tr>
<tr>
<td>4</td>
<td>excess HCl(g), Et$_2$O, 0 °C</td>
<td>10.0 equiv. PhLi, -78 °C</td>
<td>C.M.</td>
</tr>
<tr>
<td>5</td>
<td>excess HCl(g), Et$_2$O, 0 °C</td>
<td>10.0 equiv. PhMgBr, -40 °C</td>
<td>C.M.</td>
</tr>
</tbody>
</table>

(a) Based on $^{31}$P-NMR analysis; C.M.=complex mixture,
reaction conditions listed in Table 4.3 failed to provide the desired compound, the viability of this approach was later demonstrated using model system 589 (Scheme 4.7). This compound, which was easily prepared from commercially available diazaphospholidine 588, could be treated with excess HCl gas in Et₂O and subsequently reacted with 10 molar equivalents of phenylmagnesium bromide to provide borane adduct 590 in modest yield. The product thus obtained was identical in all respects to a sample prepared by reacting triphenylphosphine with borane-dimethyl sulfide complex. The failure to identify suitable conditions for cleaving the diamine chiral auxiliary from borane adduct 586a eventually led to the abandonment this synthetic resolution approach.


Upon exhausting several of the known methods for phosphine resolution, without success, it became clear that a new optical resolution procedure would have to be developed in order to obtain the enantiopure BINAPFu ligand. Consideration of the resolution methods already attempted (vide supra), suggested that a newly developed procedure should ideally act directly on BINAPFu (509) or the corresponding bis-phosphine oxide 560 in order to minimize the number of synthetic steps. Moreover, due to the difficulties experienced in the CSA and DBTA resolution techniques, it was concluded that a successful route would likely involve appending the resolving agent via a covalent linkage thus providing two discrete diastereomeric compounds. Based on the lessons learned with respect to the ortho-palladated resolving agents 564 and 565 (Figure 4.3, page 112), the diastereomeric compounds obtained by appending a resolving agent to the phosphine ligand should be neutral intermediates in order to allow for possible chromatographic separation. Finally, considering the impasse reached with
diazaphospholidine compound 586a, cleavage of the chiral auxiliary to furnish the desired optically pure phosphine 509 or phosphine oxide 560 should not require strongly acidic reaction conditions. With these parameters in mind, it was conceived that a Staudinger reaction\textsuperscript{256} between racemic BINAPFu (509) and 2 equivalents of an enantiopure organoazide could potentially give a 1:1 mixture of diastereomeric phosphinimines, 592a and 592b (Scheme 4.8), if the P=N bond rotational barrier was low enough to prevent geometrical isomerism. A literature survey revealed that the P=N rotational barrier for simple phosphinimines has been calculated to be \textit{ca.} 2.54 kcal/mol.\textsuperscript{257} Hence it was rationalized that P=N geometrical isomerism would likely not complicate the proposed resolution technique. Separation of the phosphinimine mixture and subsequent reductive cleavage of the resolving agent from each pure isomer with LiAlH\textsubscript{4} would then furnish the desired enantiomerically pure antipodes.

In order develop a resolution procedure for (±)-BINAPFu based on phosphinimine formation, a readily available and optically pure organoazide needed to be identified. Computer aided searching of the literature\textsuperscript{258} revealed (1S)-10-camphorsulfonyl azide, which can be prepared in a single step from commercially available (1S)-(+)10-camphorsulfonyl chloride,\textsuperscript{259} as an attractive candidate for the required resolving reagent. Treatment of (±)-BINAPFu (509) with 2 molar equivalents of enantiopure sulfonyl azide 593 smoothly provided a 1:1 mixture of diastereomeric phosphinimines 594a and 594b in near quantitative yield (Scheme 4.9). \textsuperscript{31}P-NMR analysis of the crude phosphinimine mixture showed two singlets at 5.7 and 4.9 ppm corresponding to

Scheme 4.8

\begin{center}
\includegraphics[width=\textwidth]{scheme4_8.png}
\end{center}

Reagents: (a) 2 equiv. enantiopure azide (*RN\textsubscript{3}), Δ. (b) separate axial stereoisomers. (c) H\textsuperscript{+} reduction, Et\textsubscript{2}O.
compounds 594a and 594b, respectively. Signals characteristic of starting phosphine 509 (-32.3 ppm) and phosphine oxide 560 (+16.5 ppm) were not evident in the $^{31}$P-NMR spectrum thus indicating that the desired bis-phosphinimine adduct was formed without complications due to partial reaction or air oxidation. Further evidence supporting the isolation of bis-adducts 594a and 594b was found in FAB-MS analysis, which showed a M+H$^+$ peak at 1161 amu. $^1$H-NMR analysis of the phosphinimine mixture clearly showed four singlet resonances of equal intensity corresponding to the geminal dimethyl signals (Figure 4.7). From this observation, it was concluded that compounds 594a and 594b were present in an equimolar ratio since each diastereomer would exhibit two methyl singlets. Fortunately, phosphinimines 594a and 594b could be readily separated by flash chromatography on silica gel using a 9:1 CHCl$_3$/CH$_3$CN eluent mixture. The isomeric purity of compounds 594a and 594b could easily be determined by proton NMR analysis (Figure 4.7). Phosphinimine 594a, which was first to elute from the column, was characterized by methyl resonances at 0.90 and 0.53 ppm while the second diastereomer, compound 594b, exhibited corresponding signals at 0.71 and 0.45 ppm. Evidence supporting hindered rotation about the P=N bond could not be found in either the $^{31}$P-NMR or $^1$H-NMR spectra of compounds 594a and 594b recorded between -50 °C and +60 °C. With isomerically pure phosphinimines 594a and 594b in hand, attention was now focused on identifying a method for removing the chiral auxiliary to give optically pure BINAPFu (509) or the corresponding phosphine oxide 560.
Figure 4.7 $^1$H-NMR Spectra of Phosphinimines 594a and 594b Before and After Separation.
It was postulated that treatment of isomerically pure phosphinimine 594a with excess LiAlH₄ would provide optically pure BINAPFu (509) along with isobornyl-10-sulfonamide (596) (Scheme 4.10). Interestingly, heating compound 594a with 10 equivalents of lithium aluminum hydride in THF resulted in the unexpected formation of 3,3'-binaphtho[b]furan (556) and monophosphine 595. Although a small amount of the desired product was obtained and shown to be optically pure by HPLC analysis ($R_t=23.4$ min, cf. Figure 4.1 page 108), conditions to attenuate the formation of byproducts 556 and 596 could not be identified. Performing this reaction at ambient temperature resulted in a similar product mixture while employing weaker reducing agents, such as DIBAL or NaBH₄, failed to cleave the P=N bond.

Faced with the failure to prepare optically pure BINAPFu (509) in good yield via direct reduction of phosphinimine 594a, it was postulated that the P=N bond could be cleaved using an aza-Wittig process. Hence, reaction of either compound 594a or 594b with CO₂ would afford optically pure phosphine oxide 560 along with (1S)-10-camphorsulfonamide. Subsequent trichlorosilane reduction of phosphine oxide 560 thus obtained would then furnish the desired enantiopure BINAPFu ligand. Surprisingly, bubbling CO₂ gas through a solution of isomerically pure phosphinimine 594a in THF for a period of 4 hours failed to cause any detectable cleavage of the P=N bond (Table 4.4, entry 1). Changing the solvent to acetone and lengthening the exposure time did not improve this result. Moreover, no reaction was observed upon refluxing compound 594a in carbon disulfide for 24 hours (entry 3), suggesting that an aza-Wittig approach toward cleaving the phosphinimine moiety was not going to be feasible.
Table 4.4  Attempted Aza-Wittig Cleavage Phosphinimine 594a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Resulta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO₂(g)</td>
<td>THF</td>
<td>25</td>
<td>4</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>CO₂(g)</td>
<td>acetone</td>
<td>25</td>
<td>16</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>CS₂</td>
<td>45</td>
<td>24</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

(a) Based on ³¹P-NMR analysis; N.R. = no reaction.

Since phosphinimine 594a was inert towards aza-Wittig conditions, recourse was sought in the hydrolytic cleavage of the P=N bond using mineral acids.²⁶² Stirring a solution of compound 594a in THF and 1.5 M H₂SO₄ at ambient temperature for 24 h failed to give any reaction as evidenced by ³¹P-NMR analysis. Although this experiment did not result in the cleavage of the P=N bond, it is noteworthy that the binaphtho[b]furan system withstood the reaction conditions and was therefore more stable to acid than previously anticipated. Performing the reaction in refluxing THF, under otherwise identical conditions, cleanly provided the desired phosphine oxide albeit in poor conversion (~15%). Subsequent experimentation revealed phosphine oxide 560 could be obtained in near quantitative yield by refluxing compound 594a in a 3:2 mixture of 1,4-dioxane and 3 M H₂SO₄ for 24 hours (Scheme 4.11). Subsequent chromatographic removal of sulfonamide 597 and trichlorosilane reduction of the resulting phosphine oxide 560 as previously described provided the BINAPFu ligand in excellent yield. HPLC analysis of the bisphosphine thus obtained, using the protocol described in section 4.1, showed a single peak at Rₜ=23.7 minutes. Finally, optical rotation data revealed that phosphinimine 594a yielded the levo-rotatory enantiomer of BINAPFu ([α]D⁻²⁰⁻203.0° (c 1.09, CHC₃)). Performing the same hydrolysis/reduction sequence on phosphinimine 594b provided (+)-BINAPFu (509) in near quantitative yield ([α]D²⁺201.8° (c 1.28, CHC₃)). Heating the enantiopure (-)-BINAPFu ligand in p-xylanes at 150 °C for 7 days did not result in any racemization of the chiral axis as evidenced by optical rotation and HPLC analysis.
4.7 Physical Characterization of the BINAPFu Ligand: Investigation of the \( \sigma \)-Donor Ability and Absolute Configuration Assignment.

As discussed in Chapter 2, Allen and Taylor have reported that the \( ^1J(^{31}P-^{77}Se) \) coupling constant of phosphorus selenides may be used as a measure of parent phosphine basicity.\(^{51} \) A large coupling constant indicates high s-character of the phosphorus lone pair orbital. In other words, poorly donating phosphine ligands exhibit large \( ^1J(^{31}P-^{77}Se) \) coupling constants (See Table 2.3, page 23). In order to gauge the donor ability of the BINAPFu ligand, a solution of optically pure (-)-509 in CHCl\(_3\) was heated with 10 molar equivalents of selenium powder for 5 hours to afford bis-selenide 598 (Scheme 4.12). \(^{31}P\)-NMR analysis of this product clearly showed a strong singlet at +19.4 ppm with a satellite doublet \( (^{1}J_{P,Se}=762 \text{ Hz}) \) due to \( ^{31}P-^{77}Se \) coupling. Performing the same reaction and \(^{31}P\)-NMR analysis on a variety of other, commonly
used phosphine ligands yielded the $^1J_{p-Se}$ coupling constants shown in Figure 4.8. As the data clearly indicates, the BINAPFu ligand 509 is far less basic than both triphenylphosphine (609) and BINAP (505). Moreover, BINAPFu is significantly less basic that Benincori’s benzothiophene derived ligand BITIANP (525). Phosphinoaryl oxazoline ligand 602, which has gained much attention in enantioselective allylic alkylation reactions, is also less basic than triphenylphosphine but significantly more basic than either BINAPFu or BITIANP. The small difference observed between the coupling constants for bis-selenides 604 and 608 suggest that this measure of $\sigma$-donor ability can be quite a sensitive technique. The latter selenide, derived from 7,7'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-binapthalene, is slightly more basic than BINAP owing to the electron donating capacity of the remote 7,7'-methoxy substituents. Having demonstrated that the electronic properties of BINAPFu (509) and BINAP (505) are dissimilar, with the former ligand resembling those of tri-2-furylphosphine (599), attention was focused on the final task of characterization. The absolute configuration of the biaryl axis needed to be elucidated. With phosphine selenide 598 in hand, prepared from optically pure (-)-BINAPFu (vide supra), it was rationalized that X-ray diffraction using the Bijvoet method could determine the stereochemical assignment. Delightfully, single crystal
analysis of compound 598 furnished the structure depicted in Figure 4.9. By refining the inverted structure and evaluating the Flack parameter, it was shown that the S-configuration was present in the crystal. Hence phosphinimine 594a corresponds to (S)-(-)-BINAPFz while phosphinimine 594b corresponds to (R)-(+)-BINAPFz. This relationship was verified via single crystal X-ray diffraction analysis of phosphinimine 594a (Figure 4.10). In this case, Bijvoet
analysis was not required since the absolute stereochemistry of the biaryl axis could be ascertained by simple comparison to the known configurations of the camphor residues. Since (1S)-(+)\textbf{-10-camphorsulfonyl chloride was used to prepare resolving agent 593,} it follows from Figure 4.10 that phosphinimine 594a is the $S$-axial diastereomer. It is noteworthy that the mean $P=N$ bond length was determined to be 1.58 Å which is in close agreement with diffraction data obtained on other phosphorus(V) imines.\textsuperscript{270} Hence, the observed absence of $P=N$ geometrical bond isomers is likely general for this class of compounds.

Having attained the goal of preparing and optically resolving a C$_2$-symmetric bifuran analogue of BINAP, the task of evaluating the performance of this ligand in a variety of metal-mediated asymmetric transformations remained. Employment of the BINAPFu ligand in asymmetric ruthenium-catalyzed hydrogenations and the palladium-catalyzed Heck reaction is the subject of the following Chapter. Further application of the Staudinger resolution technique for the preparation of enantiomerically pure P-stereogenic compounds is presented in Chapter 6.
5. Applications of Axially-Stereogenic 2-Furyl Phosphine Ligands in Asymmetric Catalysis.

5.1 Overview.

This chapter begins with a presentation of the experimental results obtained using enantiopure BINAPfu (509) as a chiral modifying ligand for Pd(0)-catalyzed intermolecular and intramolecular Heck reactions. The asymmetric Heck arylation of 2,3-dihydrofuran (611), first reported by Hayashi and coworkers,\textsuperscript{210,271} has been studied extensively and was therefore chosen as a suitable reaction to study using the BINAPfu ligand (Scheme 5.1, equation 1). The results of this investigation are presented in section 5.2. Overman’s intramolecular Heck cyclization for the preparation of 3,3-spirooxindole products 615a and 615b\textsuperscript{149a,272} (equation 2) was also studied using the BINAPfu ligand and the results of this study are discussed in section 5.3. Based on the excellent results obtained by Benincori and coworkers using BITIANP for Ru(II)-catalyzed hydrogenations of β-ketoesters\textsuperscript{219,220} (equation 3), a study of this chemistry using the BINAPfu ligand was initiated. The details of this investigation are presented in section 5.4. Superior

\begin{scheme}
\begin{equation}
\begin{align}
&\begin{array}{c}
\ce{\text{F}}
\end{array}
\end{align}
\end{equation}
\end{scheme}

Conditions: (a) 3.0 equiv. DIPEA, 3 mol% \(\text{Pd(OAc)}_2\), 6 mol% \((R)\)-BINAP, \(C_6H_6\), 30 °C, 66 h. (b) 10 mol% \(\text{Pd}_2(\text{dba})_3\), 20 mol% \((R)\)-BINAP, 5 equiv. PMP, DMA, 80 °C, 6 d. (c) 0.1 mol% \([(R)\text{BITIANP}]\text{RuCl}_2\), \(H_2 (100 \text{ Kg/cm}^2)\), MeOH, 70 °C, 2 h.
results were obtained using BINAPFu (509) in the aforementioned Pd(0)-catalyzed Heck arylation of 2,3-dihydrofuran (611), thus prompting the synthesis and resolution of 2,2'-bis(di-2-furylphosphino)-1,1'-binaphthalene (TetFuBINAP, section 5.5). Application of TetFuBINAP toward Hayashi’s Heck arylation of 2,3-dihydrofuran and Overman’s spirocyclic ring closure reaction are the topics of sections 5.6 and 5.7, respectively.

5.2 The Asymmetric Heck Arylation of 2,3-Dihydrofuran (611).

5.2.1 Introduction.

The first example of an intermolecular asymmetric Heck reaction was reported by Hayashi and Ozawa\textsuperscript{271a} working at the Catalysis Research Center at Hokkaido University. In this pioneering work, it was discovered that treatment of 2,3-dihydrofuran (611) and phenyl triflate (359) with Hunig’s base and a Pd(OAc)\textsubscript{2}/(R)-BINAP catalyst system in benzene at 30 °C for 66 h afforded a 10:1 ratio of 2-phenyl-2,3-dihydrofuran (612) and 2-phenyl-2,5-dihydrofuran (613), respectively (Scheme 5.2). These two products, which were separable by flash chromatography, were isolated and analyzed by \textsuperscript{1}H-NMR spectroscopy using the chiral shift reagent Eu(hfc)\textsubscript{3}. The enantiomeric excess (ee) of the major isomer was determined to be 93% in favor of the

![Scheme 5.2](https://example.com/scheme5.2.png)

Conditions: (a) 3.0 equiv. DIPEA, 3 mol% Pd(OAc)\textsubscript{2}, 6 mol% (R)-BINAP, C\textsubscript{6}H\textsubscript{6}, 30 °C, 66 h. (b) excess Jones’ reagent, acetone, 0 °C, 46%. (c) 2 mol% RhCl(PPh\textsubscript{3}), H\textsubscript{2} (1 Kg/cm\textsuperscript{2}), C\textsubscript{6}H\textsubscript{6}, rt, 1 h, 100%.
The absolute configuration of compound 612 was identified to be R via chemical conversion to the known γ-butyrolactone derivative, (R)-(−)-3-phenyl-2-oxacyclopentanone (614). Chiral shift $^1$H-NMR analysis revealed that the minor isomer had an ee of 67% in favor of the S-enantiomer. The absolute configuration of the 2,5-dihydrofuran product 613 was also established by chemical conversion. Hydrogenation of this material using Wilkinson’s catalyst furnished a levorotatory sample of 2-phenyltetrahydrofuran (615) while a similar procedure using R-612 (93% ee) provided dextrorotatory product 615 (Scheme 5.2). The fact that the two isomeric products were of opposite configuration suggested that a kinetic resolution process may be responsible for the high degree of enantioselectivity observed. The same authors later reported that the type of amine base employed can have a significant impact upon the reaction outcome (Table 5.1).

Strong amine bases such as Proton Sponge® ($pK_a=12.3$) resulted in the highest enantioselectivity albeit at the expense of isomeric purity (entry 1). Weaker bases such as 2,6-lutidine ($pK_a=5$) provided exclusively the 2,3-dihydrofuran product 612 in low yield with diminished stereoselectivity (entry 5). The observed inverse relationship between the enantiopurity of compound 612 and isomeric ratio was taken as further evidence supporting a kinetic resolution mechanism.

### Table 5.1 Effect of Amine Base on the Heck Arylation of 2,3-Dihydrofuran

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conv.</th>
<th>Time (h)</th>
<th>612:613</th>
<th>% Yield ($^b$) (% ee)$^c$ (R)-612</th>
<th>(S)-613</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Proton Sponge® (P.S.)</td>
<td>100</td>
<td>216</td>
<td>71:29</td>
<td>46 (&gt;96)</td>
<td>24 (17)</td>
</tr>
<tr>
<td>2</td>
<td>Cy$_2$NH</td>
<td>100</td>
<td>17</td>
<td>86:14</td>
<td>59 (82)</td>
<td>4 (43)</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA</td>
<td>100</td>
<td>24</td>
<td>92:8</td>
<td>57 (82)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>4</td>
<td>Et$_3$N</td>
<td>100</td>
<td>26</td>
<td>98:2</td>
<td>64 (75)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>5</td>
<td>2,6-Lutidine</td>
<td>38</td>
<td>216</td>
<td>100:0</td>
<td>27 (67)</td>
<td>0 (-)</td>
</tr>
</tbody>
</table>

(a) Based on reacted PhOTf. (b) Isolated yield. (c) Determined by $^1$H-NMR using Eu(hfc)$_3$. 

The observed inverse relationship between the enantiopurity of compound 612 and isomeric ratio was taken as further evidence supporting a kinetic resolution mechanism.
Hayashi and Ozawa also noted that use of an aryl triflate as the coupling partner was required in order to obtain enantioselectivity. In addition, employing Pd(OAc)$_2$ as the pre-catalyst was found to be superior to Pd$_2$(dba)$_3$ suggesting that the acetate anion plays a crucial role in the catalytic cycle. To account for all of these observations, Hayashi has proposed the catalytic cycle shown in Figure 5.1. Oxidative insertion of the Pd(0) catalyst initially affords Pd(II) intermediate. Dissociation of the labile triflate ligand, facilitated by the 2,3-dihydrofuran starting material, produces the cationic $\eta^2$-bound olefin complex. The stereochemistry of the initial carbopalladation step is governed by the facial selectivity of the olefin binding process. Using (R)-BINAP as the phosphine ligand favors coordination of the

![Figure 5.1 Hayashi’s Proposed Mechanism for the Asymmetric Heck Arylation of 2,3-Dihydrofuran.](image-url)
enol ether via the *si* face leading to the *R*-product configuration. Subsequent β-hydride elimination would furnish π-olefin complex 620. Hayashi proposes that if the configuration at C-2 is *S*, the 2,5-dihydrofuran product 613 is quickly released from the metal fragment in a process facilitated by the acetate anion. Strong amine bases such as Proton Sponge® render the acetate anion more nucleophilic and hence assist the proposed kinetic resolution process. The pathway taken by intermediate 620 with *R*-configuration at C-2 involves subsequent carbopalladation and β-hydride elimination steps to provide olefin migrated complex 622. Dissociation of the 2,3-dihydrofuran product 612 followed by reductive elimination of the [Pd(H)(OTf)BINAP] intermediate 623 completes the catalytic cycle.

Employing iodobenzene (50) as the phenylating agent is thought to result in a similar catalytic cycle involving only neutral palladium intermediates. Hence, in order to accommodate the olefin binding process, partial dissociation of the BINAP ligand must occur thus resulting in poor levels of asymmetric induction.

Since Hayashi's initial reports of the asymmetric arylation of 2,3-dihydrofuran, numerous workers have studied this reaction using a variety of different phosphine catalysts and conditions. This reaction was therefore chosen as a suitable candidate to study using the BINAPFu ligand and it was anticipated that such an investigation would allow for valuable comparison to the results obtained by Hayashi, Tietze, Pfaltz, and Pregosin.

5.2.2 Structural Analysis of the Products from the Heck Arylation of 2,3-Dihydrofuran and Enantiopurity Assessment.

Standard samples of (±)-2-phenyl-2,3-dihydrofuran (612) and (±)-2-phenyl-2,5-dihydrofuran (613) were prepared according to procedures reported by Larock and coworkers (Scheme 5.3). Treatment of iodobenzene (50) and 2,3-dihydrofuran (611) in DMF with a Pd(OAc)$_2$/PPh$_3$ catalyst system, KOAc base, and quaternary ammonium salt at 80 °C for 24 h furnished a single regioisomer in 72% yield (equation 1). Analysis of the $^1$H-NMR spectrum of this material clearly showed two olefinic protons at 6.44 ppm (H$^a$) and 5.51 ppm (H$^b$) thus indicating that the 2,3-dihydrofuran product 612 had been isolated. Alternatively, heating a mixture of 2,3-dihydrofuran (611) and iodobenzene (50) in CH$_3$CN at 80 °C with a Pd(OAc)$_2$/PPh$_3$ catalyst in
the presence of Ag₂CO₃ furnished exclusively the 2,5-dihydrofuran product 613 in 84% yield (Scheme 5.3, equation 2). The ¹H-NMR spectrum of compound 613 displayed two vinylic proton peaks at 5.89 ppm and 5.76 ppm. A complex multiplet was also observed at 4.83 ppm (2H) for the methylene protons adjacent to the oxygen atom thus confirming that 2-phenyl-2,5-dihydrofuran (613) was indeed isolated.

Following the reports of Hayashi and Ozawa,²¹⁰,²⁷¹ racemic compounds 612 and 613 were analyzed by ¹H-NMR analysis in the presence of the chiral shift reagent Eu(hfc)₃. In contrast to these workers' findings, addition of Eu(hfc)₃ to a CDCl₃ solution of either compound did not result in the clear resolution of the vinylic proton resonances (400 MHz). The breadth of the signals, due to spin-spin coupling, does not allow for proper integration and hence it was concluded that results obtained using the chiral shift analysis method would be unreliable in the present case.

The research teams of Tietze,²²¹b Pflatz,²⁷⁵ and Reiser²⁷⁷ have studied the Heck arylation of 2,3-dihydrofuran using chiral GC analysis and thus racemic compounds 612 and 613 were used to identify suitable resolution conditions. Analysis of a dilute ethereal solution of (±)-2-phenyl-2,3-dihydrofuran (612) using a Cyclodex-B column (30 m x 0.32 mm i.d.)²⁷⁸ gave two baseline resolved signals at 26.57 min and 26.97 min in a 1:1 ratio. Using the same GC conditions, compound 613 exhibited two well resolved peaks at 31.51 min and 31.91 min in a 1:1 ratio. The significant retention time difference between compounds 612 and 613 allows for ee measurement of each regioisomer without the need for prior flash chromatographic separation.
The Heck arylation of 2,3-dihydrofuran (611) was performed using a Pd(OAc)$_2$/(R)-BINAP catalyst system according to Hayashi and Ozawa's original conditions. Although these workers have claimed to obtain a 89:11 mixture of compounds 612 and 613 with a combined isolated yield of 78% using these conditions (See Scheme 5.2),$^{27a}$ in our hands identical conditions failed to afford >35% conversion as evidenced by the previously described chiral GC analysis protocol (retention time PhOTf = 10.81 min). Numerous attempts to achieve the yields reported by Hayashi and Ozawa under these conditions were unsuccessful. Extending the reaction period beyond 6 days failed to improve the observed conversion values. Nonetheless, analyzing the product mixtures by chiral GC and using Hayashi's reported configuration assignments, allowed for identification of each enantiomer in the gas chromatogram (Figure 5.2). The elution order was consistent with that reported by Tietze,$^{22b}$ and Pfaltz$^{27c}$ who also employed GC analysis with cyclodextrin based columns to study this reaction. Surprisingly, a third product with a

**Figure 5.2** Chiral GC Trace of Asymmetric Heck Reaction Between Phenyl Triflate and 2,3-Dihydrofuran using (R)-BINAP in Benzene at 30 °C for 6 Days.

![Chiral GC Trace of Asymmetric Heck Reaction Between Phenyl Triflate and 2,3-Dihydrofuran using (R)-BINAP in Benzene at 30 °C for 6 Days.](image)
retention time of 29.11 minutes was nearly always observed as a component of the crude product mixture. Depending upon the exact conditions used, this material comprised up to 13% of the reaction mixture. In order to prove that this compound was not an artifact of the work-up procedure or analysis method, pure samples of (±)-2-phenyl-2,3-dihydrofuran (612) and (±)-2-phenyl-2,5-dihydrofuran (613) were subjected to the extraction conditions and analyzed using the chiral GC protocol. In both cases, the anomalous signal at 29.11 minutes was not detected. Moreover, analysis of the reagents also failed to identify the source of the unknown compound and it was therefore concluded that this material must indeed be a bona fide reaction product. Based on the observed retention time, it was speculated that the unknown compound likely had a molecular weight similar to known reaction products 612 and 613. The unknown material appeared as single peak in the GC indicating that this product was likely an achiral species. This line of reasoning pointed toward 2-phenyl-4,5-dihydrofuran (624) as a potential candidate for the identity of the unknown reaction product. Although the unknown compound could not be isolated from the crude reaction mixtures by column chromatography, this material was positively identified as the conjugated isomer 624 via comparison to a known sample (vide infra). 2-Phenyl-4,5-dihydrofuran (624) was prepared according to a literature procedure\textsuperscript{279} starting with commercially available phosphonium salt 625 (Scheme 5.4). Heating compound 625 with sodium benzoate in aqueous acetone smoothly afforded ester 626 in 55% isolated yield. Interestingly, treating compound 626 with 1.05 molar equivalents of sodium $t$-butoxide in toluene at ambient temperature causes an intramolecular Wittig reaction to occur thus furnishing the desired 4,5-dihydrofuran product 624. Attempted purification of compound 624 by column chromatography resulted in extensive decomposition. However, the desired product could be isolated in 67% yield after short-path distillation. The $^1$H-NMR spectrum of compound 624
showed a single vinyl proton resonance at 5.23 ppm and was consistent with many of the crude Heck arylation spectra. Moreover, chiral GC analysis of compound 624 using the previously defined parameters gave a single peak, which matched the retention time of the unexpected reaction product. It was therefore concluded that this reaction product was indeed the conjugated isomer 624.

5.2.3 Experimental Results for the Heck Arylation of 2,3-Dihydrofuran Using \((R)\)-BINAP and \((R)\)-BINAPFu.

The Heck arylation of 2,3-dihydrofuran was performed under a variety of reaction conditions on a 1.0 mmol scale (based on PhOTf) in sealed, screw-cap sample vials. In all cases, the Pd-catalysts (3 mol%) were formed \textit{in situ} at 60 °C in the presence of an amine base under argon for 30 minutes. In general, catalysts formed using \((R)\)-BINAP were bright orange in color while catalysts derived from \((R)\)-BINAPFu were bright yellow in color. After formation of the catalyst, PhOTf and 2,3-dihydrofuran (5.1 mmol) were carefully added by microliter-syringe. The argon purged vessels were subsequently sealed and placed in a thermostatically controlled oil bath for a specified period. In light of our inability to repeat Hayashi’s experimental results, coupled with the fact that the reported ee values were ascertained using the chiral shift NMR analysis method, it was deemed prudent to perform control experiments using commercially supplied \((R)\)-BINAP. To this end, all experiments were performed in parallel using both the \((R)\)-BINAP and \((R)\)-BINAPFu catalyst systems and analyzed using the previously described chiral GC analysis conditions. Some typical results from this investigation are shown in Table 5.2.

Employing Hayashi’s original Heck arylation conditions with the \((R)\)-BINAP ligand afforded 2,3-dihydrofuran product 612 in 27% yield and 86% ee (entry 1). However, the reaction was only 30% complete after a 9 day period at 30 °C. In our hands, neither Hayashi’s reported yield (78%)\textsuperscript{271a} nor the enantiomeric excess of the 2,3-dihydrofuran product 612 (93%)\textsuperscript{271a} were attainable using these reaction conditions. Utilizing \((R)\)-BINAPFu, under otherwise identical conditions, afforded a 21% yield of product 612 favoring the \(R\)-configuration in >97% ee (Figure 5.3). Extraordinarily, the enantiomeric purity of the minor isomer 613 was also greater than when \((R)\)-BINAP was employed and the sense of enantioselection was reversed. In other words, both products 612 and 613 were enriched in the \(R\)-configuration suggesting that the reaction may
Table 5.2 Experimental Results Obtained using *(R)-BINAP (505)* and *(R)-BINAPFu (509)* in the Asymmetric Heck Arylation of 2,3-Dihydrofuran (611) with Phenyl Triflate (359).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Source</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Base</th>
<th>Temp. (°C)</th>
<th>Time (d)</th>
<th>Conv. (%)</th>
<th>Ratio 612/613</th>
<th>% Yield*(R)-612 (%)</th>
<th>% Yield(R)-613 (%)</th>
<th>% ee*(R)-613 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>C₆H₆</td>
<td>DIPEA</td>
<td>30</td>
<td>9</td>
<td>33</td>
<td>1.9</td>
<td>21 (97%)</td>
<td>11 (75%)</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>C₆H₆</td>
<td>P.S.</td>
<td>30</td>
<td>9</td>
<td>17</td>
<td>0.1</td>
<td>1 (--)</td>
<td>3 (13%)</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>Dioxane</td>
<td>DIPEA</td>
<td>30</td>
<td>9</td>
<td>71</td>
<td>6.8</td>
<td>61 (97%)</td>
<td>1 (--)</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>NMP</td>
<td>DIPEA</td>
<td>30</td>
<td>9</td>
<td>41</td>
<td>4.0</td>
<td>67 (72%)</td>
<td>1 (--)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>Dioxane</td>
<td>DIPEA</td>
<td>50</td>
<td>7</td>
<td>69</td>
<td>6.7</td>
<td>53 (66%)</td>
<td>1 (2%)</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>C₆H₆</td>
<td>DIPEA</td>
<td>70</td>
<td>7</td>
<td>99</td>
<td>4.1</td>
<td>77 (54%)</td>
<td>3 (19%)</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>THF</td>
<td>DIPEA</td>
<td>70</td>
<td>7</td>
<td>83</td>
<td>1.5</td>
<td>77 (75%)</td>
<td>1 (5%)</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>DME</td>
<td>DIPEA</td>
<td>85</td>
<td>7</td>
<td>100</td>
<td>3.4</td>
<td>74 (53%)</td>
<td>4 (22%)</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>Dioxane</td>
<td>DIPEA</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>24</td>
<td>95 (73%)</td>
<td>1 (4%)</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>DMF</td>
<td>DIPEA</td>
<td>90</td>
<td>7</td>
<td>100</td>
<td>1.7</td>
<td>55 (48%)</td>
<td>13 (32%)</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>Dioxane</td>
<td>PMP</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>10</td>
<td>90 (77%)</td>
<td>1 (9%)</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>Pd₂(db)₃</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>Dioxane</td>
<td>P.S.</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>4.1</td>
<td>73 (41%)</td>
<td>9 (18%)</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)₂</td>
<td>*(R)-BINAPFu (R)-BINAP</td>
<td>Dioxane</td>
<td>DIPEA</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>1.3</td>
<td>55 (35%)</td>
<td>5 (41%)</td>
<td>—</td>
</tr>
</tbody>
</table>

(a) based on unreacted PhOTf. (b) based on chiral GC analysis. (c) S-configuration favored.
not follow Hayashi’s proposed kinetic resolution mechanism. Repeating this experiment using Proton Sponge® (3.0 equiv.) as the base provided much lower product conversion factors (entry 2). Once again, despite numerous attempts Hayashi and Ozawa’s remarkable results could not be repeated. Since the conditions reported in the literature for this reaction failed to give useful product conversions, alternative palladium sources, solvents, bases, and reaction temperatures were investigated. A significant increase in product conversion was observed upon using a polar solvent such as 1,4-dioxane with DIPEA as the base (entry 3). The effect was more pronounced for the \((R)\)-BINAPFu catalyst giving a 61% yield of the 2,3-dihydrofuran product \(612\) (97\% ee). Under identical conditions, the \((R)\)-BINAP catalyst afforded only 43\% yield of
612 (73% ee) albeit with higher regioselectivity. Again, the 2,5-dihydrofuran product 613 was formed with S-configuration selectivity using the (R)-BINAP catalyst while the R-configuration was preferred with the (R)-BINAPFu catalyst. Since NMP has been used successfully in the Stille reaction with trifurylphosphine derived catalysts, it was conceived that this polar solvent may also work well in the present case. Employing NMP as the solvent also afforded higher conversion factors (entry 4) than those observed using benzene (entry 1) but the ee of the major product 612 was diminished (79%) relative to the result obtained with dioxane (97%). The same general trend in enantioselection was observed wherein the absolute configuration of the 2,5-dihydrofuran product 613 differed between the two catalyst systems studied. The use of Pd(OAc)$_2$ as the pre-catalyst was not required to achieve good enantioselectivity. Utilizing the Pd$_2$(dba)$_3$/(R)-BINAPFu catalyst system in dioxane at 50 °C with DIPEA as the base afforded a 25% yield of compound 612 in 76% ee (entry 5). The same conditions in conjunction with a Pd$_2$(dba)$_3$/(R)-BINAP catalyst system furnished compounds 612 and 613 in higher conversion and isomeric selectivity but with reduced enantioselectivity. Using these conditions, both catalysts provided 2,5-dihydrofuran product 613 favoring the R-configuration. Virtually the same product conversion, regioselectivity, and ee was obtained using the (R)-BINAPFu ligand in benzene at 70 °C (entry 6). However, a significant increase in conversion and decrease in isomer selectivity was observed using (R)-BINAP in benzene at 70 °C. Although the conversion was certainly poorer with the (R)-BINAPFu catalyst, it was encouraging to note that respectable enantioselectivities could be also achieved at higher temperatures. In other words, this result suggested that it may be possible to get this reaction to go to completion while still obtaining reasonable levels of enantioselection. A study of various ethereal solvents at elevated temperature (entries 7-9) revealed that full conversion was attainable without a significant loss in enantioselectivity using 1,4-dioxane as the solvent at 100 °C (entry 9). Moreover, at high temperatures, the (R)-BINAPFu catalyst afforded less of the unwanted conjugated isomer 624 and higher selectivity in favor of the 2,3-dihydrofuran product 612. In all cases, utilization of high temperature conditions (>50 °C) provided the 2,5-dihydrofuran product 613 enriched in the R-isomer regardless of whether (R)-BINAP or (R)-BINAPFu was used as the ligand. Conducting the reaction in DMF at 90 °C with DIPEA as the base and a (R)-BINAPFu derived catalyst afforded excellent isomer selectivity with a slight reduction in enantioselectivity (entry 10). At
elevated temperatures, the conditions employing dioxane as the solvent and PMP as the tertiary amine base yielded the 2,3-dihydrofuran product 612 in 80% ee with only modest regioselectivity (entry 11). Hayashi and Ozawa have reported\textsuperscript{271b} higher degrees of enantioselection, at the expense of regioselectivity, using Proton Sponge\textsuperscript{®} as the base. Using this base in dioxane at 100 °C with the (R)-BINAPFu catalyst did not result in increased enantioselectivity (entry 12). However, in accordance with Hayashi's findings, a significant decrease in isomer selectivity was observed. Finally, changing back to the Pd(OAc)\textsubscript{2} catalyst and using dioxane as the solvent at 100 °C with DIPEA as the base gave a slight increase in product regioselectivity (entry 13, cf. entry 9).

Examining the results listed in Table 5.2 as a whole, a few general trends immediately emerge. Firstly, the enantiomeric purity of the 2,3-dihydrofuran isomer 612 was always higher using the (R)-BINAPFu derived catalyst system. At low temperatures (<50 °C), employing dioxane as the solvent with DIPEA as the base afforded the best balance between conversion (71%), and enantioselectivity of the 2,3-dihydrofuran product 612 (97%). However, in this temperature domain, the (R)-BINAP catalyst generally affords a much higher isomer selectivity. The (R)-BINAPFu catalyst consistently provides products 612 and 613 both enriched in the R-configuration. In contrast, the (R)-BINAP catalyst gives compounds 612 and 613 of opposite configuration only at low temperature (30 °C). At higher temperatures (>70 °C), full conversion of the phenyl triflate can be realized with either catalyst system. Under such conditions, the (R)-BINAPFu catalyst typically gives the major product in 71-80% ee while the (R)-BINAP catalyst produces product 612 in 35-57% ee. High temperature conditions, in conjunction with the (R)-BINAPFu catalyst system, give rise to higher isomeric ratios in favor of the 2,3-dihydrofuran product 612 and attenuated formation of the conjugated isomer 624, relative to the corresponding reactions employing the (R)-BINAP derived catalyst. Perhaps of greatest significance is the observation that high enantioselectivity for the 2,3-dihydrofuran isomer 612 does not seem to correlate with poor isomeric selectivity. Recall that Hayashi and Ozawa used this argument as strong evidence supporting a kinetic resolution mechanism.\textsuperscript{210} Notwithstanding our inability to repeat these workers' findings (\textit{vide supra}), the experimental results obtained using the BINAPFu ligand suggest that this assertion may indeed be incorrect.
5.2.4 Investigation of 2,3-Dihydrofuran Heck Arylation Product Distribution as a Function of Time.

In order to investigate if a kinetic resolution process was operative, a few time study experiments were conducted in 4.0 mL reactor vials capped with Teflon-faced silicone septa. Aliquots (0.1 mL) were removed at regular intervals, filtered through basic alumina with a small volume of Et₂O, and subsequently analyzed using the standard chiral GC protocol. In this manner, it was possible to follow the composition and ee of each isomer as a function of time. The following example using a Pd₂(dba)₃/(R)-BINAP catalyst system with DIPEA as the base in 1,4-dioxane at 100 °C is illustrative. Under these conditions, the reaction was complete within a 6 h period and the formation of isomeric products 612, 613 and 624 occurred according to the profiles shown in Figure 5.4. Surprisingly, formation of the 2,3-dihydrofuran isomer 612 always preceded the formation of the 2,5-dihydrofuran product. After a 1 hour period, the former

![Figure 5.4 Chiral GC Analysis Showing Distribution of Products as a Function of Time for the 100 °C Heck Arylation of 2,3-Dihydrofuran.](image)

Legend
- Percent conversion
- Yield of 2,3-dihydrofuran product 612
- Yield of 2,5-dihydrofuran product 613
- Yield of 4,5-dihydrofuran product 624

![Chemical structures](image)

a) 2 mol% Pd₂(dba)₃, 4 mol% (R)-BINAP, 3.0 equiv. DIPEA, dioxane, 100 °C.
product comprised nearly 50% of the reaction mixture while the presence of the 2,5-dihydrofuran product 613 had still not been detected. Presumably, the catalytic pathway leading to the production of the 2-phenyl-2,3-dihydrofuran product 612 must somehow involve a 2-phenyl-2,5-dihydrofuran derived organometallic intermediate (Scheme 5.5). According to Hayashi's mechanistic description, this intermediate plays a key role in a proposed kinetic resolution. The

![Scheme 5.5](image)

intermediate having the 2R-configuration 626 proceeds through the catalytic cycle via [Pd-H] addition and subsequent β-hydride elimination to furnish the 2,3-dihydrofuran product 612. Hayashi postulates that the η²-bound olefin complex with the 2S-configuration 627 quickly releases the 2,5-dihydrofuran product 613 thereby enhancing the enantioselectivity of the initial addition step. Therefore, according to Hayashi's proposed mechanism, the exclusive formation of 2,3-dihydrofuran product 613 would require 100% facial selectivity in the olefin association process leading to the production of enantiopure product. This requirement is in stark contrast to the observed results. Analysis of the product ee as a function of time clearly indicates that the 2,3-dihydrofuran product is not enantiopure during the initial 1 h reaction period (Figure 5.5). Moreover, as the product forms the enantioselectivity steadily decreases from an initial value of 67% (15 min) to a final value of 52% (6 h) in favor of the R-configuration. Extending the reaction period past the 6 h mark did not cause any significant changes to any of the parameters recorded. Interestingly, the ee of the 2,5-dihydrofuran product 613 showed a sharp dependence
Figure 5.5  Chiral GC Analysis Showing Enantiomeric Excess of 2,3-Dihydrofuran Heck Arylation Products 612 and 613 as a Function of Time.\textsuperscript{a}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.5.png}
\caption{Chiral GC Analysis Showing Enantiomeric Excess of 2,3-Dihydrofuran Heck Arylation Products 612 and 613 as a Function of Time.\textsuperscript{a}}
\end{figure}

\begin{tabular}{|c|c|}
\hline
Legend & \\
\hline
\textbullet & Yield of product 612 \\
\texttriangle & ee of product 612 \\
\hline
\end{tabular}

\begin{tabular}{|c|c|}
\hline
Legend & \\
\hline
\textbullet & Yield of product 613 \\
\textcircle & ee of product 613 \\
\hline
\end{tabular}

\textsuperscript{a}  2 \text{ mol\% Pd}(\text{dba})_3, 4 \text{ mol\% (R)-BINAP, 3.0 equiv. DIPEA, dioxane, 100 °C.}

upon conversion. At low levels of production, this compound exhibited a very poor ee (8%) which quickly increased to a stable value of \textit{ca.} 73\% in a period of 1 h. Ironically, the observed enhancement in ee of compound 613 as a function of product conversion does support the occurrence of a kinetic resolution process. However, this behavior simply does not support the mechanism proposed by Hayashi and coworkers.\textsuperscript{210}

Further evidence refuting Hayashi's proposed kinetic resolution mechanism was obtained by performing a similar experiment at 30 °C in benzene with a Pd(OAc)$_2$/(R)-BINAP catalyst system. Although the reaction occurred with poor overall conversion (\textit{ca.} 23\%), formation of the 2,3-dihydrofuran product 612 preceded the detection of the 2,5-dihydrofuran product 613 (Figure 5.6). In addition, the 2,3-dihydrofuran product was initially formed with extremely high ee and
lost enantiopurity as the reaction progressed. The 2,5-dihydrofuran product was formed with low stereoselectivity (ca. 12% ee) and was enriched in the opposite configuration to that favored by the 2,3-dihydrofuran product 612. Clearly, the kinetic resolution mechanism proposed by Hayashi and Ozawa does not explain these experimental findings.

Figure 5.6  Chiral GC Analysis Showing Distribution of Products as a Function Time for the 30 °C Heck Arylation of 2,3-Dihydrofuran. a

<table>
<thead>
<tr>
<th>Legend</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Percent conversion</td>
<td>Yield of product 612</td>
</tr>
<tr>
<td>Yield of product 613</td>
<td>Yield of product 613</td>
</tr>
</tbody>
</table>

a) 2 mol% Pd(OAc)₂, 6 mol% (R)-BINAP, 3.0 equiv. DIPEA, C₆H₆, 30 °C.

5.2.5  Mechanistic Discussion of the 2,3-Dihydrofuran Heck Arylation.

5.2.5.1  Origin of the 2,3-Dihydrofuran Product 612.

Brown and coworkers²⁸⁰ have recently studied the Heck arylation of 2,3-dihydrofuran (611) using ¹H- and ³¹P-NMR analysis in THF-d₈. Starting with (S)-BINAP derived aryl triflate 629 at -70 °C, addition of 2,3-dihydrofuran resulted in the immediate formation of a single species, which was identified by 1D and 2D NMR techniques as intermediate 632 (Scheme 5.6). These authors note that the Pd migration process takes place intramolecularly, since no exchange with
excess 2,3-dihydrofuran (611) was observed. Mechanistically, it was proposed that the Pd fragment migrates from its original position at C-3 to the C-5 site via a tandem sequence of dyotropic shifts. Although this description seems rather implausible, the fact that the Pd moiety quickly migrates to the C-5 position is strong evidence conflicting with Hayashi’s kinetic resolution postulate. Brown and coworkers have shown, by NMR analysis, that intermediate 632 is stabilized by oxygen coordination to the cationic metal center forming an oxapalladacyclopropane structure 633. Warming the solution to -30 °C results in the rapid formation of 2-phenyl-2,3-dihydrofuran (612). Interestingly, the [Pd-H] species that is generated by β-hydride elimination 634 subsequently reacts with another molecule of 2,3-dihydrofuran (611) exhibiting reversed regioselectivity and poor facial selectivity to afford a nearly 1:1 mixture of compounds 635 and 636.

Brown’s NMR investigation of this system is consistent with the finding that the 2,3-dihydrofuran product 612 forms prior to the detection of the 2,5-dihydrofuran isomer 613. The evidence presented regarding stabilization of Pd cation 633 via a dative coordination of the product oxygen atom has particular significance to the BINAPFu ligand. Since BINAPFu is a
poorer σ-donor phosphine than BINAP, it follows that the cationic Pd atom chelated by the
BINAPFu ligand should be more electrophilic (Figure 5.7). Therefore, coordination between the
Pd atom and the ether oxygen of the product should be enhanced in complex 638, relative to the
corresponding (R)-BINAP adduct 637. This may partially explain the reduced catalytic activity
of the BINAPFu derived catalyst system and the increase in conversion observed upon
employing highly polar solvents such as NMP and dioxane (Table 5.2). Furthermore, the NMR
study by Brown and coworkers, in conjunction with the experimental results presented herein,
suggests that the 2,5-dihydrofuran isomer 613 forms from the 2,3-dihydrofuran isomer 612 via a
Pd-catalyzed bond migration (vide infra). Hence, the increased isomeric selectivity observed
using the BINAPFu derived catalyst system may also be attributable to the increased oxonium
ion character of Pd-complex 638. In other words, an increased interaction between the Pd center
and the oxygen atom of the C-5 bound product would result in a decreased tendency toward β-
hydride elimination and subsequent carbon-carbon double bond migratory processes.

As previously stated, use of the (R)-BINAPFu ligand consistently resulted in higher degrees
of enantioselection for the 2,3-dihydrofuran product 612. Since the stereoselectivity of the
carbon-carbon bond forming step is governed by the enantiofacial selectivity of the olefin
binding process, one could conclude that the BINAPFu derived catalyst exhibits better facial
discrimination than the BINAP catalyst. However, recalling that the ee of product 612 tends to
decline as the reaction proceeds, this conclusion may not be entirely justified. In other words, if
the two catalyst species exhibit comparable enantiofacial selectivity, the rate of enantiopurity
loss would determine which ligand affords the best overall selectivity. In order to distinguish
between these two explanations, more experimentation is unfortunately required.
Guiry and coworkers\textsuperscript{282} have recently studied the Heck arylation of 2,2-dimethyl-2,3-dihydrofuran (639) with various phosphine ligands (Scheme 5.7). Using this olefin, greatly simplifies the system and allows for direct comparison of catalyst enantiofacial selectivity. In accordance with the results obtained using the BINAPFu ligand, these workers have also found Hunig’s base to be superior to Proton Sponge\textsuperscript{8} for realizing high product conversion. Investigating the Heck arylation of 2,2-dimethyl-2,3-dihydrofuran (639) using both the (R)-BINAP and (R)-BINAPFu ligands would help to determine if catalysts derived from the latter phosphine exhibit increased facial selectivity. Unfortunately, due to time constraints, such a study could not be conducted.

\textbf{Scheme 5.7}

\[
\begin{array}{c}
\text{639} \quad \text{OTf} \\
\text{359} \quad \rightarrow \\
\text{(R)-640}
\end{array}
\]

Conditions: (a) 3 mol\% Pd(OAc), 8 mol\% (R)-BINAP, 3.0 equiv. Proton Sponge, C\textsubscript{6}H\textsubscript{6}, 40 °C, 14 d, 52\% conversion; 76\% ee (R). (b) 3 mol\% Pd(OAc), 8 mol\% (R)-BINAP, 3.0 equiv. DIPEA, C\textsubscript{6}H\textsubscript{6}, 40 °C, 14 d, 100\% conversion; 76\% ee (R).

5.2.5.2 Origin of the 2,5-Dihydrofuran Product 613.

As previously discussed, the NMR investigation by Brown coworkers\textsuperscript{280} clearly shows that the 2,3-dihydrofuran product 612 quickly forms upon addition of 2,3-dihydrofuran (611) to oxidative addition complex 629 (Scheme 5.6). The fact that only C-5 palladated intermediate 633 was observed in the reaction mixture sharply contradicts Hayashi and Ozawa’s proposed kinetic resolution mechanism.\textsuperscript{210} Moreover, our studies of this reaction at elevated temperature furnished 2,5-dihydrofuran product 613 enriched in the same absolute configuration as the 2,3-dihydrofuran product 612 \textit{(vide supra)}. In order to explain these results, it is proposed that compound 613 forms from the initial reaction product 612 via a palladium catalyzed carbon-carbon double bond migration (Scheme 5.8). Complexation of a [Pd-H] species to either enantiomer of product 612, opposite the bulky phenyl substituent, would provide compounds 642.
and 644. Subsequent addition followed by syn β-hydride elimination with H-3 gives η²-bound olefin complexes 643 and 645, respectively. Olefin dissociation then affords [Pd-H] species 641 and the two enantiomers of 2-phenyl-2,5-dihydrofuran (613). Recalling that the initial formation of product 613 was characterized by a low enantioselectivity (ca. 8% ee in favor of the R-configuration, Figure 5.5), it is clear that both paths illustrated in Scheme 5.8 must be operative.

![Scheme 5.8](image)

Given that the concentration of (R)-2-phenyl-2,3-dihydrofuran (612) exceeds that of the S-configuration, the fact that (R)-613 and (S)-613 are formed in comparable rates suggests that [Pd-H] species 641 must be biased toward “path a” (Scheme 5.8). This conclusion is consistent with the fact that at low temperature the two isomeric products exhibit opposite configurations.

Experimental evidence supporting the formation of 2,5-dihydrofuran product 613 by a Pd-assisted carbon-carbon double bond migration of compound 612 was sought by performing a contamination experiment. The Heck arylation procedure was conducted using 2,3-dihydrofuran (611) and 1-naphthyl triflate (646) in dioxane at 100 °C spiked with ca. 20 mol% isomerically pure 2-phenyl-2,3-dihydrofuran (612) enantioenriched (42 %ee) in the S-configuration (Figure 5.8). After a 7 day reaction period, chiral GC analysis of the crude mixture revealed that approximately 3% of the 2,3-dihydrofuran contaminant had isomerized to the 2,5-dihydrofuran product 613. A separate experiment was performed by treating isomerically pure compound 612
Figure 5.8  Chiral GC Analysis of Heck Reaction Between 1-Naphthyl Triflate and 2,3-Dihydrofuran Contaminated with Pure 2-Phenyl-2,3-Dihydrofuran (612).\textsuperscript{a}

\[
\begin{align*}
\text{OTf} &+ \text{Ph} & \rightarrow & \text{Np} \\
611 &+ 646 & + 612 & \rightarrow 647 + 648 + 649 \\
\text{Pd}_2(\text{dba})_3 (\text{S}-\text{BINAPFu}) & \text{dioxane, DIPEA} & 100^\circ \text{C}, 7 \text{ d}
\end{align*}
\]

(a) Isomerically pure compound 612 (42 \% ee S). (b) Ratio 612/613=32.3; ee 612=41\%; ee 613=2\%. (c) 100\% Conversion; ratio 647/648=6.9; ee 647=24\%; ee 648=43\%; yield 649=3.1\%.
with DIPEA (3.0 equiv) and HOTf (1.0 equiv) in dioxane at 100 °C for 9 days. Since this experiment failed to result in detectable amounts of double bond migration, it was concluded that the isomerization of compound 612 to give 2,5-dihydrofuran isomer 613 must be catalyzed by a palladium hydride species. In addition to compounds 612 and 613, chiral GC analysis of the mixture obtained from the contamination experiment contained 1-naphthyl derived products 647, 648, and 649 with drastically reduced levels of enantioselectivity. Assignment of the product peaks in the gas chromatogram was made by comparison to the results obtained using phenyl triflate and are therefore only tentative.

Although the formation of 2,5-dihydrofuran product 613 via a Pd-assisted bond migration of compound 612 better fits the experimental evidence than Hayashi and Ozawa’s kinetic resolution postulate, an astute reader will have recognized that this explanation does not account for the observed trends in product ee. The production of 2,5-dihydrofuran isomer 613 in low ee from an enantioenriched sample of 2-phenyl-2,3-dihydrofuran (612) requires that the enantiopurity of the remaining starting material be increased. However, the ee of compound 612 was observed to be maximal during the initial reaction period and gradually diminished with increasing time (Figure 5.5). In addition, the ee of 2,5-dihydrofuran product 613 quickly increased from approximately 8% to a value of 73% in favor of the R-configuration over a 1 hour period. These two findings strongly indicate that a kinetic resolution process takes place whereby the (S)-2-phenyl-2,5-dihydrofuran (613) isomer selectively reacts to give back the S-configuration of compound 612. It should be noted that invoking such a process not only explains the observed trends in product ee but also justifies why both enantiomers are enriched in the same absolute configuration.

Hayashi and Ozawa have shown that the stereochemistry of the initial carbon-carbon bond forming step can be accurately predicted on the basis of the [(R)-BINAP]PdCl₂ crystal structure. As stated in Chapter 3, two of the phenyl rings from the diphenylphosphino moieties protrude out toward the palladium atom thus blocking two of the quadrants of space surrounding the metal center (Figure 5.9). In this manner, approach of the 2,3-dihydrofuran starting material (611) is efficiently biased toward the si face of the olefin, which results in selective formation of the R-configuration at C-2. Applying this analysis to the 2,5-dihydrofuran isomer 613, yields two possible π-olefin complexes 651 and 652 (Figure 5.9) leading to compound 612. Coordination of the (R)-2,5-dihydrofuran adduct to the palladium hydride...
species furnishes complex 651 having an unfavorable steric interaction between the C-2 phenyl moiety and lower protruding phenyl substituent. Alternatively, the S-configuration of product 613 complexes to the [Pd-H] fragment to yield adduct 652, which displays significantly less steric congestion between the C-2 hydrogen atom and the lower “filled” quadrant of the coordination sphere. Hence, it is predicted that the S-enantiomer of compound 613 will react selectively to give back the 2,3-dihydrofuran isomer 612 thus diminishing the ee of the latter compound as a function of time. Moreover, in accordance with the experimental results, the 2,5-dihydrofuran isomer will be enriched in the same absolute configuration as the 2,3-dihydrofuran product.

5.2.5.3 Origin of the 4,5-Dihydrofuran Product 624.

Although the conjugated product 624 was generally formed in low yield, the fact that it was detected is strong evidence that the olefin ligand can dissociate away from the Pd atom and re-associate from the opposite face of the double bond. In other words, the initial product of the catalytic cycle is a viable starting material for unwanted catalytic processes. Logistically, it is
clear that this previously unreported reaction product forms from the 2,5-dihydrofuran isomer 613. Since β-hydride elimination is a stereospecific syn process, it follows that the palladium hydride species must complex to the heterocycle from the opposite side to the phenyl substituent (Scheme 5.9). Subsequent addition of [Pd-H] to give C-3 palladated intermediate 654 followed by elimination of the C-2 hydride would produce η^2-olefin complex 655. Dissociation of the

π complex to give the free enol ether completes the sequence. Note that the thermodynamic stability of compound 624, relative to products 612 and 613, is increased and the reverse process may not be feasible. In any case, the stereochemical integrity of the C-2 position is lost through the formation of the 4,5-dihydrofuran product 624.

The experimental results presented in Table 5.2 clearly show that at elevated reaction temperatures the production of compound 624 is attenuated by using a BINAPFu derived catalyst. This observation is likely a manifestation of the fact that employing the BINAPFu ligand results in decreased production of the 2,5-dihydrofuran precursor 613 (Scheme 5.9). As previously postulated, the increased isomer selectivity enjoyed by BINAPFu can be explained through Brown’s oxygen stabilized cationic intermediate 656 (Figure 5.10). It is therefore

Figure 5.10 Stabilization of the C-5 Palladium Intermediate in THF and DME.
interesting to note that the highest amount of product 624 was obtained with a Pd$_2$(dba)$_3$/(R)-BINAP catalyst in DME (Table 5.2, entry 8). This Lewis basic solvent could potentially bind to the Pd atom in a bidentate fashion thereby inhibiting formation of the oxapalladacyclopropane intermediate (Figure 5.10). The decreased interaction between the Pd center and the oxygen atom of the product would therefore translate to an increased tendency toward β-hydride elimination and subsequent carbon-carbon double bond isomerization reactions.

5.2.6 Conclusions.

The BINAPFu ligand clearly outperforms BINAP in the Heck arylation of 2,3-dihydrofuran (611) over a wide range of reaction conditions. Employing the original procedure, reported by Hayashi and coworkers, generally led to poor product conversion factors. However, utilizing elevated temperatures (100 °C), the reaction could be forced to completion with reasonable degrees of enantio- and regioselectivity. The results presented herein, in conjunction with Brown’s NMR investigation, cast serious doubt on Hayashi and Ozawa’s proposed kinetic resolution mechanism. The promising results obtained with the BINAPFu ligand prompted the synthesis and resolution of 2,2’-bis(di-2-furylphosphino)-1,1’-binaphthalene (TetFuBINAP). Application of this ligand in the Heck arylation of 2,3-dihydrofuran is the subject of section 5.6.

5.3 Overman’s Intramolecular Heck Cyclization Reaction for the Synthesis of 3,3’-Spirooxindoles.

Overman and coworkers have extensively studied the asymmetric Heck cyclization of various (E)-α,β-unsaturated 2-haloanilides for the production enantioenriched spirocyclic heterocycles. Rigorous investigation of these systems has provided much insight into the possible mechanistic pathways surrounding Heck ring closure reactions. Of particular significance was the discovery that either enantiomer of spirocyclic product 615a could be prepared with good selectivity using a (R)-BINAP derived catalyst (Scheme 5.10). Overman and coworkers explained this result by postulating that silver salts cause the reaction to occur via a cationic mechanism while tertiary amine bases such as PMP result in a neutral pathway. Previous to this discovery, it had been proposed by Hayashi and Shibasaki that cationic
intermediates were obligatory for realizing high enantioselection in asymmetric Heck reactions of halide substrates. The fact that (R)-615a could be obtained in 89-95% ee from aryl iodide 614, without the presence of silver ions, implied that the bidentate (R)-BINAP ligand had to be fully coordinated to the Pd center during the stereochemistry-determining step. To this end, it was proposed that the neutral pathway proceeds through a five coordinate intermediate 661 whereby the halide ligand is displaced by axial association of the olefin function (Scheme 5.11).

Intrigued by Overman’s involution of a fifth coordination site, it was reasoned that increasing the electrophilicity of the Pd center by employing a poorer σ-donor ligand than BINAP may serve to enhance this mode of reactivity.

Iodoanilides 614 and bromoanilide 666 were prepared in a straightforward manner, according to Overman’s original procedure, starting with commercially available 1-cyclohexene-1-carboxylic acid (663) (Scheme 5.12). Aryl iodide 614 was obtained in 75% overall yield as a light yellow solid, which displayed characteristic 1H-NMR signals at 3.43 ppm (s, 3H) for the
Scheme 5.12

Conditions: (a) 5.2 equiv. SOCl₂, rt, 18 h. (b) 1.2 equiv. o-iodoaniline, Et₃N, toluene, 80 °C, 18 h, 79% (2 steps). (c) 1.2 equiv. o-bromoaniline, Et₃N, toluene, 80 °C, 18 h, 71% (2 steps). (d) 1.5 equiv. NaH, 2.5 equiv. Mel, THF, reflux, 3.5 h; >95% 614, 92% 666.

N-methyl group and 5.91 ppm (m, 1H) for the solitary vinyl proton. Bromide 666 was isolated as a light yellow powder in 65% yield and exhibited N-methyl and vinyl proton resonances at 3.00 ppm (s, 3H) and 5.83 ppm (m, 1H), respectively.

Treating a DMA solution of iodide 614 with a Pd₂(dba)₃/(R)-BINAP and Ag₃PO₄ base at 70 °C for 18 h furnished 3,3-spirooxindole product 615a in 79% isolated yield (63% ee) after flash chromatographic purification (Table 5.3, entry 1). The ee of the product was easily ascertained by ¹H-NMR analysis (200 MHz) in the presence of chiral shift reagent Eu(hfc)₃ and verified by HPLC (Chiralcel® OJ, 9:1 hexane/IPA, 1.0 mL/min).²⁷⁸ The N-methyl singlet resonance of the product, which appears in an isolated region of the spectrum, provides a convenient NMR handle for chiral shift analysis. The low field methyl signal was assigned to the R-product configuration by comparison to Overman’s results. Performing this experiment, under otherwise identical conditions, using a (S)-BINAP Fu derived catalyst provided cyclized product 615a in 61% isolated yield with very low enantioselectivity (4% ee). In accordance with Overman’s findings, performing the reaction using PMP as the base gave the desired heterocycle 615a with high stereoselectivity (82% ee) in favor of the R-enantiomer (entry 2). Employing these conditions in conjunction with the (S)-BINAP Fu ligand resulted in the production of compound 615a in 65% yield and 59% ee. Although the cyclization of iodide 614 was more efficacious with BINAP, these experimental findings suggest that the BINAP Fu derived catalyst requires a neutral reaction pathway in order to realize modest degrees of stereoisounduction.

Treatment of bromide 666 in DMA at 70 °C for 18 h with a Pd₂(dba)₃/(R)-BINAP catalyst and Ag₃PO₄ base resulted in 21% conversion to the desired spirocyclic product 615a as evidenced by ¹H-NMR analysis (Table 5.3, entry 3). Identical conditions in conjunction with a
Table 5.3 Experimental Results Obtained in the Asymmetric Heck Cyclization of Haloanilides 614 and 666 Using the BINAP and BINAPFu Derived Catalysts.

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Ligand</th>
<th>Base</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>% Yield 615a&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>% ee 615a&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>(R)-BINAP</td>
<td>Ag&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>70</td>
<td>18</td>
<td>79</td>
<td>63&lt;sup&gt;d&lt;/sup&gt;</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S)-BINAPFu</td>
<td></td>
<td></td>
<td></td>
<td>61</td>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
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<td>PMP</td>
<td>110</td>
<td>18</td>
<td>61</td>
<td>82</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S)-BINAPFu</td>
<td></td>
<td></td>
<td></td>
<td>65</td>
<td>59</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>(R)-BINAP</td>
<td>Ag&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>70</td>
<td>18</td>
<td>21&lt;sup&gt;e&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S)-BINAPFu</td>
<td></td>
<td></td>
<td></td>
<td>10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>(R)-BINAP</td>
<td>Ag&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>100</td>
<td>20</td>
<td>60</td>
<td>12</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>48</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>(R)-BINAP</td>
<td>PMP</td>
<td>110</td>
<td>18</td>
<td>77</td>
<td>28</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S)-BINAPFu</td>
<td></td>
<td></td>
<td></td>
<td>58</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

(a) Isolated yield. (b) Yield of Δ<sup>3a</sup>-isomer not recorded. (c) Enantiomeric purity determined by <sup>1</sup>H-NMR analysis at 200 MHz in the presence of Eu(hfc)<sub>3</sub>. (d) Also measured by HPLC analysis using a Chiralcel<sup>®</sup> OJ column. (e) Based on <sup>1</sup>H-NMR analysis.

(S)-BINAPFu catalyst provided only a 10% product conversion. Increasing the reaction temperature to 100 °C significantly improved the rate of cyclization and, consistent with Overman's results,<sup>149a</sup> provided very low enantioselectivity (12% ee, entry 4). Employing the (S)-BINAPFu catalyst furnished product 615a in 48% isolated yield as a racemate. Utilizing PMP as the base with a (R)-BINAP ligated catalyst afforded a 77% yield of compound 615a having an ee of 28% in favor of the R-configuration (entry 5). Once again, such conditions applied with (S)-BINAPFu resulted in a lower product yield than obtained with (R)-BINAP, indicating that the former ligand imparts reduced catalytic activity to the Pd catalyst. Moreover, the BINAPFu ligand consistently exhibited poorer enantioselectivity than that realized with BINAP, an observation which ultimately forced the abandonment of this line of research.
5.4 Ruthenium(II)-Catalyzed Asymmetric Hydrogenation of α- and β-Ketoesters.

5.4.1 Introduction.

The homogeneous asymmetric hydrogenation of α- and β-functionalized ketones, using various Ru(II) complexes of optically pure BINAP (505), has been shown by Noyori\textsuperscript{285} and Takaya\textsuperscript{286} to be a highly efficient chemo- and enantioselective process of wide scope. While ruthenium(II)-catalyzed enantioselective reduction of the carbonyl group is certainly a powerful tool for the synthetic research chemist, this chemistry has also been successfully applied to the industrial production of pharmacologically active targets in scales reaching hundreds of tons per annum\textsuperscript{286a}. Remarkable degrees of enantioselection have been demonstrated for a wide variety of substrates using exceptionally low catalyst loading (Table 5.4). The reactions are typically

Table 5.4 Ru(II) Catalyzed Asymmetric Reduction of α- and β-Ketoesters Using the (R)-BINAP Ligand.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>S/C\textsuperscript{a}</th>
<th>H\textsubscript{2} (atm)</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Conv. (%)</th>
<th>% ee (Config.)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\overset{667}{\text{\text{H}}\text{\text{O}}\text{Me}})</td>
<td>2000</td>
<td>100</td>
<td>36</td>
<td>30</td>
<td>99</td>
<td>&gt;99 (R)</td>
<td>285j</td>
</tr>
<tr>
<td>2</td>
<td>(\overset{668}{\text{\text{H}}\text{\text{O}}\text{Et}})</td>
<td>1000</td>
<td>103</td>
<td>58</td>
<td>30</td>
<td>99</td>
<td>99 (R)</td>
<td>285j</td>
</tr>
<tr>
<td>3</td>
<td>(\overset{669}{\text{\text{Cl}}\text{\text{O}}\text{Me}})</td>
<td>2060</td>
<td>4</td>
<td>6</td>
<td>100</td>
<td>97</td>
<td>93 (S)</td>
<td>285d</td>
</tr>
<tr>
<td>4</td>
<td>(\overset{670}{\text{\text{Ph}}\text{\text{O}}\text{Me}})</td>
<td>1000</td>
<td>100</td>
<td>100</td>
<td>25</td>
<td>99</td>
<td>85 (S)</td>
<td>285b</td>
</tr>
<tr>
<td>5</td>
<td>(\overset{671}{\text{\text{Me}}\text{O}})</td>
<td>580</td>
<td>100</td>
<td>95</td>
<td>30</td>
<td>100</td>
<td>88 (R)</td>
<td>286a</td>
</tr>
<tr>
<td>6</td>
<td>(\overset{672}{\text{\text{O}}\text{Me}})</td>
<td>1000</td>
<td>100</td>
<td>2</td>
<td>70</td>
<td>100</td>
<td>88 (1R,2R)\textsuperscript{b}</td>
<td>285e</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Pre-catalyst [RuCl\textsubscript{2}(C\textsubscript{6}H\textsubscript{5})(R-BINAP)]. \textsuperscript{b} 99:1 trans:cis diastereoselectivity.
performed using substrate to catalyst ratios (S/C) exceeding 500 in an alcoholic solvent under elevated \( \text{H}_2 \) pressure (>4 atm). Although the mechanism of rhodium(I)-catalyzed hydrogenation of prochiral olefins has been studied in considerable detail, very little is known about the mechanism of Ru(II)-catalyzed hydrogenations.\(^{287,288}\) Moreover, many of the complexes used as pre-catalysts are formed as complicated mixtures\(^{285b,286a}\) and have not been fully characterized. For this reason, it is difficult to speculate about the structural characteristics of the active catalytic species.

A wide variety of ruthenium complexes have served as hydrogenation pre-catalysts and numerous methods for their preparation have been devised.\(^{287}\) The most generally applied and conveniently prepared pre-catalysts are typically cationic BINAP-Ru(II)(arene) complexes with the general formula \([\text{RuX(BINAP)(arene)}]X\), where \(X\) represents a halogen function.\(^{286a}\) The chloride adduct can be readily prepared by mixing benzeneruthenium(II) chloride dimer (673) and 2 molar equivalents of (R)-BINAP (505) in degassed DMF and heating the resulting suspension at 100 °C for 10 minutes (Scheme 5.13). Subsequent removal of the solvent under reduced pressure affords a red-brown, air sensitive solid, which can be used directly.\(^{286a}\) Takaya and coworkers have investigated the ruthenium(II)-catalyzed hydrogenation of various \( \alpha \)- and \( \beta \)-functionalized ketones using numerous pre-catalyst derivatives.\(^{286a}\) Substitution of dimer 673 with the analogous \( \eta^6 \) bound \( \text{p-cymene} \) and ethyl benzoate complexes allows for the variation of the arene ligand. The same workers have prepared numerous enantiopure derivatives of BINAP by installing various functional groups at the \( \text{meta} \) and \( \text{para} \) positions of the four phenyl moieties.\(^{286a}\) Although placing electron withdrawing halide groups at the \( \text{para} \) positions of the

---

**Scheme 5.13**

\[
\begin{align*}
\text{[}\begin{array}{c}
\text{RuC}l_2 \\
\text{arene}
\end{array}\text{]}_2 & \quad + \quad \text{(R)-505} \quad \xrightarrow{a} \quad \text{[}\begin{array}{c}
\text{Ph}_2\text{P} \\
\text{Ph}_2\text{P} \\
\text{Ph}_2\text{P} \\
\text{Ph}_2\text{Cl}
\end{array}\text{]}_+ \\
\end{align*}
\]

Conditions: (a) DMF, 100 °C, 10 min then 50 °C at 0.1 mm Hg for 1 h.
BINAP phenyl rings resulted decreased catalytic activity and stereoselectivity, the converse effect was not observed upon utilizing p-methyl or p-methoxy BINAP analogues.

Despite evidence suggesting that less electron rich phosphines can adversely effect the catalytic activity and stereoselectivity of reduction, Benincori and coworkers have sought to apply their bibenzothiophene ligand BITIANP\textsuperscript{219,220} (525, Figure 4.8) in ruthenium(II)-catalyzed hydrogenations of α- and β-ketoesters (Table 5.5). As previously discussed, BITIANP is a poorer σ-donor ligand than BINAP and it is therefore surprising that the hydrogenation results reported by Benincori closely match those previously obtained using Noyori’s (R)-BINAP derived catalyst system (Table 5.4). Prompted by Benincori’s study of the BITIANP ligand,\textsuperscript{219,220} an investigation of Ru(II)-catalyzed hydrogenation of α- and β-ketoesters using BINAPFu was initiated. The experimental results obtained from this study are the topic of the following section.

**Table 5.5 Ru(II) Catalyzed Asymmetric Reduction of α- and β-Ketoesters Using the (R)-BINAP and (R)-BITIANP Ligands at 100 atm H\textsubscript{2}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst Ligand</th>
<th>S/C</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>(R)-BINAP\textsuperscript{a}</td>
<td>1000</td>
<td>58</td>
<td>30</td>
<td>99</td>
<td>99</td>
<td>R\textsuperscript{285j}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(R)-BITIANP</td>
<td>1000</td>
<td>2</td>
<td>70</td>
<td>95</td>
<td>99</td>
<td>R\textsuperscript{220}</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>(R)-BINAP</td>
<td>1000</td>
<td>100</td>
<td>25</td>
<td>99</td>
<td>85</td>
<td>S\textsuperscript{285b}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(R)-BITIANP</td>
<td>1000</td>
<td>100</td>
<td>25</td>
<td>92</td>
<td>90</td>
<td>S\textsuperscript{220}</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(R)-BINAP</td>
<td>580</td>
<td>95</td>
<td>30</td>
<td>100</td>
<td>88</td>
<td>R\textsuperscript{286a}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(R)-BITIANP</td>
<td>600</td>
<td>100</td>
<td>25</td>
<td>100</td>
<td>88</td>
<td>R\textsuperscript{220}</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>(R)-BINAP</td>
<td>1000</td>
<td>2</td>
<td>70</td>
<td>100</td>
<td>88\textsuperscript{b}</td>
<td>1R,2R\textsuperscript{285c}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(R)-BITIANP</td>
<td>1000</td>
<td>2</td>
<td>70</td>
<td>92</td>
<td>99\textsuperscript{c}</td>
<td>1R,2R\textsuperscript{219}</td>
</tr>
</tbody>
</table>

(a) 103 atm H\textsubscript{2}. (b) 99:1 \textit{trans}:\textit{cis} diastereoselectivity. (c) 93:7 \textit{trans}:\textit{cis} diastereoselectivity.
5.4.2 Experimental Results Obtained Using $(R)$-BINAPFu (509) for Ruthenium(II)-Catalyzed Asymmetric Reduction of $\alpha$- and $\beta$-Ketoesters.

Following the reports of Noyori,$^{285b}$ Takaya,$^{286a}$ and Benincori,$^{220}$ commercially available benzeneruthenium(II) chloride dimer (673) was treated with 2.0 molar equivalents of $(R)$-BINAPFu (509) in DMF at 100 °C for 30 minutes (Scheme 5.14). Removal of the solvent under reduced pressure (0.1 mmHg) at 50 °C for 1 h furnished a brick-red solid residue, which was used without purification. Unlike the corresponding $(R)$-BINAP complex 674, prepared in the same manner, the pre-catalyst derived from $(R)$-BINAPFu 675 was only sparingly soluble in most organic solvents. $^{31}$P-NMR analysis of compound 675 (162 MHz, DMSO-$d_6$) showed a complex pattern of signals between +15 and +30 ppm indicating that the material was a mixture of various DMF adducts. A small amount of unbound phosphine (-31.3 ppm) could also be detected as a component of the pre-catalyst mixture. Similarly, $^{31}$P-NMR analysis of $(R)$-BINAP complex 674 (162 MHz, CDCl$_3$) exhibited a complex set of signals between +50 and +65 ppm, which was consistent with the literature.$^{285b}$ Both complexes 674 and 675 were stored under an inert atmosphere of nitrogen and used as hydrogenation pre-catalysts without purification.

Treatment of a freeze/thaw degassed methanolic solution of methyl acetoacetate (667) and $(R)$-BINAP complex 674 with H$_2$ (100 atm) at rt for 48 h furnished methyl 3-hydroxybutanoate (676) in >95% conversion as evidenced by $^1$H-NMR analysis of the crude product (Table 5.6, entry 1). A small aliquot of the product was treated with (S)-MTPA-Cl (>98% ee) in dry pyridine and analyzed by GC.$^{278}$ A single peak was observed with a retention time of 29.9 min. A racemic sample of methyl 3-hydroxybutanoate (676), obtained by NaBH$_4$ reduction of methyl
Table 5.6  Asymmetric Hydrogenation of Methyl Acetoacetate (667) with Ru(II) Chloride Complexes of (R)-BINAP and (R)-BINAPFu.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Ligand</th>
<th>S/C</th>
<th>H$_2$ (atm)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conv. (%)$^a$</th>
<th>ee (%)$^b$</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP</td>
<td>1110</td>
<td>100</td>
<td>48</td>
<td>rt</td>
<td>&gt;95</td>
<td>&gt;99</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>(R)-BINAPFu</td>
<td>2052</td>
<td>100</td>
<td>40</td>
<td>rt</td>
<td>&lt;5</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>(R)-BINAPFu</td>
<td>882</td>
<td>100</td>
<td>2.0</td>
<td>100</td>
<td>&gt;95</td>
<td>90</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>(R)-BINAPFu</td>
<td>882</td>
<td>100</td>
<td>0.2</td>
<td>100</td>
<td>&gt;95</td>
<td>86</td>
<td>R</td>
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<tr>
<td>5</td>
<td>(R)-BINAPFu</td>
<td>882</td>
<td>20</td>
<td>3.0</td>
<td>100</td>
<td>&gt;95</td>
<td>40</td>
<td>R</td>
</tr>
</tbody>
</table>

(a) based on $^1$H-NMR analysis.  (b) based on GC analysis of the (S)-MTPA ester.

Acetoacetate, was treated with (S)-MTPA-Cl in the same manner and analyzed by GC to give two peaks with retention times of 29.9 min ($R,S$) and 30.9 min ($S,S$), respectively. Treatment of a methanolic solution of ketoester 667 and ruthenium (R)-BINAPFu complex 675 with H$_2$ (100 atm) for 40 h at ambient temperature afforded only unreacted starting material as evidenced by $^1$H-NMR analysis (entry 2). However, raising the temperature to 100 °C gave >95% product conversion (90% ee) after a 2 h reaction period (entry 3). Hence the (R)-BINAPFu derived catalyst system 675 shows reduced catalytic activity relative to the corresponding ruthenium (R)-BINAP complex 674. Repeating the reduction with a shorter reaction period (entry 4) or reduced H$_2$ pressure (entry 5) also provided product 676 in high conversion but with diminished enantiopurity.

Employing the (R)-BINAP catalyst 674 for the reduction of ethyl acetoacetate (668) gave similar results to those obtained above. Treatment of an ethanolic solution of β-ketoester 668 and RuCl$_2$[(C$_6$H$_5$)$_2$(R-BINAP)] with H$_2$ (100 atm) at rt for 58 hours smoothly furnished ethyl 3-hydroxybutanoate (677) in >95% conversion as a single enantiomer (Table 5.7, entry 1). The ee of product 677 was assessed by GC analysis of the corresponding (S)-MTPA ester. Utilization of the (R)-BINAPFu catalyst system 675, under otherwise identical conditions, failed to provide the desired β-hydroxy ester 677 in >5% conversion (entry 2). Performing the reaction at elevated temperature caused reduction to occur with only modest stereoselectivity (60% ee). Although methyl acetoacetate could be hydrogenated with the (R)-BINAPFu catalyst system in
Table 5.7  Asymmetric Hydrogenation of Ethyl Acetoacetate (668) with Ru(II) Chloride Complexes of (R)-BINAP and (R)-BINAPFu.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Ligand</th>
<th>S/C</th>
<th>H₂ (atm)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP</td>
<td>2092</td>
<td>100</td>
<td>58</td>
<td>rt</td>
<td>&gt;95</td>
<td>&gt;99</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>(R)-BINAPFu</td>
<td>1494</td>
<td>100</td>
<td>60</td>
<td>rt</td>
<td>&lt;5</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>(R)-BINAPFu</td>
<td>1494</td>
<td>100</td>
<td>96</td>
<td>100</td>
<td>&gt;95</td>
<td>60</td>
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<td>1494</td>
<td>100</td>
<td>96</td>
<td>70</td>
<td>&gt;95</td>
<td>18</td>
<td>R</td>
</tr>
</tbody>
</table>

(a) based on <sup>1</sup>H-NMR analysis. (b) based on GC analysis of the (S)-MTPA ester.

relatively high ee (90%), reduction of ethyl acetoacetate failed to provide product in greater than 60% ee. This surprising finding demonstrates that the ruthenium (R)-BINAPFu complex 675 is far less general than the corresponding (R)-BINAP catalyst 674. Interestingly, the enantioselectivity of reduction decreased from 60% to 18% upon lowering the reaction temperature by 30 °C (entry 4). Although this type of behavior has been well documented in the Rh(I)-catalyzed Monsanto process,<sup>289</sup> elevated reaction temperatures are not generally required for achieving high enantioselectivity in Ru(II)-catalyzed hydrogenations.<sup>286a</sup> Given that the hydrogen-carbon bond forming step is likely a kinetically governed process, a trend toward higher levels of enantioselectivity with increasing temperature supports a preceding thermodynamically controlled step in the reaction mechanism.

Hydrogenation of ethyl 4-chloroacetoacetate (669) with (R)-BINAP catalyst 674 in ethanol at 100 °C for 5 min afforded ethyl (S)-3-hydroxy-4-chlorobutanoate (678) in >95% conversion (Table 5.8, entry 1). The enantiopurity of product 678 was determined to be >99% by chiral GC analysis of the corresponding acetate.<sup>278</sup> Performing the reaction with (R)-BINAPFu pre-catalyst 675, under otherwise identical conditions, furnished the desired product in very low conversion (10%) as evidenced by <sup>1</sup>H-NMR analysis (entry 2). Increasing the reaction period to 1 h allowed for better product conversion but unfortunately furnished product in low enantiopurity (45% ee, entry 3). In this case, lowering the temperature to 50 °C provided product in slightly higher enantioselectivity (entry 4).
Table 5.8  Asymmetric Hydrogenation of Ethyl 4-Chloroacetoacetate (669) with Ru(II) Chloride Complexes of (R)-BINAP and (R)-BINAPFu.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Ligand</th>
<th>S/C</th>
<th>H₂ (atm)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conv. (%)ᵃ</th>
<th>ee (%)ᵇ</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP</td>
<td>1110</td>
<td>100</td>
<td>0.1</td>
<td>100</td>
<td>&gt;95</td>
<td>&gt;99</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>(R)-BINAPFu</td>
<td>1832</td>
<td>100</td>
<td>0.1</td>
<td>100</td>
<td>&gt;95</td>
<td>N.D.</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>(R)-BINAPFu</td>
<td>1832</td>
<td>100</td>
<td>1.0</td>
<td>100</td>
<td>&gt;95</td>
<td>45</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>(R)-BINAPFu</td>
<td>370</td>
<td>100</td>
<td>1.0</td>
<td>50</td>
<td>87</td>
<td>52</td>
<td>S</td>
</tr>
</tbody>
</table>

ᵃ based on ¹H-NMR analysis. ᵇ based on chiral GC analysis of the corresponding acetate; N.D.=not determined.

In excellent agreement with Noyori's results, asymmetric hydrogenation of ethyl benzoyleacetate (670) with (R)-BINAP pre-catalyst 674 provided ethyl (R)-3-hydroxy-3-phenylpropionate (679) in high yield and modest enantioselectivity (Table 5.9, entries 1 and 2). The ee of the product was readily determined by chiral HPLC analysis (Chiralcel® OB, 80/20 hexane/IPA, 1.0 mL/min) with 254 nm UV detection. Performing the reaction with (R)-BINAPFu pre-catalyst 675 produced the desired product 679 in good yield (>95%) but with a disappointingly low ee (8%, entry 3). Lowering the reaction temperature to 60 °C significantly retarded the conversion rate (entry 4).

Table 5.9  Asymmetric Hydrogenation of Ethyl Benzoyleacetate (670) with Ru(II) Chloride Complexes of (R)-BINAP and (R)-BINAPFu.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Ligand</th>
<th>S/C</th>
<th>H₂ (atm)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conv. (%)ᵃ</th>
<th>ee (%)ᵇ</th>
<th>Config.</th>
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<tbody>
<tr>
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<td>610</td>
<td>100</td>
<td>100</td>
<td>60</td>
<td>&gt;95</td>
<td>85</td>
<td>R</td>
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<tr>
<td>2</td>
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<td>96</td>
<td>60</td>
<td>&gt;95</td>
<td>81</td>
<td>R</td>
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<tr>
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<td>(R)-BINAPFu</td>
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<td>100</td>
<td>100</td>
<td>&gt;95</td>
<td>8</td>
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<td>100</td>
<td>96</td>
<td>60</td>
<td>12</td>
<td>N.D.</td>
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ᵃ based on ¹H-NMR analysis. ᵇ based on HPLC analysis; N.D.=not determined.
Hydrogenation of methyl pyruvate (671) using RuCl₂[(C₆H₆)(R-BINAP)] (674) in methanol at 30 °C efficiently provided methyl (S)-lactate (680) in 88% ee (Table 5.10, entry 1) as evidenced by chiral HPLC analysis (Chiralcel® OB, 90/10 hexane/IPA, 1.0 mL/min) with 205 nm UV detection. Utilizing similar conditions in conjunction with (R)-BINAPFu pre-catalyst 675 failed to provide the desired alcohol 680. Once again, increasing the reaction temperature gave the desired product in high yield (>95%) but with low stereoselectivity (29% ee, entry 3).

Table 5.10 Asymmetric Hydrogenation of Methyl Pyruvate (671) with Ru(II) Chloride Complexes of (R)-BINAP and (R)-BINAPFu.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Ligand</th>
<th>S/C</th>
<th>H₂ (atm)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conv. (%)ᵃ</th>
<th>ee (%)ᵇ</th>
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<td>88</td>
<td>R</td>
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<td>96</td>
<td>30</td>
<td>N.R.</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
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<td>100</td>
<td>96</td>
<td>50</td>
<td>&gt;95</td>
<td>29</td>
<td>R</td>
</tr>
</tbody>
</table>

(a) based on ¹H-NMR analysis; N.R.=no reaction. (b) based on HPLC analysis.

Finally, the reduction of methyl 2-oxocyclopentanecarboxylate (672) was investigated using both the (R)-BINAP and (R)-BINAPFu pre-catalysts in methanol at 70 °C (Table 5.11). Utilizing the (R)-BINAP system 674 provided the desired alcohol 681 in high yield (>95%) and

Table 5.11 Asymmetric Hydrogenation of Methyl 2-oxocyclopentanecarboxylate (672) with Ru(II) Chloride Complexes of (R)-BINAP and (R)-BINAPFu.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Ligand</th>
<th>S/C</th>
<th>H₂ (atm)</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conv. (%)ᵃ</th>
<th>de (%)ᵇ,c</th>
<th>Config.</th>
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<td>90</td>
<td>2</td>
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<td>22</td>
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<td>trans</td>
</tr>
<tr>
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<td>(R)-BINAPFu</td>
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<td>90</td>
<td>48</td>
<td>100</td>
<td>&gt;95</td>
<td>21</td>
<td>trans</td>
</tr>
</tbody>
</table>

(a) based on ¹H-NMR analysis. (b) based on GC analysis. (c) enantiopurity not determined.
diastereoselectivity (86% de) in favor of the trans isomer. The diastereomeric excess (de) of product 681 was readily ascertained by GC analysis. Employment of (R)-BINAPFu catalyst 675 at 70 °C for 2 h under 90 atm H₂ resulted in low product conversion (22%) and diastereoselectivity (44% de, entry 2). Increasing the reaction time and temperature provided product 681 in high yield and low isomeric selectivity (entry 3).

The experimental results obtained using (R)-BINAPFu catalyst 675 indicate that reduced phosphine basicity adversely effects the rate of ruthenium(II)-catalyzed hydrogenation reactions. Since the pre-catalyst must release the η⁶-bound arene ligand to form the active catalytic species, reduced σ-donor ability may inhibit this process by making the metal center more electrophilic. While this hypothesis is consistent with the findings of Takaya and coworkers, it remains unclear why Benicori’s analogous BITIANP ligand²¹⁹,²²⁰ gives results comparable to those obtained with BINAP.

It is difficult to conclude whether or not reduced phosphine basicity has a detrimental effect on the stereoselectivity of Ru(II)-catalyzed hydrogenations of α- and β-ketoesters. Noyori,²⁸⁵a Takaya,²⁸⁶ and Schmid²⁰³ have all independently reported that perturbing the steric properties of a phosphine ligand can have a significant impact upon the stereoselectivity of these reactions. In any case, the BINAPFu ligand does not show promise for this chemistry and it is therefore concluded that further study is not warranted.

5.5 Development of a Second Generation Atropisomeric 2-Furyl Phosphine Ligand for Asymmetric Synthesis.

5.5.1 Synthesis of 2,2'-Bis(di-2-furylphosphino)-1,1'-binaphthalene (TetFuBINAP).

Driven by the favorable results obtained using BINAPFu (509) in the asymmetric Heck arylation of 2,3-dihydrofuran (vide supra), a synthesis of 2,2'-bis(di-2-furylphosphino)-1,1'-binaphthalene (TetFuBINAP, Figure 5.11) was undertaken. This ligand, which contains two added 2-furyl moieties relative to BINAPFu, should be an even poorer σ-donor phosphine. Moreover, employing TetFuBINAP (682) in Hayashi’s Heck arylation process should shed light on whether or not reduced phosphine donor capacity is responsible for the increase in ee of 2,3-dihydrofuran product 612 using the BINAPFu ligand.
It was originally conceived that TetFuBINAP (682) could be prepared in an analogous manner to the Merck synthesis of BINAP. However, treatment of readily available (±)-ditriflate 683 and chlorodi-2-furylphosphine (684) with Zn dust and a NiCl₂(dppe) catalyst in DMF at 110 °C for 76 h failed to afford the desired product (Scheme 5.15). Under these conditions, only unreacted triflate 683 and the hydrolysis product di-2-furylphosphine oxide (686) were isolated from the reaction mixture. Similar results were obtained using bromodi-2-furylphosphine (685) as the cross-coupling partner. Faced with these results, recourse was sought in the modification of Noyori’s BINAP synthesis.

Treatment of β-naphthol (687) with hydrazine monohydrate at 180 °C in a sealed stainless steel vessel for 3 d, according to Clemo and Dawson’s original procedure, afforded 2,2-diamino-1,1'-binaphthalene (688) in 45% yield (Scheme 5.16). Efficient stirring of the reaction mixture and strict temperature control were found to be crucial for the successful production of diamine 688. Subsequent diazotization followed by treatment with a HgBr₂/KBr mixture afforded known tribromomercurate 689 as a bright orange, light sensitive solid. Treatment of
diazonium metal complex 689 with a 10-fold excess of KBr at 95 °C under high vacuum smoothly afforded, after chromatographic purification, the required 2,2'-dibromo-1,1'-binaphthalene (690) in 69% isolated yield.

Halogen-metal exchange of dibromide 690 in Et₂O at -78 °C with 2.2 equivalents of n-BuLi provided 2,2'-dilitho-1,1'-binaphthalene (691) in quantitative yield as evidenced by deuterium quenching studies (Scheme 5.17). However, treatment of this dianion with 2.5 equivalents of chlorodi-2-furylphosphine (684) at -78 °C gave a complex mixture of products from which only 15-20% of the desired TetFuBINAP (682) could be isolated. Superior results were obtained upon treating Grignard reagent 692, prepared in a mixture of THF and toluene, with phosphorus chloride reagent 684 at -30 °C. Using this procedure, racemic TetFuBINAP could be isolated in 55% yield as a colorless, amorphous powder. ³¹P-NMR analysis of compound 682 showed a single resonance at -58.6 ppm and the low resolution mass spectrum confirmed a molecular weight of 582 amu. Moreover, ¹H and ¹³C-NMR analysis of phosphine 682 were consistent with
a C$_2$-symmetrical molecule. With racemic TetFuBINAP in hand, attention was now focused on the resolution, absolute configuration assignment, and physical characterization of this novel ligand.

### 5.5.2 Resolution and Absolute Configuration Assignment of the TetFuBINAP Ligand.

In an analogous manner to the optical resolution of the BINAPFu ligand, racemic TetFuBINAP (682) was treated with 2.2 equivalents of (1S,2R)-O-(r-butyldimethylsilyl)isobornyl-10-sulfonyl azide (693) in refluxing THF for 24 h (Scheme 5.18). Fortunately, the resulting 1:1 mixture of diastereomeric phosphinimines 694a and 694b were separable by flash chromatography. Hydrolysis of isomerically pure phosphinimine 694a in a refluxing mixture of THF and 3M H$_2$SO$_4$ (ca. 17:1 by volume) for 0.5 h smoothly afforded phosphine oxide 695 in excellent yield (Scheme 5.19). It is noteworthy that acid promoted decomposition of the furyl moieties did not occur under the phosphinimine hydrolysis conditions. $^{31}$P-NMR
analysis of phosphine oxide 695 showed a single resonance at +2.2 ppm and low resolution mass spectral analysis confirmed a molecular weight of 614 amu. Trichlorosilane reduction of compound 695 provided levorotatory TetFuBINAP (682) ([α]_D^{19} -78.3 (c 0.95, CHCl₃)) in 70% isolated yield. Conversely, subjecting isomerically pure phosphinimine 694b to this hydrolysis/reduction sequence furnished dextrorotatory TetFuBINAP (682) in 77% yield ([α]_D^{17} +77.5 (c 1.03, CHCl₃)).

Treatment of (-)-TetFuBINAP with elemental selenium dust in refluxing CHCl₃ furnished the corresponding diselenide 696 in 86% isolated yield (Scheme 5.20). Analysis of the $^{31}$P-NMR spectrum of bis-phosphine selenide 696 showed a singlet resonance at -4.5 ppm with a satellite doublet ($^{31}$P-$^{77}$Se = 767 Hz) due to $^{31}$P-$^{77}$Se coupling. This coupling constant, which is slightly greater in magnitude than that obtained for the bis-selenide of BINAPFu (compound 598, Figure 4.8), indicates that TetFuBINAP is a poorer α-donor ligand. Unfortunately, X-ray quality crystals of bis-selenide 696 could not be obtained thus prohibiting the assignment of absolute configuration via the Bijvoet method. Moreover, suitable crystals of isomerically pure phosphinimines 694a and 694b could not be obtained. In order to circumvent this problem, the absolute configuration of (-)-TetFuBINAP (682) was assigned by careful analysis of its circular dichroism (CD) spectrum (vide infra).

The chiroptical property of circular dichroism, which is a measure of the differential absorption of left-handed and right-handed circularly polarized light as a function of wavelength, has been used to assign the absolute stereochemistry of biaryl compounds. Such materials normally show two bisignate Cotton effects (CE) centered about the UV$_{max}$ due to coupling of π-π* chromophores of the aromatic rings. This phenomenon, known as exciton chirality, can be either “negative” or “positive” as defined by Harada and Nakanishi. A “negative” chirality is
characterized by the longer wavelength CE of the couplet being negative while the shorter wavelength CE is positive. Sector rules have been established for a variety of compound classifications and serve as predictive tools for determining the absolute configuration of unknown compounds. In order to develop such rules, the CD behavior of structurally similar materials of known configuration must be first be studied. In other words, comparison of the CD spectra of a configurationally known solution of BINAP (505) with that of experimentally obtained TetFuBINAP (682), in the $\lambda_{\text{max}}$ region, serves as a method for determining the absolute stereochemistry of the latter compound.

In order to experimentally apply the CD method, dilute ethanolic solutions of (S)-BINAP (505) and (-)-TetFuBINAP (682) were prepared and subjected to UV analysis. The former solution exhibited a UV$_{\text{max}}$ of 260 nm while the TetFuBINAP solution displayed a UV$_{\text{max}}$ at

![CD Spectrum of (S)-BINAP and (S)-TetFuBINAP in EtOH at 25 °C.](image)

**Figure 5.12** CD Spectrum of (S)-BINAP and (S)-TetFuBINAP in EtOH at 25 °C.
The CD spectra of these two solutions, measured at 25 °C under a nitrogen atmosphere, are shown in Figure 5.12. The (S)-BINAP spectrum exhibits “negative” chirality with Cotton effects at 265 nm (Δε -6) and 252 nm (Δε +37), respectively. The solution of (-)-TetFuBINAP displayed a very similar CD spectrum with Cotton effects at 264 nm (Δε -36) and 244 nm (Δε +51). It was therefore concluded that these two compounds share a common configurational assignment and (-)-TetFuBINAP was assigned as the S-axial isomer. Moreover, it follows that phosphinimine 694a also corresponds to the S-axial configuration.

5.6 Application of TetFuBINAP (682) in the Asymmetric Heck Arylation of 2,3-Dihydrofuran (611).

With optically pure TetFuBINAP (682) in hand, attention was now directed at the application of this novel ligand in Hayashi’s asymmetric Heck arylation of 2,3-dihydrofuran (611). Employing (R)-TetFuBINAP at 30 °C in either dioxane or C₆H₆ with DIPEA as the base afforded only unreacted PhOTf after a 7 d reaction period. Hence, the TetFuBINAP ligand provides a less active Pd catalyst than the corresponding (R)-BINAP and (R)-BINAPFu derived systems. Performing the reaction with a Pd₂(dba)₃/(R)-TetFuBINAP catalyst system at 50 °C in dioxane for 7 d yielded only 17% of the desired product 612 (Table 5.12, entry 1). Although the reaction did not go to completion, the enantiomeric purity of 2,3-dihydrofuran product 612 exceeded the values obtained using (R)-BINAPFu and (R)-BINAP derived catalysts under identical conditions. However, (R)-TetFuBINAP provided the poorest level of isomer selectivity. Conducting the reaction at a higher temperature (100 °C) solved the conversion problem but resulted in an unexpected enantioselectivity trend (entry 2). The (R)-TetFuBINAP derived catalyst afforded 2,3-dihydrofuran product 612 in only 19% ee in favor of the R-configuration. In addition, poor isomeric selectivity was observed with an increased production of 4,5-dihydrofuran product 624. Similar results were obtained using Pd(OAc)₂ as the pre-catalyst (entry 3). Again, the highest levels of enantioselectivity and regioselectivity were enjoyed by the (R)-BINAPFu (509) catalyst while the (R)-TetFuBINAP (682) species afforded both the lowest ee and isomer selectivity. Clearly, factors other than phosphine σ-donor capacity also play a significant role in determining the reaction outcome.
**Table 5.12 Application of \((R)\)-TetFuBINAP in the Heck Arylation of 2,3-Dihydrofuran.**

\[
\begin{align*}
\text{Entry} & \quad \text{Pd Source} & \quad \text{Ligand} & \quad \text{Cond.} & \quad \text{Conv. (\%)} & \quad \text{Ratio} & \quad \% \text{ Yield (\% ee)} \\
1 & \quad \text{Pd}_2(\text{dba})_3 & \quad (R)\text{-TetFuBINAP} & \quad \alpha & \quad 22 & \quad 3.4 & \quad 17 (89) & \quad 0 & \quad 5 (63) \\
& & \quad (R)\text{-BINAPFu} & & \quad 30 & \quad 5.0 & \quad 25 (76) & \quad 0 & \quad 5 (37) \\
& & \quad (R)\text{-BINAP} & & \quad 56 & \quad 27 & \quad 53 (66) & \quad 1 & \quad 2 (15) \\
2 & \quad \text{Pd}_2(\text{dba})_3 & \quad (R)\text{-TetFuBINAP} & \quad \beta & \quad 100 & \quad 2.3 & \quad 60 (19) & \quad 14 & \quad 26 (2) \\
& & \quad (R)\text{-BINAPFu} & & \quad 100 & \quad 10 & \quad 90 (77) & \quad 1 & \quad 9 (40) \\
& & \quad (R)\text{-BINAP} & & \quad 100 & \quad 4.1 & \quad 73 (41) & \quad 9 & \quad 18 (26) \\
2 & \quad \text{Pd(OAc)}_2 & \quad (R)\text{-TetFuBINAP} & \quad \beta & \quad 100 & \quad 2.5 & \quad 64 (49) & \quad 10 & \quad 26 (16) \\
& & \quad (R)\text{-BINAPFu} & & \quad 100 & \quad 13 & \quad 92 (74) & \quad 1 & \quad 7 (64) \\
& & \quad (R)\text{-BINAP} & & \quad 100 & \quad 7.2 & \quad 86 (57) & \quad 2 & \quad 12 (79)
\end{align*}
\]

a) Conditions \(\alpha\): dioxane, 3.0 equiv. DIPEA, 50 °C, 7 d; conditions \(\beta\): dioxane, 3.0 equiv. DIPEA, 100 °C, 7 d. (b) based on unreacted PhOTf. (c) based on GC analysis.

Since TetFuBINAP (682) provided the highest enantioselectivity at 50 °C (entry 1), it follows that incorporation of the four furyl moieties into the ligand design did not compromise the phosphine’s ability to discriminate between the two enantiotopic faces of 2,3-dihydrofuran (611). However, it is clear that reduced phosphine donor capacity has an adverse effect upon the rate of conversion. In order to explain the low degrees of enantio- and regioselectivity obtained using TetFuBINAP (100 °C), in connection with the amended reaction mechanism (section 5.2.5), it is proposed that the bond migration process converting 2,5-dihydrofuran isomer 613 to the 2,3-dihydrofuran product 612 becomes less selective (Figure 5.13). In other words, relative to the BINAP ligand, the 2-furyl rings of TetFuBINAP may not as effectively crowd the lower “filled” quadrant of the Pd coordination sphere. Reduced disparity between structures 697 and 698 would result in racemization of the 2,3-dihydrofuran product 612 and prevent the kinetic resolution of 2,5-dihydrofuran product 613. In order to gain further evidence for such a hypothesis, a time study experiment, similar to those described in section 5.2.4, could be performed. Unfortunately, due to time restrictions, such a study could not be completed.
5.7 Application of TetFuBINAP in the Asymmetric Heck Cyclization of Haloanilides 614 and 666.

Heating iodoanilide 614 and PMP (5.0 equiv) in dimethylacetamide at 110 °C with a Pd$_2$(dba)$_3$/(R)-TetFuBINAP catalyst system for 3 days furnished cyclized products 615a and 615b in a 5.6:1 ratio as evidenced by $^1$H-NMR analysis (Table 5.13, entry 1). Chromatographic separation of the product mixture afforded a 74% yield of the desired $\Delta^{2,3}$-isomer 615a having an ee of 85% in favor of the $R$-configuration. Under otherwise identical conditions, employing a (R)-BINAP derived catalyst also resulted in high enantioselectivity (85% ee $R$) but diminished isomer selectivity. Performing the reaction in DMF at 110 °C for 3 days resulted in nearly identical results (entry 2). In light of the poor results obtained using (S)-BINAPFu for the cyclization of amides 614 and 666 (vide supra), it was encouraging to find that the (R)-TetFuBINAP catalyst provided cyclized product 615a in reasonably high enantioselectivity. However, similar to the results obtained for the 2,3-dihydrofuran Heck arylation reaction, using (R)-TetFuBINAP as the chiral modifying ligand resulted in reduced catalyst activity. Therefore, in order to force the reaction to proceed to completion, it was necessary to employ long reaction times at elevated temperatures, resulting in elevated production of the unwanted $\Delta^{3,4}$-isomer 615b.

Delightfully, the cyclization of bromoanilide 666 in DMA at 110 °C for 3 d furnished cyclized product 615a in 57% isolated yield with 64% ee (entry 3). Although this enantioselectivity is clearly modest in comparison to the results obtained with iodide precursor 614,
Table 5.13 Results Obtained for the Asymmetric Heck Cyclization of Haloanilides 614 and 666 Using (R)-BINAP and (R)-TetFuBINAP Fu Derived Catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Base</th>
<th>Ratio 615a/615b</th>
<th>% Yield 615a</th>
<th>% Yield 615b</th>
<th>% ee 615a (Config.)</th>
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<td>PMP</td>
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<td>74</td>
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<td></td>
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<td>PMP</td>
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<td>PMP</td>
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<td>(R)</td>
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<tr>
<td>4</td>
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<td></td>
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<td></td>
<td>1.0</td>
<td>46</td>
<td>36</td>
<td>(R)</td>
</tr>
</tbody>
</table>

(a) based on $^1$H-NMR analysis of the crude reaction mixture. (b) Isolated yield. (c) Enantiomeric purity determined by $^1$H-NMR analysis at 200 MHz in the presence of Eu(hfc)$_3$.

The cyclization of bromide 666 with a (R)-BINAP derived catalyst afforded product 615b in only 18% ee. Overman has reported that the PMP-promoted cyclization of bromide 666 in DMA (120 °C) with a (R)-BINAP catalyst optimally provides product 615a in 51% yield having an ee of 32% in favor of the R-configuration.\textsuperscript{149a} Moreover, using these conditions, double bond isomer 615b was also produced in 36% yield. In short, employing TetFuBINAP (682) for the Heck cyclization of bromoanilide 666 has improved the best reported ee for this reaction by a factor of two. Similar results were obtained performing the reaction in DMF at 110 °C with a Pd$_3$(dba)$_3$/(R)-TetFuBINAP catalyst (entry 4). Unfortunately, these intriguing results could not be studied in further detail due to time limitations.
5.8 Future Work.

Application of BINAPFu (509) in the asymmetric Heck arylation of 2,3-dihydrofuran (611) has shown extremely promising results. Further study of the mechanism should provide useful insight for the design of new, more efficient phosphine ligands. The enhanced enantioselectivity obtained using BINAPFu may be a result of increased enantiofacial discrimination of the catalyst or a reduced rate of racemization (vide supra). To address this question, an investigation of the enantioselectivity of the carbon-carbon bond forming step, via arylation of 2,2'-dimethyl-2,3-dihydrofuran (639), should be undertaken. Studying the BINAPFu-mediated arylation of 2,3-dihydrofuran (611) with low temperature $^1$H- and $^{31}$P-NMR, similar to the work of Brown and coworkers, could provide useful corroborating evidence for the proposed reaction mechanism. Employing the BINAPFu ligand toward the Heck arylation of various other heterocyclic and carbocyclic substrates would be a natural extension of the work presented herein.

Application of the TetFuBINAP ligand in Hayashi’s Heck arylation reaction provided mixed results. Using this phosphine at low temperature (50 °C) provided product in high ee albeit with a poor level of conversion. Although high temperature conditions (100 °C) allowed for complete conversion, the enantioselectivity of the process suffered dramatically. As previously discussed, the reduced steric size of the 2-furyl group, relative to a phenyl substituent, could be responsible for the reduced levels of stereoselectivity observed at high temperature. Performing time study experiments, as described in section 5.2.4, on TetFuBINAP-mediated Heck arylation reactions may confirm this hypothesis. Acceleration of the reaction through microwave irradiation could allow for enhanced product conversion at moderate reaction temperatures. If this is possible, synthesis and application of alternative stereogenic furylphosphine ligands such as compounds 699a-699c (Figure 5.14) would be justified.

Figure 5.14 Potential 2-Furyl Phosphine Ligands for Further Investigation.
The favorable results obtained using TetFuBINAP (682) for the asymmetric Heck cyclization of bromoanilide 666 certainly warrants further study. If the increased enantioselectivity observed using this ligand proves to be general for a wide variety of bromide precursors, the scope of the asymmetric Heck reaction would be significantly broadened.

Enantioselective hydrocyanation, hydroformylation, and hydroacylation reactions have recently been performed with various stereogenic phosphinite ligands with considerable degrees of success. These ligands, which are less Lewis basic than typical triaryl phosphines, have been shown to provide higher degrees of enantio- and regioselectivity by increasing the rate of reductive elimination. Since this process is thought to be the “turnover limiting step” of all three reactions, enhanced rates of reductive elimination translate to more active catalyst species and attenuated formation of byproducts. It is therefore proposed that similar studies of asymmetric hydrocyanation, hydroformylation, and hydroacylation reactions should be conducted with BINAPFu (509) and TetFuBINAP (682) derived catalyst systems.

6.1 P-Stereogenic Phosphines.

Having demonstrated that the Staudinger reaction between enantiopure sulfonylazide 593 and racemic BINAPFu (509) could be exploited for the purpose of optical resolution, it was conceived that such a process may prove very useful for the preparation of P-stereogenic phosphine oxides.\textsuperscript{302} Although such materials are not generally useful for metal-mediated asymmetric synthesis, the corresponding enantiomerically pure phosphines hold great potential for asymmetric catalysis. However, efforts to use P-stereogenic phosphines in enantioselective transformations have been infrequent due, in part, to the relative difficulty of obtaining these compounds by resolution procedures or diastereoselective synthesis.\textsuperscript{303} Since reliable methods have been developed to stereospecifically reduce P-stereogenic phosphine oxides to the corresponding phosphines with either retention or inversion of configuration,\textsuperscript{304} new methods for the preparation of optically pure phosphine oxides are highly valuable. Relatively few methods are available for obtaining enantiomerically pure phosphine oxides and thus a research project aimed at applying the new Staudinger resolution technique toward P-stereogenic phosphines was initiated.

6.1.1 Synthesis of P-Stereogenic phosphines.

Unfortunately, a commercial source of (±)-P-stereogenic tertiary phosphines could not be identified and thus these materials had to be synthesized according to known general methods.\textsuperscript{305} Phosphines containing two alkyl substituents, one of which was methyl, and an aryl group were prepared via LiAlH\textsubscript{4} reduction of a suitably substituted phosphonium salt 701 (Scheme 6.1). Since phosphines bearing alkyl groups are prone to air oxidation, these materials were generally

![Scheme 6.1](image_url)

Scheme 6.1

Conditions: (a) 2 equiv. Mel, CHCl\textsubscript{3}, rt, 24 h. (b) 5 equiv. LiAlH\textsubscript{4}, Et\textsubscript{2}O, reflux. 6 h.
prepared under an argon atmosphere immediately prior to use. Racemic phosphines 703-705 (Figure 6.1), prepared according to the phosphonium salt procedure, exhibited physical and spectral properties consistent with reported literature data. Phosphines bearing two or more aryl substituents were prepared in a stepwise fashion starting with phosphonamidous chloride reagent 706 (Scheme 6.2). For example, treatment of compound 706 with 1 molar equivalent of MeMgBr in Et₂O at -40 °C for 1 hour afforded phosphonamide 707 in 85% yield. Subsequent reaction of this compound with 2.2 equivalents of anhydrous HCl (1.0 M solution in Et₂O) furnished chloromethylphenylphosphine (708), after removal of the unwanted amine hydrochloride salt by vacuum filtration. Treatment of chlorophosphine 708 in ether at -40 °C with a variety of freshly prepared aryl Grignard reagents afforded racemic phosphines 710-714 in 32-67% yield (Figure 6.2). In all cases, phosphines 710-714 exhibited spectral properties either consistent with those reported in the literature or in agreement with their proposed
structures. Known triaryl phosphine $715^{111}$ was prepared in a similar stepwise manner with the exception that 1-naphthylmagnesium bromide was used in place of MeMgBr (step a, Scheme 6.2).

6.1.2 Attempted Resolution of Cyclohexylmethylphenylphosphine (703) Using (1S)-10-Camphorsulfonyl Azide (593).

Treatment of cyclohexylmethylphenylphosphine (703) with 1.1 molar equivalents of (1S)-10-camphorsulfonyl azide (593) clearly gave a 1:1 mixture of diastereomeric phosphinimines $716a$ and $716b$ (Scheme 6.3) as evidenced by $^1H$ and $^31P$-NMR analysis. Unfortunately, this mixture was determined to be inseparable by crystallization and flash chromatographic techniques. Although organoazide 593 may have proved useful for the resolution of other racemic tertiary phosphines, this line of research was not explored. Rather, efforts were directed at identifying an organoazide resolving agent which would be highly general for a wide variety of racemic phosphines. To this end, (+)-neomenthyl azide (717), $314$ 3β-azido-5α-cholestan (718), $315$ and 6-azido-6-deoxy-1,2,3,4-di-O-isopropyliden-α-D-galactopyranose (719) $316$ (Figure 6.3) were
prepared according to literature procedures and screened as potential resolving agents. Treatment of cyclohexylmethylphenylphosphine (703) with enantiopure azides 717-719 furnished phosphinimines which were generally found to be highly sensitive toward hydrolytic cleavage of the P=N bond. Attempts to purify these materials by crystallization or flash chromatography were impeded by concomitant formation of cyclohexylmethylphenylphosphine oxide. Since phosphinimines formed using alkyl azides 717-719 seemed to be less robust than those prepared from (1S)-10-camphorsulfonyl azide (593), attention was focused on derivatizing the latter compound in hopes of identifying a more general phosphine resolving agent. Due to the highly reactive nature of the azide functional group, it was deemed prudent to structurally modify camphorsulfonic acid and subsequently form the N-sulfonyl moiety rather than attempt to derivatize compound 593 directly.

6.1.3 Structural Modification of Camphorsulfonic Acid.

The C-2 ketone group of camphorsulfonic acid provided a convenient handle for possible derivatization and was therefore chosen as the target for synthetic manipulation. Moreover, since this group is responsible for the asymmetry of the CSA molecule, it was postulated that increasing the steric size of the functional group at C-2 may indeed result in the production of a better, more stereodifferentiated resolving agent. Initially, efforts were directed at the possibility of forming a C-2 ketal functionality. Due to hydrogen bonding with the C-10 sulfonic acid residue, it was postulated ketalization could be achieved at C-2 in an autocatalytic manner. Heating (+)-CSA•H₂O with 1.1 molar equivalents of ethylene glycol in benzene with azeotropic removal of water for 12 h did not furnish the desired ketal (Table 6.1, entry 1). Increasing both the amount of diol used to 3 equivalents and the reflux period to 76 hours failed to improve this result (entry 2). Employing a higher boiling solvent such as toluene for 48 h also failed to provide the desired product (entry 3). Use of 2,2-dimethyl-1,3-propane diol, which has been shown to be kinetically faster in ketal formation with cyclohexanone, only resulted in the isolation of unreacted camphorsulfonic acid (entries 4-6). These unfortunate results led to the abandonment of the C-2 ketalization approach and forced the investigation of alternative derivatization methods.
Table 6.1  Attempted Ketalization of (1S)-10-Camphorsulfonic Acid (517)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diol</th>
<th>Equiv. of Diol</th>
<th>Solvent</th>
<th>Reflux Period (h)</th>
<th>Result(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{HO} \rightleftharpoons \text{HO}) 722</td>
<td>1.1</td>
<td>benzene</td>
<td>12</td>
<td>N.R.</td>
</tr>
<tr>
<td>2</td>
<td>722</td>
<td>3.0</td>
<td>benzene</td>
<td>76</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>722</td>
<td>3.0</td>
<td>toluene</td>
<td>48</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>(\text{HO} \rightleftharpoons \text{HO}) 723</td>
<td>1.1</td>
<td>toluene</td>
<td>48</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>723</td>
<td>1.1</td>
<td>toluene (5% TFA)</td>
<td>48</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>723</td>
<td>3.0</td>
<td>dioxane (4Å MS)</td>
<td>76</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

(a) Based on \(^1\)H-NMR analysis; N.R. = no reaction.

Since the formation of a C-2 ketal was deemed infeasible, recourse was sought in the nucleophilic addition of hydride to the ketone functionality. A search of the literature revealed that (+)-CSA monohydrate (517) can be reduced with NaBH\(_4\) in aqueous solution to give exclusively the \(\text{exo}\) alcohol in near quantitative yield\(^{318}\) (Scheme 6.4). Treating known isobornyl derivative 722 with 3.3 equivalents of TBSCl in a mixture of triethylamine and DMF for 3 h furnished silyl ether 723. Subsequent heating of sodium salt 723 with excess SOCl\(_2\) in benzene for 12 h furnished the corresponding sulfonyl chloride (not shown) which was then

---

Scheme 6.4

Conditions: (a) 2.4 equiv. NaBH\(_4\), H\(_2\)O, rt, 1 h, 95%. (b) 3.3 equiv. TBSCl, Et\(_3\)N, DMF, rt, 3 h. (c) 6.0 equiv. SOCl\(_2\), C\(_6\)H\(_6\), DMF, reflux 12 h. (d) 3.2 equiv. NaN\(_3\), DMA, H\(_2\)O, 60 °C, 12 h, 57% (3 steps).
reacted with NaN₃ in aqueous solution to provide the desired (1S,2R)-O-(t-butyl-
dimethylsilyl)isobornyl-10-sulfonyle azide (693) in 57% overall yield. Compound 693 was
characterized by a strong band at 2131 cm⁻¹ in the infrared spectrum corresponding to the N₃
stretching frequency. Moreover, the ¹H-NMR spectrum of azide 693 clearly confirmed the
presence of the TBS group with singlet resonances at 0.90 ppm (9H), 0.11 ppm (3H), and 0.08
ppm (3H), respectively. With sulfonyl azide 693 in hand, attention was focused on the optical
resolution P-stereogenic phosphines 703-705 (Figure 6.1) and 710-715 (Figure 6.2).

6.1.4 Optical Resolution of P-Stereogenic Phosphines With Isobornyl Sulfonyle Azide 724.

In stark contrast to enantiopure alkyl azides 717-719 (Figure 6.3), phosphinimines formed
using sulfonyl azide 693 were found to be stable toward flash chromatography on silica gel and
prolonged storage under an ambient atmosphere. In addition, the diastereomeric phosphinimines
produced from the reaction of racemic phosphines 703-705 and 710-715 with enantiopure
sulfonyl azide 693 were readily separable by fractional crystallization or flash chromatography
on silica gel (Table 6.2). For example, the phosphinimine mixture obtained upon treatment of

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>R¹</th>
<th>R²</th>
<th>Products⁴</th>
<th>Separation Method</th>
<th>Yield (%) ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>703</td>
<td>Me</td>
<td>C₆H₁₁</td>
<td>726a and 726b</td>
<td>crystallization</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>704</td>
<td>Me</td>
<td>C₅H₉</td>
<td>727a and 727b</td>
<td>crystallization</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>705</td>
<td>Me</td>
<td>CH(CH₃)₂</td>
<td>728a and 728b</td>
<td>crystallization ³</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>710</td>
<td>Me</td>
<td>1-Np</td>
<td>729a and 729b</td>
<td>chromatography</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>711</td>
<td>Me</td>
<td>2-Me-1-Np</td>
<td>730a and 730b</td>
<td>chromatography</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>712</td>
<td>Me</td>
<td>2-MeO-1-Np</td>
<td>731a and 731b</td>
<td>chromatography</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>713</td>
<td>Me</td>
<td>2-Np</td>
<td>732a and 732b</td>
<td>crystallization</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>714</td>
<td>Me</td>
<td>9-phenanthryl</td>
<td>733a and 733b</td>
<td>chromatography</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>715</td>
<td>1-Np</td>
<td>p-PhC₆H₄</td>
<td>734a and 734b</td>
<td>chromatography</td>
<td>89</td>
</tr>
</tbody>
</table>

(a) Diastereomer to elute first or crystallize first designated “a”; (b) Combined isolated yield of
both diastereomers; (c) Not fully separated.
of cyclohexylmethylphenylphosphine (703) with azide 693 showed two strong singlets of equal intensity in the $^3\text{P}$-NMR spectrum at 23.3 and 23.2 ppm corresponding to compounds 726a and 726b, respectively (entry 1). Dissolving this mixture in petroleum ether and cooling the resulting solution to $-5 \degree C$ resulted in the precipitation of diastereomERICally pure phosphinimine 726a in excellent yield. This compound, which crystallized as long colorless needles, showed a single peak in the $^3\text{P}$-NMR spectrum at 23.3 ppm and gave a sharp melting point at 175-177 °C. A second crop of crystals taken from the mother liquor afforded compound 726b as thick colorless prisms with a melting point of 147-149 °C. The combined total yield of pure phosphinimines 726a and 726b, obtained in this manner, was 94%. Similar results were obtained using petroleum ether as a crystallization solvent for phosphinimines 727a and 727b (entry 2). However, isopropylmethylphenylphosphine (705) could not be fully resolved by this technique (entry 3). For this phosphinimine mixture, a single crystallization from petroleum ether provided pure compound 728a in 43% yield leaving a ca. 7:1 ratio of diastereomers in the mother liquor. Under these circumstances, phosphinimine 728b could not be further purified by crystallization. Moreover, it was not possible to obtain an analytical sample of compound 728b using various chromatographic techniques including reversed phase HPLC. Many of the phosphinimine diastereomers were readily separable by simple flash chromatography on silica gel using mixtures of hexanes/ethyl acetate as eluent (entries 4-6, 8-9). For these systems, the first isomer to elute from the column was designated as phosphinimine “a” while the opposite diastereomer was designated as the “b” isomer.

In addition to $^3\text{P}$-NMR analysis, the isomeric purity of phosphinimines 726-734 was easily ascertained by examination of the $^1\text{H}$-NMR spectra. The TBS silyl ether provides an excellent NMR handle for determining isomeric purity, since the Si-methyl signals reside in a remote region of the spectrum. For example, the $^1\text{H}$-NMR spectrum of crude phosphinimines 729a and 729b, prior to separation, exhibited four equal intensity singlets in the 0.00-0.30 ppm range corresponding to the diastereotopic Si-methyl signals (Figure 6.4, panel a). These four singlets can clearly be used as a diagnostic tool for diastereomeric purity assessment. In a similar fashion, the geminal methyl signals of the camphor moiety also show four distinct singlet resonances in the phosphinimine mixture spectrum. Using these signals to evaluate isomeric purity is also feasible but in many cases the lower field methyl signals may interfere with
other regions of the spectrum. The AX pattern of doublets corresponding to the C-10 camphor methylene (labeled signal 7 in Figure 6.4) typically showed very large chemical shift differences in each phosphinimine diastereomer. For example, the $^1$H-NMR spectrum of pure isomer 729a (Figure 6.4, panel b) clearly shows two doublets ($J_{\text{gem}}=13.3$ Hz) at 2.40 and 3.45 ppm for the two
diastereotopic protons next to the sulfur atom. The corresponding signals in the \(^1\)H-NMR spectrum of phosphinimine \(729b\) (Figure 6.4, panel c) occur at 1.97 and 3.39 ppm, respectively with a slightly larger coupling constant \((J_{gem}=14.0 \text{ Hz})\). With isomerically pure phosphinimines \(726-734\) in hand, an investigation of the hydrolytic cleavage of these materials to provide the corresponding enantiopure phosphine oxides was initiated.

Delightfully, treatment of phosphinimine \(726a\) with 3 M \(\text{H}_2\text{SO}_4\) solution in refluxing dioxane smoothly afforded cyclohexylmethylphenylphosphine oxide \((738)\) in 93\% isolated yield after chromatographic removal of the sulfonamide byproduct \(737\) (Table 6.3, entry 1). The optical rotation of compound \(738\), measured in MeOH at 20 °C, was +19.2 degrees, which compares very favorably to the reported \([\alpha]^{20}_D\) value of +19.0 degrees.\(^{319}\) Moreover, since the absolute stereochemistry of phosphine oxide \(738\) has been previously established by Mislow and coworkers,\(^{319}\) it can be concluded that the R isomer was obtained from phosphinimine \(726a\) in reasonably high optical purity. Similar hydrolytic cleavage of isomerically pure phosphinimines \(727-734\) provided optically active phosphine oxides \(739-746\), respectively (Table 6.3).

![Table 6.3 Hydrolysis of Isomerically Pure Phosphinimines](image)

| Entry | S.M. | \(R^1\) | \(R^2\) | Prod. | Expt. \([\alpha]^{20}_D; \) 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>[c] (g/100 mL)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>726a</td>
<td>Me</td>
<td>(\text{C}<em>6\text{H}</em>{11})</td>
<td>738</td>
<td>+19.2; [0.93]</td>
</tr>
<tr>
<td>2</td>
<td>727b</td>
<td>Me</td>
<td>(\text{C}_5\text{H}_9)</td>
<td>739</td>
<td>+33.3; [1.62]</td>
</tr>
<tr>
<td>3</td>
<td>728a</td>
<td>Me</td>
<td>(\text{CH}((\text{CH}_3)_2)</td>
<td>740</td>
<td>-22.6; [1.00]</td>
</tr>
<tr>
<td>4</td>
<td>729a</td>
<td>Me</td>
<td>1-Np</td>
<td>741</td>
<td>+19.8; [2.92]</td>
</tr>
<tr>
<td>5</td>
<td>730b</td>
<td>Me</td>
<td>2-Me-1-Np</td>
<td>742</td>
<td>-73.6; [1.50]</td>
</tr>
<tr>
<td>6</td>
<td>731a</td>
<td>Me</td>
<td>2-MeO-1-Np</td>
<td>743</td>
<td>+128.0; [1.58]</td>
</tr>
<tr>
<td>7</td>
<td>732a</td>
<td>Me</td>
<td>2-Np</td>
<td>744</td>
<td>-12.0; [0.90]</td>
</tr>
<tr>
<td>8</td>
<td>733a</td>
<td>Me</td>
<td>9-phenanthryl</td>
<td>745</td>
<td>+71.4; [1.14]</td>
</tr>
<tr>
<td>9</td>
<td>734b</td>
<td>1-Np</td>
<td>(\text{p-PhC}_6\text{H}_4)</td>
<td>746</td>
<td>+26.9; [0.62]</td>
</tr>
</tbody>
</table>

\(^a\) Rotation in methanol except as noted; \(^b\) Isolated yields; \(^c\) Phosphorus configuration assigned according to literature correlation; \(^d\) Rotation in CHCl\(_3\).
general, the phosphine oxides obtained from the hydrolysis procedure exhibited optical rotation values, which closely matched the known specific rotations reported in the literature. Hence it may be concluded that the phosphine oxide products obtained using this method are generally of high stereochemical purity. Unfortunately, corroborating evidence for the stereochemical purity of phosphine oxides 738-746 could not be obtained using chiral shift NMR ($^1$H or $^3$P), GC or HPLC techniques. A search of the literature revealed that the enantiomeric resolution of phosphine oxides by GC and HPLC analysis can be quite troublesome and often requires the preparation of non-standard chiral stationary phases. Hence the stereochemical purity of phosphine oxides 739, 742, and 745, for which specific rotation data has not been reported, is assumed to be high on the basis of the good agreement observed in the optical rotation data for known oxides 738, 740, 741, 743, 744, and 746 (Table 6.3). Moreover, the phosphine oxides obtained from the hydrolysis of the opposite phosphinimine diastereomers, 727a, 730b, and 733a provided oxides 739, 742, and 745 respectively with optical rotations equal in magnitude but opposite in sign to those reported in Table 6.3. Unfortunately, assignment of the absolute configuration to phosphine oxide products 739, 742, and 745 was not possible since the relationship between rotation sign and configuration has not been deduced for these materials. Moreover, it is clear from the data presented in Table 6.3 that the absolute configuration of the product cannot be predicted based on which phosphinimine diastereomer is hydrolyzed.

In order to investigate the stereochemical course of the phosphinimine hydrolysis step, a single-crystal X-ray structure determination of compound 729a was undertaken (Figure 6.5). Since (1S,2R)-O-[(R)-2-isopropylcyclohexyl]isobornyl-10-sulfonyl azide (693) was used to prepare phosphinimine 728a, it was unambiguously concluded from the X-ray analysis that the phosphorus stereocenter was of $R$ configuration. Since the hydrolysis of phosphinimine 728a provided (-)-isopropylmethylphenylphosphine oxide (740), known to be of $S$ configuration, it can be concluded that the hydrolysis proceeds stereospecifically with inversion at phosphorus. While the hydrolysis of phosphinimines under basic conditions has been shown to occur with inversion of configuration at phosphorus, such a relationship has not been previously established for acidic media. Having shown that the hydrolysis step occurs with inversion of configuration, many of the stereochemical configurations of phosphinimines 726-734 may be assigned (Table 6.4) based on the optical rotation data reported for oxides 738-746 (vide supra).
Figure 6.5 X-Ray Crystal Structure of Phosphinimine 728a. Showing Absolute Configuration.

(a) Hydrogen atoms omitted for clarity.

Table 6.4 Assignment of Phosphinimine Absolute Configuration Based on Hydrolysis Product Optical Rotation Data.

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Prod.</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Oxide Config.&lt;sup&gt;b&lt;/sup&gt;</th>
<th>S.M. Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>726a</td>
<td>Me</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>738</td>
<td>93</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>727b</td>
<td>Me</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>739</td>
<td>93</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>728a</td>
<td>Me</td>
<td>CH(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>740</td>
<td>94</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>729a</td>
<td>Me</td>
<td>1-Np</td>
<td>741</td>
<td>96</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>730b</td>
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<td>2-Me-1-Np</td>
<td>742</td>
<td>94</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>731a</td>
<td>Me</td>
<td>2-MeO-1-Np</td>
<td>743</td>
<td>91</td>
<td>S</td>
<td>R</td>
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<tr>
<td>7</td>
<td>732a</td>
<td>Me</td>
<td>2-Np</td>
<td>744</td>
<td>96</td>
<td>S</td>
<td>R</td>
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<tr>
<td>8</td>
<td>733a</td>
<td>Me</td>
<td>9-phenanthryl</td>
<td>745</td>
<td>99</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>734b</td>
<td>1-Np</td>
<td>p-PhC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>746</td>
<td>93</td>
<td>R</td>
<td>S</td>
</tr>
</tbody>
</table>

(a) Isolated yields; (b) Phosphorus configuration assigned according to literature correlation.
6.2 Resolution of Axially Stereogenic Bidentate Phosphines.

In addition to demonstrating the synthetic utility of resolving agent 693 toward a variety of $P$-stereogenic phosphines, a project was undertaken to apply azide 693 in the resolution of C$_2$-symmetric diphosphines. As discussed in Chapter 4, the resolution of ($\pm$)-BINAPFu (509) was found to be efficient with (1S)-10-camphorsulfonyl azide (593) providing a readily separable mixture of phosphinimines 594a and 594b (Scheme 6.5). It is therefore not surprising that treatment of racemic BINAPFu (509) with 2 molar equivalents of TBS substituted azide 693 in refluxing THF provided a 1:1 mixture of diastereomeric phosphinimines 747a and 747b, which were easily separated by column chromatography. Although the latter separation was more facile, this route is clearly less practical due to the increased cost and poorer availability of isobornyl azide 693. Application of resolving agent 693 to Benincori’s BITIANP$_{263}$ ligand 525 was also successful giving phosphinimines 748a and 748b, which were separable by flash

**Scheme 6.5**

Conditions: (a) THF, reflux, 5 h.
chromatography. Hydrolysis of phosphinimines $747a$ and $748a$ provided the enantiomerically pure bis-phosphine oxides of (S)-BINAPFu and (S)-BITIANP, respectively as evidenced by optical rotation measurements.

Interestingly, the resolution of (±)-BINAP (505) and (±)-MeOBIPHEP (498) using sulfonyl azide 693 did not proceed as planned. Treatment of racemic BINAP (505) with 2 equivalents of TBS substituted azide 693 in refluxing THF afforded a mixture of four phosphinimine products 749-753 (Scheme 6.6). Fortunately, these materials could be separated by preparative TLC and were identified on the basis of their $^1$H, $^{31}$P, and $^{13}$C-NMR spectra. The mono-phosphinimine products 751 and 752 exhibited much more complex $^1$H and $^{13}$C-NMR spectra than bis-phosphinimines 749 and 750, which is consistent with the loss of C$_2$-symmetry in the former molecules. The $^{31}$P-NMR spectrum of mono-phosphinimine product 751, which closely resembled that of compound 752, showed two distinct singlet resonances at +26.1 ppm (P=O) and +12.9 ppm (P=N), respectively. Low resolution FAB-MS analysis of compound 751 indicated a molecular weight of 984 amu thus confirming that the mono-phosphine oxide products had been isolated. This surprising result was initially attributed to partial air oxidation.

**Scheme 6.5**

Conditions: (a) THF or C$_6$H$_6$, reflux, 5 h.
under the reaction conditions. Subsequent experimentation, with \textit{rigorous} exclusion of oxygen, revealed that the source of oxidation must be internal to the reaction mixture. Similar results were obtained in the attempted resolution of (±)-MeOBIPHEP (498) using azide 693 (Scheme 6.5). Bis-phosphinimine product 693 was obtained in 19\% yield after extensive chromatographic purification while products 754-756 could not be obtained in analytically pure form.

The competitive formation of phosphine oxide products 751, 752, 755, and 756 can be rationalized by considering the mechanism of the Staudinger reaction (Figure 6.6). The first step involves nucleophilic attack of the phosphine on the terminal nitrogen of the azide reactant 758 producing a triazo intermediate 759. Although some intermediates of type 759 have been isolated,\textsuperscript{326} such compounds normally decompose rapidly through a four membered transition state 760\textsuperscript{327} to provide the phosphinimine product 760 with the expulsion of N\textsubscript{2} gas. It is postulated that due to steric hindrance, a four-membered cyclic transition state is not easily attained upon reacting BINAP (505) or MeOBIPHEP (498) with sulfonyl azide 693 (Figure 6.7). Instead, a six-membered cyclic transition state is possible leading to oxygen transfer from the
sulfonyl moiety to the phosphorus atom. Such a hypothesis is consistent with $^{31}\text{P}$-NMR studies of the $(\pm)$-BINAP/azide 693 reaction mixture, which showed the formation of all four products 749-752 prior to work-up. Sulfonamide 737 was also obtained from the reaction mixture and presumably formed via hydrolysis of intermediate 765. Although $(\pm)$-BINAP (505) could be resolved by using TBS substituted azide 693, the method is clearly not very practical and requires a difficult chromatographic purification step. Moreover, the complication of oxygen transfer made the complete resolution of $(\pm)$-MeOBIPHEP (498) infeasible via the Staudinger method.

### 6.3 Conclusions and Future Work.

By exploitation of the Staudinger reaction between racemic tertiary phosphines and an enantiomERICALLY pure organoazide, a 1:1 mixture of diastereomERIC phosphinimines can be formed and separated by either crystallization or flash chromatography. Subsequent hydrolysis of the isomerically pure phosphinimines gives enantiopure phosphine oxides with inversion of configuration at phosphorus. Although this method works very well for $P$-stereogenic systems, its use is somewhat limited for axially stereogenic diphosphines such as BINAP (505) and MeOBIPHEP (498). In principle, the Staudinger resolution method should be applicable to tertiary phosphines bearing substituents other than alkyl and aryl groups. For example, using a racemic phosphonamide 766 as the starting material could potentially give access to a wide variety of enantiopure $P$-$N$ compounds 768 or the corresponding phosphorus electrophiles 769.

(Scheme 6.6). The former compounds may serve as useful chiral auxiliaries for enantioselective synthesis while the latter compounds could be used for the preparation of more complex systems containing $P$-stereogenic centers.
7. Experimental Section.

7.1 General Comments.

7.1.1 Compound Characterization and Identification.

Melting points were determined using either an Electrothermal\textsuperscript{\textregistered} melting point apparatus in sealed capillary tubes or an A.H. Thomas hot-stage and are uncorrected. Boiling points are uncorrected and refer to measured air-bath temperatures using a Kugelrohr short path distillation apparatus. Optical rotation data was obtained on a Rudolph Autopol III polarimeter using a quartz cell with a 10 cm path length. Infrared spectra were recorded on a Mattson Galaxy Series 4030 FT-IR spectrometer. Solid samples were handled as pressed KBr pellets or as CCl\textsubscript{4} thin films while liquid samples were analyzed neat between NaCl plates. Characteristic absorptions are listed in wavenumbers followed by the assignment in parentheses.

Proton and carbon NMR spectra were obtained on a Bruker ACE 200 (\textsuperscript{1}H, 200 MHz; \textsuperscript{13}C, 50 MHz), a Bruker AM 400 (\textsuperscript{1}H, 400 MHz; \textsuperscript{13}C, 100 MHz), or a Bruker DRX 400 (\textsuperscript{1}H, 400 MHz; \textsuperscript{13}C, 100 MHz) spectrometer. Unless otherwise noted, deuteriochloroform was used as the NMR solvent and residual chloroform or tetramethylsilane were used as internal standards for chemical shift referencing. \textsuperscript{1}H-NMR spectra are listed in the following format: chemical shift (in ppm), (multiplicity, coupling constant (Hz), number of protons, assignment). For all \textsuperscript{13}C-NMR spectra, the signals were assigned as C, CH, CH\textsubscript{2} or CH\textsubscript{3} by DEPT experiments.\textsuperscript{328} \textsuperscript{13}C-NMR spectra are listed in the following format: chemical shift (in ppm), (multiplicity, coupling constant (Hz), (methyl (CH\textsubscript{3}), methylene (CH\textsubscript{2}), methine (CH) or quaternary carbon (C), assignment). \textsuperscript{31}P-NMR spectra were obtained on a Varian XL 200 (\textsuperscript{31}P, 81 MHz), a Bruker AMX 300 (\textsuperscript{31}P, 121.5 MHz), or a Bruker DRX 400 (\textsuperscript{31}P, 162 MHz) spectrometer using an external reference of 30% H\textsubscript{3}PO\textsubscript{4} in D\textsubscript{2}O set to 0 ppm. Unless specified otherwise, \textsuperscript{31}P-NMR samples were prepared using deuteriochloroform as the solvent.

GC-MS analysis was performed on a Hewlett Packard 5890 Series II gas chromatograph equipped with a Hewlett Packard OV 101, low polarity, 12 m x 0.2 mm column in conjunction with a Hewlett Packard 5971A mass selective detector. Low resolution mass spectra on non-volatile samples were obtained on a VG 7070 or a Kratos MS80 mass spectrometer by Ms. Q.
Wu or Ms. D. Fox using 70 eV ionization with direct probe sample introduction. HRMS and FAB-MS analyses were also obtained by Ms. D. Fox using a Kratos MS80 spectrometer. Mass spectral data is listed in the following format: mass (m/z), (relative intensity, assignment). Elemental analyses were performed by Ms. D. Fox using a Control Equipment Corporation 440 Elemental Analyzer. X-ray structure determination was performed by Dr. M. Parvez (University of Calgary) using a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation or by Dr. R. McDonald (University of Alberta) using a Bruker P4 diffractometer equipped with a SMART 1000 CCD area detector and 18 kW rotating anode X-ray generator.

7.1.2 Chromatographic Techniques.

Analytical TLC was carried out with aluminum sheets coated with Merck silica gel 60 F254 to a uniform thickness of 0.2 mm and the spots were visualized under UV light, or by dipping in a stain solution (118.4 g (NH₄)₈Mo₇O₂₄•4H₂O, 200 mL concentrated H₂SO₄, and 2 L deionized water) followed by heat development. Preparative TLC was carried out on Analtech 20 cm x 20 cm glass plates coated with silica gel GF to a uniform thickness of 1 mm. Radial chromatography was performed on a Harrison Research model 7924T Chromatotron using glass plates coated with EM Science silica gel 60 PF254 with gypsum binder to a uniform thickness of 1 mm, 2 mm or 4 mm. Column chromatography was performed using silica gel 60 (E. Merck, 0.04-0.063 mm, 230-400 mesh) using the flash method. Solvent systems refer to mixtures, by volume, of hexanes and ethyl acetate unless specified otherwise.

Analytical HPLC analyses were performed on an ICI LC 1440 instrument equipped with an ICI LC 1150 HPLC Pump (C₁₈ column or Chiralcel® OJ column with an ICI LC 12010 UV/Vis detector) or a Waters 4886 instrument (Nova-Pak C₁₈ reverse phase column or Chiralcel® OB column with a Waters 486 UV detector). Preparative HPLC was done on the latter instrument equipped with a 25 mm x 100 mm Water Nova-Pak C₁₈ reversed phase column. Chiral gas chromatography was performed on either a Shimadzu GC-9a gas chromatograph (25 m x 0.33 mm (i.d.) Cydex-B fused silica column with a flame ionization detector) or a Varian Star 3400 CX instrument (30 m x 0.32 mm (i.d.) Cyclodex-B fused silica column with a flame ionization detector).
7.1.3 Experimental Conditions.

All Glassware employed in anhydrous reactions was dried overnight in a 120 °C oven and subsequently cooled in a dessicator containing Drierite® or under a stream of dry argon. Moisture or oxygen sensitive reactions were performed using Schlenk techniques under argon. When required, solvents and reagents were purified by standard methods. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled immediately prior to use from sodium benzophenone ketyl, while methylene chloride, toluene, and diethyl ether were freshly distilled from calcium hydride. Acetone (HPLC grade), acetonitrile, and N,N-dimethylformamide (DMF) were purchased as anhydrous solvents in Sure/Seal® bottles from the Aldrich Chemical Company. Other solvents and reagents including benzene, triethylamine, diisopropylamine, pentane, dioxane, dimethylacetamide (DMA), pyridine, and carbon tetrachloride were dried by distillation from CaH₂ and stored in Sure/Seal® bottles. Methanol was distilled from magnesium chips according to a published procedure. Benzyl bromide and iodomethane were passed through a short column of activated basic alumina immediately prior to use. n-Butyllithium and t-butyllithium were titrated prior to use with 2,5-dimethoxybenzyl alcohol or N-benzylbenzamide as the indicator, respectively. Solutions of NaCl, NaHCO₃, and NH₄Cl used for washing organic phases were saturated unless specified otherwise. High pressure hydrogenation reactions were performed in a 50 mL Parr micro-reactor, model 4592.

7.1.4 Naming Conventions.

Many of the structures presented in this chapter are numbered for convenience and do not necessarily follow IUPAC rules. The designators a and b in the compound number are used to distinguish between stereoisomeric structures. The designator a applies to the first compound to elute in cases where compounds were separated by column chromatography or the first compound to crystallize when recrystallization was used to separate isomers.

7.2 Experiments Pertaining to Chapter One.

2-(2-Bromophenyl)-1,3-dioxolane (63) and 1,8-dihydroxynaphthalene (84) were prepared according to literature procedures with minor modification. Biphenyl (51), 2,2'-
dimethoxybiphenyl (53), 2,2'-dimethylbiphenyl (55), 2,2'-dimethoxy-1,1'-binaphthyl (57), 3,3'-trifluoromethylbiphenyl (71), 3,3'-dicyanobiphenyl (72), 2,2'-(1,1'-biphenyl)-2,2'-diylbis-1,3-dioxolane (75), 2,2',5,5'-tetramethoxybiphenyl (76), 4,4'-dihydroxybiphenyl (77), 1,1-binaphthalene (79), 2,2'-binaphthalene (80), and 2,2'-bithiophene (81) exhibited spectral and physical properties consistent to those reported in the literature.

### 7.2.1 General Procedure for the in Situ C₂-Symmetric Suzuki Biaryl Synthesis.

A solution of the haloarene (1 mmol) in dry THF (10 mL) is cooled to -78 °C under a N₂ atmosphere. To the stirred solution is then added 0.5 equivalents n-BuLi followed by 1.5 equivalents of B(OMe)₃. The resulting solution is warmed to rt over a 4 h period and subsequently stirred overnight. To the solution is then added toluene (10 mL), ethanol (10 mL), water (5 mL), Na₂CO₃ (1.5 mmol) and Pd(PPh₃)₄ (0.01 mmol). The resulting mixture is heated to reflux for 24 h. The cooled reaction mixture is then extracted with CH₂Cl₂ (3 x 25 mL). The organic phases are combined, washed with H₂O (25 mL), dried (MgSO₄), and concentrated in vacuo to afford the crude biaryl which is purified by flash chromatography and/or distillation.

### 7.2.2 Scope and Limitations Study Starting Materials.

#### 7.2.2.1 Preparation of 1-Bromo-2-methoxynaphthalene (56).

![structure of 56]

A suspension of sodium hydride (0.45 g, 19 mmol) in DMF (50 mL) was prepared in a 100 mL, 3-neck round bottom flask equipped with a reflux condenser and pressure equalized addition funnel. The NaH suspension was cooled to 0 °C under a N₂ atmosphere and to it was added 1-bromo-2-hydroxynaphthalene (3.8 g, 17 mmol) in portions. The mixture was then warmed to rt and stirred for 1 h. The mixture was treated with iodomethane (3.2 mL, 51 mmol) via the addition funnel and subsequently heated to 40 °C for 3 h. The cooled reaction mixture was then quenched with H₂O (50 mL) and extracted with Et₂O (3 x 100 mL). The combined organic
extracts were washed with 10% NaOH (100 mL) and NaCl (5 x 200 mL) solutions. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford compound 56 as a light tan solid (3.76 g, 92%): mp 82-83 °C (CH$_2$Cl$_2$/hexanes, lit.$^{345}$ 82-84 °C); $^1$H-NMR (200 MHz) $\delta$ 4.04 (s, 3H, H-11), 7.28 (dd, $J$=7.7, 2.6 Hz, 1H), 7.41 (td, $J$=6.9, 1.1 Hz, 1H, H-6 or H-7), 7.59 (td, $J$=7.7, 1.2 Hz, 1H, H-6 or H-7), 7.81 (m, 2H), 8.25 (d, $J$=8.5 Hz, 1H, H-4); $^{13}$C NMR (50 MHz) ppm 57.1 (CH$_3$, C-11), 108.7 (C, C-1), 113.7 (CH, C-3), 124.3 (CH), 126.1 (CH), 127.7 (CH), 128.0 (CH), 128.9 (CH), 129.8 (C, C-10), 133.2 (C, C-9), 153.8 (C, C-2). The NMR spectral data was in good agreement with the literature.$^{346}$

7.2.2.2 Preparation of 1-Iodo-2-methoxynaphthalene (58).

![Diagram of 58]

To a solution of 1-bromo-2-methoxynaphthalene (56) (3.03 g, 12.8 mmol) in THF (150 mL) was added $n$-BuLi (2.5 M solution in hexanes, 5.6 mL, 14 mmol) at -78 °C. To the cooled solution was then added I$_2$ (0.30 M solution in THF, 50 mL, 15 mmol). The vessel was then warmed to rt and stirred for 1 h under a N$_2$ atmosphere. The reaction contents were diluted with water (150 mL) and Et$_2$O (250 mL). The organic phase was washed with Na$_2$S$_2$O$_3$ solution (100 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo to afford a red solid residue. The crude material was recrystallized from hexanes to afford the title compound (3.63 g) in quantitative yield: mp 86-87 °C (lit.$^{347}$ 88.5-89 °C); $^1$H-NMR (200 MHz) $\delta$ 4.04 (s, 3H, H-11), 7.22 (d, $J$=9.0 Hz, 1H, H-3), 7.39 (td, $J$=7.4, 1.0 Hz, 1H, H-6 or H-7), 7.56 (td, $J$=7.7, 1.2 Hz, 1H, H-6 or H-7), 7.75 (d, $J$=7.8 Hz, 1H, H-5), 7.84 (d, $J$=9.0 Hz, 1H, H-4), 8.16 (d, $J$=8.5 Hz, 1H, H-8); $^{13}$C-NMR (50 MHz) ppm 57.2 (CH$_3$, C-11), 87.8 (C, C-1), 113.0 (CH, C-3), 124.3 (CH), 128.1 (CH), 128.2 (CH), 129.9 (C, C-10), 130.3 (CH), 131.2 (CH), 135.7 (C, C-9), 156.7 (C, C-2). The NMR spectral data was in good agreement with the literature.$^{348}$
7.2.2.3 Preparation of Isopropyl 2-Iodobenzoate (61).

To a solution of 2-iodobenzoic acid (2.49 g, 10.0 mmol) in DMF (80 mL) was added K$_2$CO$_3$ (3.47 g, 25.1 mmol) and isopropyl iodide (1.0 mL, 10 mmol). The resulting mixture was stirred at rt for 24 h after which time the solution was extracted with Et$_2$O (3 x 100 mL). The combined organic extracts were washed with 10% NaOH (75 mL) and NaCl solutions (75 mL). The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo to afford an orange oil. The crude material was purified by distillation under reduced pressure to furnish 2.76 g (95%) of compound 61 as a colorless oil: bp 60-65 °C (0.1 mm Hg); IR (neat) 1724 (ester CO), 1291, 1254, 1101, 1016 cm$^{-1}$; $^1$H-NMR (200 MHz) δ 1.39 (d, J=6.2 Hz, 6H, H-9), 5.28 (sept, J=6.2 Hz, 1H, H-8), 7.14 (td, J=7.6 Hz, 1.8 Hz, 1H, H-5), 7.40 (td, J=7.6 Hz, 1.2 Hz, 1H, H-4), 7.76, (dd, J=7.7 Hz, 1.7 Hz, 1H, H-3), 7.97 (dd, J=7.9 Hz, 1.1 Hz, 1H, H-6); $^{13}$C-NMR (50 MHz) ppm 21.8 (CH$_3$, C-9), 69.5 (CH, C-8), 93.8 (C, C-2), 127.8 (CH), 130.6 (CH), 132.3 (CH), 136.0 (C, C-1), 141.1 (CH, C-3), 166.2 (C, C-7); mass spectrum, m/z (relative intensity, %) 290 (29, M$^+$), 248 (58, M$^+$-C$_3$H$_6$), 231 (79, M$^+$-C$_3$H$_2$O), 203 (29, M$^+$-C$_4$H$_2$O$_2$), 76 (100, M$^+$-C$_4$H$_2$IO$_2$). Exact mass calcd for C$_{10}$H$_{11}$IO$_2$: 289.9800. Found: 289.9786.

7.2.2.4 Preparation of N,N-Diisopropyl-2-bromobenzamide (62).

2-Bromobenzoic acid (1.82 g, 9.06 mmol) was dissolved in hexanes (20 mL) and cooled to 0 °C under a N$_2$ atmosphere. To the solution was then added thionyl chloride (1.3 mL, 18 mmol) and the resulting mixture was refluxed 17 h. The solvent and excess reagent were removed in vacuo and the remaining oil was distilled (bp 75-80 °C, 0.15 mm Hg) to afford the intermediate acyl chloride (1.69 g, 85%). The acyl chloride was then dissolved in Et$_2$O and transferred to an
ice cooled flask containing diisopropylamine (4.5 mL, 32 mmol) in Et₂O (25 mL). The reaction mixture was stirred for 1 h and subsequently quenched with 5% HCl solution (80 mL). The organic phase was then washed with brine (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure to afford a light yellow crystalline solid. The product was purified by recrystallization from a CH₂Cl₂/hexanes mixture (2.11 g, 96%): mp 147-149 °C (lit.²⁶ 141-145 °C); IR (CCl₄) 1628 (ester C=O), 1440, 1341 cm⁻¹; ¹H-NMR (200 MHz) δ 1.06 (d, J=6.7 Hz, 3H), 1.23 (d, J=6.7 Hz, 3H), 1.56 (d, J=6.8 Hz, 3H), 1.58 (d, J=6.8 Hz, 3H), 3.56 (sept, J=6.8 Hz, 2H, H-8 and H-11), 7.35 (m, 3H), 7.55 (d, J=7.9 Hz, 1H, H-6); ¹³C-NMR (50 MHz) ppm 20.1 (CH₃), 20.5 (CH₃), 20.6 (CH₃), 20.7 (CH₃), 46.0 (CH), 51.1 (CH), 119.0 (C, C-2), 126.6 (CH), 127.5 (CH), 129.4 (CH), 132.9 (CH), 140.2 (C, C-1), 168.1 (C, C-7); mass spectrum, m/z (relative intensity, %) 283/285 (15/15, M⁺), 282/284 (15/15, M⁺-H), 240/242 (43/43, M⁺-C₃H₇), 183/185 (100/100, M⁺-N(C₃H₇)₂). Anal. calcd for C₃₆H₃₂BrNO: C, 54.94; H, 6.38; N, 4.93. Found: C, 55.02; H, 6.45; N, 4.91.

7.2.2.5 Preparation of 1-[(t-Butyldiphenylsilyl)oxy]-4-bromobenzene (65).

To a solution of 4-bromophenol (3.96 g, 22.9 mmol) in DMF (50 mL) was added t-butyldiphenylsilyl chloride (4.82 mL, 27.5 mmol) and imidazole (3.90 g, 57.2 mmol). The resulting solution was stirred for 2 d at rt and subsequently quenched with H₂O (50 mL). After a 30 min reaction period, the solution was diluted with Et₂O (150 mL) and washed with 10% HCl (2 x 25 mL) and brine (25 mL) solutions. The organic phase was dried (Na₂SO₄) and concentrated in vacuo to afford a light yellow oil. The crude silane was distilled under reduced pressure to afford a clear, colorless oil which later solidified (9.10 g, 97%): mp 43.5-45 °C; bp 130-150 °C (0.1 mm Hg); IR (neat) 1486, 1272, 1251, 1113, 819, 701 cm⁻¹; ¹H-NMR (200 MHz)
δ 1.12 (s, 9H, H-6), 6.66 (d, J=8.8 Hz, 2H, H-2), 7.20 (d, J=8.7 Hz, 2H, H-3), 7.41 (m, 6H, H-8 and H-10), 7.72 (t, J=7.4 Hz, 1.6 Hz, 4H, H-9); 13C-NMR (50 MHz) ppm 19.4 (C, C-5), 26.5 (CH3, C-6), 113.4 (C, C-4), 121.5 (CH, C-2), 127.9 (CH, C-9), 130.1 (CH, C-3), 132.1 (CH, C-10), 132.5 (C, C-7), 135.5 (CH, C-8), 154.8 (C, C-1); mass spectrum, m/z (relative intensity, %) 410/412 (4/4, M+), 353/355 (100/100, M+ - C4H9), 273 (52, M+ - C4H10Br), 197 (39), 181 (31), 152 (54), 105 (56). Anal. calcd for C22H23BrOSi: C, 64.23; H, 5.64. Found: C, 64.23; H, 5.55.

7.2.2.6 Preparation of 4,4-Dimethyl-2-(2-iodophenyl)-2-oxazoline (66).

2-Iodobenzoic acid (3.00 g, 12.1 mmol) in CH2Cl2 (60 mL) was treated with oxalyl chloride (2.21 mL, 25.4 mmol) and a catalytic amount of DMF. The resulting solution was refluxed under a N2 atmosphere for 12 h and subsequently concentrated in vacuo to afford a brown oil. The crude acyl chloride thus obtained was distilled under reduced pressure (bp 65-70 °C, 0.1 mm Hg) to afford a white solid (2.64 g, 9.91 mmol). The material was then dissolved in CH2Cl2 (60 mL) and treated with 2-amino-2-methyl-1-propanol (1.04 mL, 10.9 mmol) and triethylamine (1.52 mL, 10.9 mmol). The resulting mixture was stirred at rt for 12 h and subsequently quenched with 10% HCl solution (50 mL). The organic phase was dried (Na2SO4), and concentrated under reduced pressure to afford a clear, colorless oil. The residual oil was dissolved in CH2Cl2 (60 mL) and treated with thionyl chloride (1.57 mL, 21.8 mmol) for a 12 h period. The reaction mixture was then quenched with 10% NaHCO3 solution and extracted with CH2Cl2 (3 x 25 mL) and the combined organic extracts were washed with brine, dried (Na2SO4), and concentrated in vacuo to afford a yellow oil. The material thus obtained was subsequently dissolved in a mixture of CH3CN (60 mL) and H2O (7.5 mL). The solution was then treated with K2CO3 (1.65 g, 11.9 mmol) and heated to reflux for 24 h. The cooled reaction mixture was then extracted with CH2Cl2 (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na2SO4), and concentrated under reduced pressure to afford the title compound. The
crude product was purified by distillation to afford iodide 66 as a colorless oil (2.01 g, 55%): bp 95-100 °C (0.15 mm Hg); IR (neat) 1657 (C=N), 1303, 1082, 989 cm⁻¹; 1H-NMR (200 MHz) δ 1.42 (s, 6H, H-6), 4.14 (s, 2H, H-5), 7.09 (td, J=7.7, 1.7 Hz, 1H, H-11), 7.36 (td, J=7.5, 1.1 Hz, 1H, H-10), 7.57 (dd, J=7.7, 1.7 Hz, 1H, H-9), 7.90 (dd, J=7.9, 1.1 Hz, 1H, H-12); 13C-NMR (50 MHz) ppm 28.2 (CH₃, C-6), 68.2 (C, C-4), 79.4 (CH₂, C-5), 94.7 (C, C-8), 127.7 (CH), 130.5 (CH), 131.4 (CH), 134.3 (C, C-7), 140.1 (CH), 162.7 (C, C-2); mass spectrum, m/z (relative intensity, %) 301 (45, M⁺), 286 (70, M⁺-CH₃), 230 (55), 103 (100). Exact mass calcd for C₁₁H₁₂INO: 300.9960. Found: 300.9967. Anal. calcd for C₁₁H₁₂INO: C, 43.88; H, 4.02; N, 4.65. Found: C, 43.74; H, 3.98; N, 4.62.

7.2.3 Scope and Limitations Study Biaryl Products.

7.2.3.1 Preparation of Diisopropyl 2,2'-biphenyldicarboxylate (73).

![Diisopropyl 2,2'-biphenyldicarboxylate (73)]

Compound 73 was prepared according to the general procedure for in situ C₂-symmetric Suzuki cross-coupling (see section 7.2.1). Employing isopropyl 2-iodobenzoate (61) (1.15 g, 3.95 mmol) as the starting haloarene furnished 0.206 g (32%) of the desired biaryl 73. Purification of the product was accomplished by flash chromatography (20:1) to afford a light yellow solid: mp 68-70 °C (CH₂Cl₂/hexanes); IR (KBr) 1699 (C=O, ester), 1267, 1097, 769 cm⁻¹; 1H-NMR (200 MHz) δ 0.90 (d, J=6.2 Hz, 3H, H-9 or H-10), 1.00 (d, J=6.2 Hz, 3H, H-9 or H-10), 4.92 (sept, J=6.2 Hz, 1H, H-8), 7.19 (dd, J=4.0 Hz, 1.3 Hz, 1H, H-6), 7.46 (m, 2H), 8.02 (dd, J=4.1 Hz, 1.4 Hz, 1H, H-3); 13C-NMR (50 MHz) ppm 21.3 (CH₃, C-9), 67.9 (CH, C-8), 126.9 (CH), 129.9 (CH), 130.1 (CH), 130.4 (C, C-2), 130.9 (CH), 143.3 (C, C-1), 166.7 (C, C-7); mass spectrum, m/z (relative intensity, %) 326 (1, M⁺), 239 (23, M⁺-CO₂C₃H₇), 197 (100, M⁺-C₇H₁₃O₂). Exact mass calcd for C₂₀H₂₂O₄: 326.1518. Found: 326.1540. Anal. calcd for C₂₀H₂₂O₄: C, 73.60; H, 6.70. Found: C, 73.60; H, 6.80.
7.2.3.2 Preparation of N,N,N’,N’-Tetraisopropyl-2-2-biphenyldicarboxamide (74).

Compound 74 was prepared according to the general procedure for in situ C$_2$-symmetric Suzuki cross-coupling (see section 7.2.1). Utilizing N,N-diisopropyl-2-bromobenzamide (62) (1.07 g, 3.77 mmol) as the starting haloarene furnished 0.610 g (79%) of the title compound 74. The product was purified by flash chromatography (7:1) to afford a white crystalline solid: mp 167-168 °C (CH$_2$Cl$_2$/hexanes); IR (KBr) 1627 (CO, amide), 1429, 1342, 1330, 761 cm$^{-1}$; $^1$H-NMR (200 MHz) δ 0.79 (d, J=6.5 Hz, 3H), 1.07 (d, J=6.5 Hz, 3H), 1.33 (d, J=6.8 Hz, 3H), 1.49 (d, J=6.8 Hz, 3H), 3.37 (sept, J=6.8 Hz, 1H), 3.96 (sept, J=6.5 Hz, 1H), 7.28 (m, 3H), 7.50 (m, 1H); $^{13}$C-NMR (50 MHz) ppm 19.7 (CH$_3$), 20.3 (CH$_3$), 20.6 (CH$_3$), 21.0 (CH$_3$), 45.6 (CH), 50.4 (CH), 126.4 (CH), 127.3 (CH), 127.7 (CH), 130.3 (CH), 136.2 (C, C-2), 138.4 (C, C-1), 169.8 (C, C-7); mass spectrum, m/z (relative intensity, %) 408 (19, M$^+$), 308 (100, M$^+$-C$_6$H$_4$N). Exact mass calcd for C$_{26}$H$_{36}$N$_2$O$_2$: 408.2777. Found: 408.2777. Anal. calcd for C$_{26}$H$_{36}$N$_2$O$_2$: C, 76.43; H, 8.88; N, 6.86. Found: C, 76.26; H, 9.17; N, 6.86.

7.2.4 Preparation of 1-Hydroxy-8-methoxynaphthalene (86).

A solution of 1,8-dihydroxynaphthalene$^{38}$ (85) (0.27 g, 1.7 mmol) in DMF (10 mL) was treated with sodium hydride (0.041 g, 1.7 mmol) at 0 °C. Iodomethane (0.6 mL, 9 mmol) was then added and the resulting mixture was stirred for 15 minutes. The reaction mixture was then quenched with H$_2$O (10 mL) and subsequently extracted with Et$_2$O (3 x 20 mL). The combined organic extracts were washed with brine (3 x 25 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo to afford a brown solid residue. The crude material was purified by radial chromatography (4
mm rotor, 5:1) to yield 0.283 g (95%) of the desired product (86) which was subsequently recrystallized from CH₂Cl₂/hexanes: mp 55-56 °C (lit. 349 55-56 °C); ¹H-NMR (200 MHz) δ 4.03 (s, 3H, H-11), 6.76 (dd, J=7.6, 0.8 Hz, 1H), 6.92 (dd, J=7.0, 1.8 Hz, 1H), 7.29-7.48 (m, 4H), 9.34 (s, 1H, OH); ¹³C-NMR (50 MHz) ppm 56.0 (CH₃, C-11), 103.9 (CH, C-7), 110.3 (CH, C-2), 115.3 (C, C-9), 118.8 (CH), 121.8 (CH), 125.5 (CH), 127.6 (CH), 136.7 (C, C-10), 154.5 (C, C-1), 156.1 (C, C-8). The NMR spectral data was in good agreement with the literature. 350

7.2.5 Preparation of 4-Bromo-1-hydroxy-8-methoxynaphthalene (87).

![Diagram](image)

1-Hydroxy-2-methoxynaphthalene (86) (1.0 g, 5.9 mmol) was dissolved in CCl₄ (50 mL) and the resulting solution was treated with sodium hydride (0.14 g, 5.9 mmol) followed by bromine (0.30 mL, 5.9 mmol). The solution was stirred for 15 min at rt, diluted with Et₂O (100 mL) and subsequently washed with H₂O (50 mL) and Na₂S₂O₃ (50 mL) solution. The Et₂O layer was dried (Na₂SO₄) and concentrated under reduced pressure to afford a blue oil. The crude material was recrystallized from CH₂Cl₂/hexanes to give 0.98 g (67%) light blue crystals which were determined by ¹H-NMR spectroscopy to be a 9:1 mixture of bromide 87 and 2-bromo-1-hydroxy-8-methoxynaphthalene. This mixture was used without further purification in the subsequent benzylation step. An analytical sample of bromide 87 was obtained by radial chromatography (2 mm rotor, 9:1) followed by recrystallization from a CH₂Cl₂/hexanes mixture: mp 111.5-113.5 °C; IR (KBr) 1392, 1260, 1080, 745 cm⁻¹; ¹H-NMR (200 MHz) δ 4.08 (s, 3H, H-11), 6.77 (d, J=8.3 Hz, 1H, H-2), 6.86 (d, J=7.8 Hz, 1H, H-7), 7.44 (t, J=8.5 H, 1H, H-6), 7.65 (d, J=8.3 Hz, 1H, H-3), 7.84 (d, J=8.7 Hz, 1H, H-5), 9.48 (s, 1H, OH); ¹³C-NMR (50 MHz) ppm 56.4 (CH₃, C-11), 104.9 (CH, C-7), 111.1 (CH, C-2), 111.3 (C, C-4), 116.2 (C, C-9), 121.3 (CH), 127.0 (CH), 131.7 (CH), 134.3 (C, C-10), 154.6 (C, C-1), 156.2 (C, C-8); mass spectrum, m/z

7.2.6 Preparation of 1-(Benzyloxy)-4-bromo-8-methoxynaphthalene (88).

A mixture of 4-bromo-1-hydroxy-8-methoxynaphthalene (87) and 2-bromo-1-hydroxy-8-methoxynaphthalene (9:1 ratio) (1.02 g, 4.04 mmol) was dissolved in DMF (25 mL) and subsequently treated with sodium hydride (0.107 g, 4.44 mmol) followed by benzyl bromide (528 \(\mu\)L, 4.44 mmol). The resulting solution was stirred at rt for 36 h, quenched with H\(_2\)O (25 mL), and extracted with Et\(_2\)O (3 x 50 mL). The combined organic layers were then washed with 10% NaOH solution (75 mL) and brine (3 x 75 mL). The organic phase was dried (Na\(_2\)SO\(_4\)) and concentrated \textit{in vacuo} to afford a yellow solid. The two isomeric products were separated by fractional recrystallization from CH\(_2\)Cl\(_2\)/hexanes to afford 1.25 g (90%) of compound 88: mp 95-96 °C; IR (KBr) 1582, 1568, 1364, 1268, 1051, 796, 740 cm\(^{-1}\); \(^1\)H-NMR (200 MHz) \(\delta\) 3.97 (s, 3H, H-11), 5.20 (s, 2H, H-12), 6.80 (d, \(J=8.4\) Hz, 1H, H-2), 6.96 (d, \(J=7.8\) Hz, 1H, H-7), 7.28-7.75 (m, 7H), 7.86 (dd, \(J=8.5\) Hz, 1.0 Hz, 1H, H-5), \(^{13}\)C-NMR (50 MHz) ppm 56.4 (CH, C-11), 71.7 (CH\(_2\), C-12), 107.2 (CH), 109.0 (CH), 114.3 (C, C-4), 119.4 (C, C-9), 120.1 (CH), 127.0 (CH, C-15), 127.7 (CH), 127.8 (CH), 128.4 (CH, C-14), 130.3 (CH), 135.0 (C), 137.3 (C), 156.2 (C), 157.5 (C); mass spectrum, \(m/z\) (relative intensity, %) 342/344 (15/15, M\(^+\)), 263 (3, M\(^+\)-Br), 193/195 (25/25), 114 (26), 91 (100, C\(_7\)H\(_7\)^+). Anal. calcd for C\(_{18}\)H\(_{13}\)BrO\(_2\): C, 62.99; H, 4.40. Found: C, 62.89; H, 4.40.
7.2.7 Preparation of 4,4’-(Dibenzyloxy)-5,5’-dimethoxy-1,1’-binaphthalene (89).

![Image of compound 89]

Compound 89 was prepared according to the general procedure for in situ C₂-symmetric Suzuki cross-coupling (see section 7.2.1). Utilizing 1-(benzyloxy)-4-bromo-8-methoxynaphthalene (88) (0.349 g, 1.02 mmol) as the starting haloarene furnished 0.193 g (72%) of the desired biaryl 89. Purification of the product was accomplished by recrystallization from 1:1 hexanes:ethyl acetate. Biaryl 89 had: mp 243-245 °C; IR (KBr) 1586, 1277, 1103, 1054, 1033, 809 cm⁻¹; ¹H-NMR (200 MHz) δ 4.00 (s, 3H, H-11), 5.30 (s, 2H, H-12), 6.90 (m, 2H), 7.05 (d, J=8.0 Hz, 1H), 7.14-7.50 (m, 5H), 7.68 (d, J=6.8 Hz, 2H); ¹³C-NMR (100 MHz) ppm 56.4 (CH₃), 71.6 (CH₂, C-12), 106.3 (CH), 108.2 (CH), 118.1 (C, C-10), 119.7 (CH), 126.3 (CH), 127.1 (CH, C-14), 127.5 (CH), 128.4 (CH, C-13), 132.0 (C), 136.9 (C), 137.8 (C), 155.8 (C, C-4 or C-5), 157.4 (C, C-4 or C-5); mass spectrum, m/z (relative intensity, %) 526 (28, M⁺), 435 (36, M⁺-C₇H₇), 345 (20), 91 (100, C₇H₇⁺). Exact mass calcd for C₃₆H₃₀O₄: 526.2144. Found: 526.2124.

7.2.8 Preparation of 4,4’-Dihydroxy-5,5’-dimethoxy-1,1’-binaphthalene (82).

![Image of compound 82]

4,4’-(Dibenzyloxy)-5,5’-dimethoxy-1,1’-binaphthalene (89) (68.5 mg, 0.130 mmol) in CH₂Cl₂ (3 mL) and absolute EtOH (1 mL) was treated with 10% Pd on carbon (100 mg, 70 mol%) under an atmosphere of H₂ at rt for 12 h. The reaction mixture was subsequently filtered through Celite® and the residue was washed with MeOH (2 x 2 mL). The filtrate was then concentrated under reduced pressure to afford a white crystalline solid material (44.8 mg, 100%):
mp 269-271 °C (CH₂Cl₂/hexanes); ¹H-NMR (200 MHz) δ 4.11 (s, 3H, H-11), 6.79 (dd, J=7.6 Hz, 0.8 Hz, 1H, H-6), 6.88-7.04 (m, 2H), 7.13 (t, J=7.6 Hz, 1H, H-7) 7.33 (d, J=7.8 Hz, 1H), 9.54 (s, 1H, OH); ¹³C-NMR (50 MHz) ppm 56.3 (CH₃, C-11), 104.0 (CH, C-6), 110.1 (CH, C-3), 115.1 (C, C-10), 120.8 (CH), 125.5 (CH), 129.6 (C, C-9), 130.2 (CH), 136.1 (C, C-1), 154.2 (C, C-4), 156.4 (C, C-5); mass spectrum, m/z (relative intensity, %) 346 (100, M⁺), 331 (6, M⁺-CH₃), 316 (10, M⁺-C₂H₆), 300 (14, M⁺-C₂H₄O). Exact mass calcd for C₂₂H₁₈O₄: 346.1205. Found: 346.1188. The NMR spectral data was in good agreement with the literature.³⁶

7.2.9 Preparation of 1,8-Di(benzyloxy)naphthalene (90).

![Chemical Structure](image)

1,8-Dihydroxynaphthalene³⁸ (0.264 g, 1.65 mmol) in DMF (10 mL) was treated with sodium hydride (0.044 g, 1.83 mmol) at ambient temperature. To the solution was then added freshly distilled benzyl bromide (196 µL, 1.65 mmol) and the mixture was allowed to stir for 1 h. To the vessel was then added a further portion of NaH (0.44 g, 1.8 mmol) followed by benzyl bromide (196 µL, 1.65 mmol). The resulting mixture was left to stir overnight at room temperature and was subsequently quenched with 10% HCl solution (25 mL). The mixture was extracted with Et₂O (3 x 25 mL) and the combined organic extracts were washed with brine (5 x 50 mL). The organic layer was then dried (Na₂SO₄) and concentrated in vacuo to afford a brown oil. The crude material was then subjected to flash chromatography (20:1) and subsequently recrystallized from a CH₂Cl₂/hexanes mixture to afford tan colored needles (0.532 g, 95%): mp 95-96 °C; IR (KBr) 1576, 1275, 1048, 750, 732 cm⁻¹; ¹H-NMR (200 MHz) δ 5.23 (s, 2H, H-11), 6.94 (d, J=7.4 Hz, 1H, H-2), 7.24-7.47 (m, 7H); ¹³C-NMR (50 MHz) ppm 71.7 (CH₂, C-11), 108.8 (CH, C-2), 118.7 (C, C-9), 121.3 (CH), 126.3 (CH), 127.4 (CH), 127.5 (CH), 128.4 (CH), 137.4 (C, C-12), 137.6 (C, C-10), 156.2 (C, C-1); mass spectrum, m/z (relative intensity, %) 340 (35, M⁺), 249 (42, M⁺-C₇H₇), 181 (22), 115 (22), 91 (100, C₇H₇⁺). Exact mass calcd for C₂₄H₂₀O₂: 340.1463. Found: 340.1461.
7.2.10 Preparation of 1,8-Di(benzyloxy)-4-bromonaphthalene (91).

1,8-Bis(benzyloxy)naphthalene (90) (0.158 g, 0.465 mmol) was dissolved in CCl₄ (5 mL) and to the solution was then added finely powdered K₂CO₃ (0.643 g, 4.65 mmol). To the vessel was then added bromine (24 μL, 0.47 mmol). The mixture was allowed to react for 2 min and subsequently quenched with H₂O (25 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 25 mL) and the combined organic extracts were washed with Na₂S₂O₃ solution (25 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure to afford a light yellow solid material. The product was purified by recrystallization from a mixture of CH₂Cl₂/hexanes to afford bromide 91 as light green needles (0.174 g, 89%): mp 113-114 °C; IR (KBr) 1573, 1265, 1057, 730, 694 cm⁻¹; ¹H-NMR (200 MHz) δ 5.19 (s, 2H, H-1 or H-16), 5.22 (s, 2H, H-11 or H-16), 6.78 (d, J=8.4 Hz, 1H, H-2), 7.01 (d, J=7.8 Hz, 1H, H-7), 7.28 (m, 6H), 7.45 (m, 5H), 7.65 (d, J=8.4 Hz, 1H, H-3), 7.88 (dd, J=8.5, 0.9 Hz, 1H); ¹³C-NMR (100 MHz) ppm 71.7 (CH₂, C-11 or C-16), 71.8 (CH₂, C-11 or C-16), 109.0 (CH, C-2 or C-7), 109.5 (CH, C-2 or C-7), 114.1 (C, C-4), 119.8 (C, C-9), 120.5 (CH), 127.3 (CH), 127.6 (CH), 128.4 (CH), 130.3 (CH), 135.0 (C, C-10), 136.9 (C, C-12 or C-17), 137.0 (C, C-12 or C-17), 156.2 (C, C-1 or C-8), 156.4 (C, C-1 or C-8); mass spectrum, m/z (relative intensity, %) 418/420 (24/24, M⁺), 339 (4, M⁺-Br), 327/329 (28/28, M⁺-C₇H₇), 181 (54), 91 (100, C₇H₇⁺). Exact mass calcd for C₂₄H₁₉BrO₂: 418.0569/420.0553. Found: 418.0549/420.0529. Anal. calcd for C₂₄H₁₉BrO₂: C, 68.74; H, 4.56. Found: C, 68.74; H, 4.83.
7.2.11 Preparation of 4,4',5,5'-Tetrabenzyloxy-1,1'-binaphthalene (92).

Compound 92 was prepared according to the general procedure for in situ C$_2$-symmetric Suzuki cross-coupling (see section 7.2.1). Employing 1,8-bis(benzyloxy)-4-bromonaphthalene (91) (0.454 g, 1.08 mmol) as the starting haloarene furnished 0.270 g (74%) of the desired biaryl (92). Purification of the product was accomplished by recrystallization from CH$_2$Cl$_2$/hexanes: mp 181-182 °C; IR (KBr) 1577, 1369, 1267, 1088 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 5.28 (s, 2H, H-11 or H-16), 5.32 (s, 2H, H-11 or H-16), 6.96 (d, $J$=7.6 Hz, 1H), 7.01 (d, $J$=8.3 Hz, 1H), 7.06 (d, $J$=8.0 Hz, 1H), 7.18 (t, $J$=8.1 Hz, 1H), 7.33 (m, 7H), 7.53 (m, 4H); $^{13}$C-NMR (100 MHz) ppm 71.6 (CH$_2$, C-11 or C-16), 71.7 (CH$_2$, C-11 or C-16), 108.1 (CH, C-3 or C-6), 108.6 (CH, C-3 or C-6), 118.5 (C, C-10), 120.2 (CH), 126.2 (CH), 127.4 (CH), 127.5 (CH), 128.4 (CH), 128.6 (CH), 131.8 (C, C-1), 136.9 (C, C-9), 137.4 (C, C-12 and C-17), 155.9 (C, C-4 or C-5), 156.4 (C, C-4 or C-5); mass spectrum, m/z (relative intensity, %) 678 (9, M$^+$), 494 (5, M$^+$-C$_{14}$H$_{14}$O), 181 (8), 91 (100, C$_7$H$_7$). Exact mass calcd for C$_{48}$H$_{38}$O$_4$: 678.2770. Found: 678.2809.

7.2.12 Preparation of 4,4',5,5'-Tetrahydroxy-1,1'-binaphthalene (83).

4,4',5,5'-(Tetrabenzyloxy)-1,1'-binaphthalene (92) (0.106 g, 0.157 mmol) in a mixture of CH$_2$Cl$_2$ (2 mL) and EtOH (3 mL) was treated with 10% palladium on carbon (0.100 g, 60 mol%) under an atmosphere of H$_2$ gas for 18 h. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo. The crude product was purified by radial chromatography (4 mm rotor, 2:1) to afford a dark reddish brown solid material (0.032 g, 64%): mp. >300 °C.
\textsuperscript{211} \textsuperscript{37} >350 \textdegree C); \textsuperscript{1}H-NMR (400 MHz, acetone-\textsubscript{d\textsubscript{6}}) \delta 6.74 (d, J=7.9 Hz, 1H, H-6), 6.78 (d, J=7.7 Hz, 1H, H-3), 6.91 (d, J=7.7 Hz, 1H, H-8), 7.09 (t, J=8.0 Hz, 1H, H-7), 7.21 (d, J=7.7 Hz, 1H, H-2). The physical and NMR spectral data were in good agreement with the literature.\textsuperscript{37}

\textbf{7.2.13 Preparation of 4,4',5,5'-Tetramethoxy-1,1'-binaphthalene (93).

\begin{center}
\textbf{93}
\end{center}

4,4',5,5'-Tetrahydroxy-1,1'-binaphthalene (83) (0.032 g, 0.10 mmol) in DMF (3 mL) was treated with finely powdered K\textsubscript{2}CO\textsubscript{3} (0.200 g, 1.45 mmol) and iodomethane (0.5 mL, 8.03 mmol) at rt for 2 days. The mixture was then quenched with NH\textsubscript{4}Cl solution (10 mL) and extracted with Et\textsubscript{2}O (3 x 10 mL). The combined organic extracts were then washed with brine (5 x 20 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated \textit{in vacuo} to afford the title compound as a blue solid (0.026 g, 69\%): mp 278-280 \textdegree C (CH\textsubscript{2}Cl\textsubscript{2}/hexanes); IR (KBr) 1583, 1380, 1269 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (400 MHz) \delta 4.02 (s, 3H, H-11 or H-12), 4.06 (s, 3H, H-11 or H-12), 6.86 (d, J=7.8 Hz, 1H, H-3), 6.92 (d, J=8.6 Hz, 1H, H-6), 6.96 (d, J=8.0 Hz, 1H, H-2), 7.17 (t, J=8.1 Hz, 1H, H-7), 7.35 (d, J=8.0 Hz, 1H, H-8); \textsuperscript{13}C-NMR (100 MHz) ppm 56.5 (CH\textsubscript{3}, C-11 or C-12), 56.6 (CH\textsubscript{3}, C-11 or C-12), 105.9 (CH, C-3 or C-6), 106.3 (CH, C-3 or C-6), 117.6 (C, C-10), 119.8 (CH), 126.2 (CH), 128.6 (CH), 131.5 (C, C-1), 136.8 (C, C-9), 155.9 (C, C-4 or C-5), 157.3 (C, C-4 or C-5); mass spectrum, \textit{m/z} (relative intensity, \%) 374 (100, M\textsuperscript{+}), 359 (26, M\textsuperscript{+}-CH\textsubscript{3}), 344 (16, M\textsuperscript{+}-2 CH\textsubscript{3}), 188 (15). Exact mass calcd for C\textsubscript{24}H\textsubscript{22}O\textsubscript{4}: 374.1518. Found: 374.1497.

\textbf{7.3 Experiments Pertaining to Chapter Three.}

Naphtho[2,1-\textit{b}]furan (536),\textsuperscript{222} hexachloro-2,4-cyclohexadiene,\textsuperscript{227} and Eaton's reagent\textsuperscript{228} were prepared according to literature procedures with minor modification.
7.3.1 Bromination of Bromobenzo[b]furan (511).

![512](image) ![513](image)

Benzo[b]furan (3.2 g, 27 mmol) in dry CCl₄ (75 mL) was cooled to -10 °C and treated with 1 equiv. Br₂ (1.4 mL, 27 mmol) dropwise via syringe. After 1 h at -10 °C, the reaction mixture was poured into water (150 mL) and subsequently extracted with CHCl₃ (3 x 100 mL). The combined organic extracts were washed with saturated Na₂S₂O₃ solution (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure to afford a white solid residue (7.15 g, 95%), mp 82-84 °C (lit. 215 82-84 °C). The dibromide thus obtained was then dissolved in dry t-BuOH (125 mL) and treated with an excess of potassium t-butoxide (35.6 g, 309 mmol) at rt under a N₂ atmosphere for 12 h. The reaction mixture was then poured into water (250 mL) and subsequently extracted with Et₂O (3 x 200 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to afford a light yellow oil. The crude material was then distilled (bp 100-110 °C, 20 mm Hg) to afford a clear, colorless oil (3.91 g, 72%). ¹H-NMR analysis of the product showed a 9:1 mixture of 3-bromobenzo[b]furan and 2-bromobenzo[b]furan. Chromatographic separation of the regioisomers was not possible and hence the mixture was used directly in the subsequent in situ Suzuki cross-coupling step.

7.3.2 Preparation of 3,3'-Bibenzo[b]furan (514) and the 2,3'-Bibenzo[b]furan (515) Isomer.

The desired 3,3'-bibenzo[b]furan product was prepared according to the general procedure for in situ C₂-symmetric Suzuki cross-coupling (see section 7.2.1). Utilizing the 9:1 mixture of 3-bromobenzo[b]furan and 2-bromobenzo[b]furan, respectively (1.05 g, 5.34 mmol) as the
starting haloarene furnished 0.414 g (74%) of 3,3'-bibenzofuran (514) and 0.033 g (6%) of 2,3'-bibenzofuran. (515). Purification and separation of the two products was achieved by recrystallization from CH$_2$Cl$_2$/hexanes. Compound 514 gave the following analytical data: mp 135-136 °C (lit. 220 110-115 °C); IR (KBr) 1448, 1127, 1090 cm$^{-1}$; $^1$H-NMR (200 MHz) δ 7.30-7.58 (m, 2H, H-5 and H-6), 7.61 (dd, J=7.0, 1.3 Hz, 1H, H-7), 7.76 (dd, J=6.8, 2.0 Hz, 1H, H-4), 8.01 (s, 1H, H-2); $^{13}$C-NMR (50 MHz) ppm 111.8 (CH, C-7), 112.4 (C, C-3), 120.6 (CH), 123.1 (CH), 124.9 (CH), 126.6 (C, C-9), 141.6 (CH, C-2), 155.5 (C, C-8); mass spectrum, m/z (relative intensity, %) 234 (100, M$^+$), 205 (67, M$^+$-CHO). Anal. calcd for C$_{16}$H$_{10}$O$_2$: C, 82.04; H, 4.30. Found: C, 81.80; H, 4.05. The NMR spectral data obtained for compound 515 was in good agreement with the literature. 2,3'-Bibenzo[b]furan (515) gave the following analytical data: mp 103-104 °C; IR (KBr) 1448, 1127, 1089 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 7.07 (s, 1H, H-3), 7.34 (m, 2H), 7.44 (m, 2H). 7.52-7.71 (m, 3H), 8.00 (dd, J=5.0, 1.5 Hz, 1H), 8.17 (s, 1H, H-2'); $^{13}$C-NMR (100 MHz) ppm 111.0 (CH, C-7 or C-7'), 111.9 (CH, C-7 or C-7'), 112.4 (CH, C-3), 113.3 (C, C-3'). 120.7 (CH), 120.8 (CH), 123.0 (CH), 123.5 (CH), 124.3 (CH), 124.5 (C, C-9 or C-9'), 125.1 (CH), 128.9 (C, C-9 or C-9'), 142.7 (CH, C-2'), 149.7 (C), 154.3 (C), 155.6 (C); mass spectrum, m/z (relative intensity, %) 234 (100, M$^+$), 205 (55, M$^+$-CHO), 176 (63). Exact mass calcd for C$_{16}$H$_{10}$O$_2$: 234.0681. Found: 234.0663.

7.3.3 Preparation of 2,2'-Bis(diphenylphosphinyl)-3,3'-bibenzo[b]furan (516).

![516](image)

3,3'-Bibenzo[b]furan (514) (0.151 g, 0.645 mmol) in dry Et$_2$O (12 mL) was cooled to −78 °C and treated with n-BuLi (2.2 M solution in hexanes, 0.88 mL, 1.9 mmol). The solution was warmed to 0 °C and allowed to stir under a N$_2$ atmosphere for 1 h. To the solution was then added freshly distilled diphenylphosphinic chloride (0.37 mL, 1.9 mmol) and the resulting mixture was allowed to stir at rt for 12 h. Following this period, the reaction mixture was quenched with water (20 mL) and subsequently extracted with Et$_2$O (3 x 50 mL). The combined
organic extracts were washed with 10% NaHCO₃ solution (20 mL), dried (MgSO₄), and concentrated \textit{in vacuo} to afford a yellow oil. The crude material was purified by radial chromatography (4 mm rotor, 3:1 hexanes/CHCl₃ → 99:1 CHCl₃/MeOH) to afford 0.292 g (71%) of the desired phosphine oxide \textbf{516} as a white solid, which was purified by recrystallization from CH₂Cl₂/hexanes: mp 202-204 °C (lit.\textsuperscript{220} 206-207 °C); \textsuperscript{1}H-NMR (400 MHz) δ 7.00 (dt, \(J=7.7, 3.0\) Hz, 2H, H-12 or H-16), 7.12 (t, \(J=7.4\) Hz, 1H, H-5 or H-6), 7.20 (d, \(J=7.9\) Hz, 1H, H-4), 7.22 (dt, \(J=7.6, 0.9\) Hz, 1H, H-13 or H-17), 7.35 (t, \(J=7.6\) Hz, 1H, H-5 or H-6), 7.44 (d, \(J=8.4\) Hz, 1H, H-7), 7.47 (dt, \(J=7.6, 2.9\) Hz, 2H, H-12 or H-16), 7.55 (dt, \(J=6.8, 0.9\) Hz, 1H, H-13 or H-17), 7.66 (dd, \(J=12.7, 7.4\) Hz, 2H, H-11 or H-15), 7.86 (dd, \(J=12.8, 7.2\) Hz, 2H, H-11 or H-15); \textsuperscript{13}C-NMR (100 MHz) ppm 111.8 (CH, C-7), 121.8 (CH, C-4), 122.8 (d, \(J=16\) Hz, C, C-3), 123.4 (CH, C-5 or C-6), 127.0 (CH, C-5 or C-6), 127.8 (d, \(J=13\) Hz, CH, C-12 or C-16), 128.5 (d, \(J=13\) Hz, CH, C-12 or C-16), 130.4 (d, \(J=110\) Hz, C, C-10 or C-14), 131.7 (d, \(J=11\) Hz, CH, C-11 or C-15), 131.9 (CH, C-13 or C-17), 131.9 (d, \(J=111\) Hz, C, C-10 or C-14), 132.0 (d, \(J=10\) Hz, CH, C-11 or C-15), 132.2 (CH, C-13 or C-17), 146.4 (d, \(J=126\) Hz, C, C-2), 156.6 (d, \(J=8\) Hz, C, C-8); \textsuperscript{31}P-NMR (81 MHz) ppm +16.7; mass spectrum, \textit{m/z} (relative intensity, %) 634 (3, \(M^+\)), 557 (5, \(M^+\)-Ph), 433 (100, \(M^+\)-P(O)Ph\textsubscript{2}). Exact mass calcd for C\textsubscript{40}H\textsubscript{28}O\textsubscript{4}P\textsubscript{2}: 634.1463. Found: 634.1412. The NMR spectral data was in good agreement with the literature.\textsuperscript{220}

\textbf{7.3.4 Preparation of 2,2'-Bis(diphenylphosphino)-3,3'-bibenzo[b]furan (508).}

\textbf{508}

2,2'-Bis(diphenylphosphinyl)-3,3'-bibenzo[b]furan (\textbf{516}) (0.171 g, 0.270 mmol) in a mixture of dry xylenes (2.5 mL) and triethylamine (0.90 mL) was treated with SiCl\textsubscript{3}H (0.54 mL, 5.4 mmol) under an atmosphere of N\textsubscript{2}. The resulting mixture was then heated to 120 °C for 1 h and subsequently to 165 °C for 5 h. The mixture was cooled to rt and 30% NaOH solution (20 mL) was carefully added over a 30 min period. The mixture was then heated to 60 °C for 1 h during which time the two phases clarified. The cooled mixture was extracted with CHCl\textsubscript{3} (3 x 50 mL)
and the combined extracts were dried (MgSO₄). After concentration under reduced pressure, a light yellow solid residue was obtained. The crude material was purified by crystallization from CHCl₃/MeOH to give 0.154 g (90 %) of the title compound as a white solid: mp 202-204 °C (lit.¹²⁰ 198-202 °C); ¹H-NMR (400 MHz) δ 7.13-7.33 (m, 14H), 7.34-7.50 (m, 12H), 7.55 (d, J=8.2 Hz, 2H); ¹³C-NMR (100 MHz) ppm 111.9 (CH, C-7), 121.2 (CH), 122.8 (CH), 124.4 (t, J=12 Hz, C, C-3), 125.8 (CH), 128.1 (CH, C-13 and C-17), 128.3 (d, J=15 Hz, CH, C-11 or C-15), 128.6 (d, J=17 Hz, CH, C-11 or C-15), 128.8 (C, C-9), 133.6 (d, J=10 Hz, CH, C-12 and C-16), 133.7 (d, J=30 Hz, C, C-10 and C-14), 135.8 (d, J=75 Hz, C, C-2), 157.8 (C, C-8); ³¹P-NMR (81 MHz) ppm -31.1; mass spectrum, m/z (relative intensity, %) 622 (5, M⁺), 525 (13, M⁺-Ph), 431 (100, M⁺-PPh₂). Exact mass calcd for C₄₀H₂₈O₂P₂: 602.1475. Found: 602.1461. The NMR spectral data was in good agreement with the literature.²²⁰

7.3.5 Procedure for the Attempted Resolution of Phosphine Oxide 516 via Complexation with (1S)-(+) -10-Camphorsulfonic Acid Monohydrate (517).

A solution of phosphine oxide 516 (300 mg, 0.47 mmol) and (+)-CSA•H₂O (517) (118 mg, 0.47 mmol) in ethyl acetate (10 mL) was heated to reflux. Acetic acid (3.3 mL) was added dropwise to this solution and heating was continued until a clear solution was obtained. The mixture was slowly cooled to 0 °C over a 2 h period and then left standing in the freezer (-10 °C) for 1 week. Unfortunately, a crystalline complex was not obtained.

7.3.6 Procedure for the Attempted Resolution of Phosphine Oxide 516 via Complexation with (2R,3R)-(−)-2,3-O-Dibenzoyltartaric Acid Monohydrate (519), Table 3.1, Entry 1.

To a refluxing solution of phosphine oxide 516 (350 mg, 0.51 mmol) in chloroform (6.2 mL) was quickly added a warm solution of (-)-DBTA•H₂O (519) (192 mg, 0.51 mmol) in ethyl acetate (6.2 mL). The mixture was refluxed for 30 min and then left to stand overnight at room temperature. The white solid thus obtained was collected by filtration and washed with cold ethyl acetate. ¹H-NMR analysis of the solid showed only unreacted resolving agent 519.

Other entries in Table 3.1 were carried out in a similar fashion using the solvents and reaction conditions specified. In every case, only unreacted (-)-DBTA•H₂O (519) precipitated from the reaction mixture.
7.3.7 Bromination of Naphtho[2,1-b]furan (536).

7.3.7.1 Table 3.2, Entry 1.

Naphtho[b]furan (536) (156 mg, 0.926 mmol) in CCl$_4$ (3 mL) was treated with bromine (0.19 M solution in CCl$_4$, 5.3 mL, 1.0 mmol) and the solution was stirred under an atmosphere of N$_2$ at rt for 1.5 h. The mixture was then transferred into a flask, which contained a solution of t-BuOK (1.04 g, 9.26 mmol) in t-BuOH (15 mL) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was then diluted with water (50 mL) and subsequently extracted with hexanes (2 x 100 mL). The combined organic extracts were washed with 10% NaOH solution (3 x 75 mL), dried (MgSO$_4$), and concentrated in vacuo to afford a reddish brown oil. $^1$H-NMR analysis of the crude material showed a 41:59 mixture of compounds 535 and 541, which could not be separated by column chromatography.

7.3.7.2 Table 3.2, Entry 2.

This experiment was conducted as described in section 7.3.7.1, except that the addition of bromine was done at 0 °C rather than at room temperature. The $^1$H-NMR spectrum of the crude product indicated a mixture of bromides 535 and 541 in a ratio of 34:66.

7.3.7.3 Table 3.2, Entry 3.

To a solution of naphtho[b]furan (536) (101 mg, 0.601 mmol) in CCl$_4$ (3 mL) was added a solution of bromine (31 µL, 0.60 mmol) in CCl$_4$ (4 mL). The mixture was stirred under an atmosphere of N$_2$ at rt for 1.5 h. The mixture was then transferred into a flask, which contained a slurry of KOAc (590 mg, 6.01 mmol) in CCl$_4$ (10 mL) and the resulting mixture was stirred at 45 °C for 12 h. The reaction mixture was then diluted with water (50 mL) and extracted with Et$_2$O
The combined organic extracts were washed with 10% HCl solution (50 mL), brine (50 mL), dried (MgSO₄), and concentrated in vacuo to afford a light blue solid. The crude 2-bromo isomer 541 had: ¹H-NMR (400 MHz) δ 7.22 (s, 1H, H-3), 7.53 (t, J=7.0 Hz, 1H, H-7 or H-8), 7.61 (m, 2H), 7.71 (m, 1H), 7.95 (d, J=8.2 Hz, 1H, H-11 or H=12), 8.06 (d, J=8.2 Hz, 1H, H-11 or H-12). Compound 541 was not stable to column chromatography, and hence was not fully characterized.

7.3.7.4 Table 3.2, Entry 4.

Bromine (63 µL, 1.2 mmol) and KOAc (12 mg, 0.12 mmol) were added to a solution of naphtho[b]furan (536) (97 mg, 0.58 mmol) in CHCl₃ (5 mL) and the mixture was stirred under an atmosphere of N₂ at 50 °C for 12 h. The mixture was diluted with Et₂O (20 mL) and washed with 10% HCl solution (10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to afford a dark blue oil. The crude material was purified by distillation under reduced pressure to furnish 120 mg (63%) of compound 542 as a light blue solid: mp 40-42 °C; bp 100-105 °C (0.1 mm Hg); IR (KBr) 1352, 1086, 752 cm⁻¹; ¹H-NMR (400 MHz) δ 7.13 (s, 1H, H-3), 7.62 (m, 2H), 7.91 (s, 1H, H-11), 7.97 (dd, J=6.2, 2.1 Hz, 1H, H-6 or H-9), 8.31 (dd, J=6.7, 2.2 Hz, 1H, H-6 or H-9); ¹³C-NMR (100 MHz) ppm 107.5 (CH, C-3), 115.9 (CH), 119.0 (C), 123.6 (CH), 124.2 (C), 126.1 (CH), 126.8 (C), 126.9 (C), 127.3 (CH), 128.0 (CH), 128.6 (C, C-2), 152.4 (C, C-13); mass spectrum m/z (relative intensity, %) 328/326/324 (26/54/26, M⁺), 219/217 (94/94, M⁺-COBr), 138 (100). Exact mass calcd for C₁₂H₆⁷⁹Br₈¹BrO: 326.8766. Found: 326.8752.

7.3.7.5 Table 3.2, Entry 5.

To a solution of naphtho[b]furan (536) (64 mg, 0.38 mmol) in CHCl₃ (4 mL) was added bromine (39 µL, 0.76 mmol) and the mixture was stirred for 1.5 h under an atmosphere of nitrogen. The mixture was then transferred into a flask, which contained a solution of t-BuOK (0.43 g, 3.8 mmol) in t-BuOH (8 mL) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with water (25 mL) and extracted with hexanes (2 x 40 mL). The combined organic extracts were washed with 10% NaOH solution (3 x 50 mL), dried (MgSO₄),
and concentrated \textit{in vacuo} to afford a blue oil. Purification of the product was accomplished by distillation under reduced pressure (bp 104-108 °C, 0.1 mm Hg) to give 75 mg (60%) of dibromide 542 as a light blue oil which later solidified. The \textsuperscript{1}H-NMR spectrum was identical to that listed in section 7.3.7.4.

\subsection*{7.3.8 Preparation of 2,3-Dihydronaphtho[2,1-b]furan (543).}

\begin{center}
\includegraphics[width=2cm]{543}
\end{center}

Bromine (34 \textmu L, 0.66 mmol) was added to a solution of naphtho[b]furan (536) (111 mg, 0.66 mmol) in benzene (8 mL). The mixture was stirred at rt for 30 min under a nitrogen atmosphere and then was transferred via cannula to a slurry of lithium aluminum hydride (125 mg, 3.29 mmol) in Et\textsubscript{2}O (10 mL) at 0 °C. The mixture was warmed to rt and stirred for 12 h. The solution was then cooled to 0 °C and H\textsubscript{2}O (0.15 mL), 15% NaOH solution (0.15 mL), and H\textsubscript{2}O (0.45 mL) were added sequentially. The resulting heterogeneous mixture was filtered through a pad of Celite\textsuperscript{®} and the filtrate was concentrated \textit{in vacuo} to furnish a colorless oil. The crude product was purified by radial chromatography (2 mm rotor, 50:1) to afford 79 mg (71%) of compound 543. The \textsuperscript{1}H-NMR spectrum was in excellent agreement with the literature spectrum of 2,3-dihydronaphtho[2,1-b]furan prepared by a different route.\textsuperscript{223}

\subsection*{7.3.9 Reaction of 2,3-Dihydronaphtho[2,1-b]furan (543) with N-Bromosuccinimide.}

To a solution of 2,3-dihydronaphtho[b]furan (543) (14 mg, 0.081 mmol) in CHCl\textsubscript{3} (2 mL) was added NBS (30 mg, 0.17 mmol) and benzoyl peroxide (1 mg, 0.004 mmol). The solution was refluxed under a nitrogen atmosphere for 1 h. The mixture was then cooled to rt, quenched with H\textsubscript{2}O (10 mL), and extracted with Et\textsubscript{2}O (3 x 10 mL). The combined organic layers were washed with Na\textsubscript{2}SO\textsubscript{3} solution (10 mL), H\textsubscript{2}O (10 mL), dried (MgSO\textsubscript{4}), and concentrated under reduced pressure to give a light blue solid which was used directly in the next step. The crude
product and t-BuOK (91 mg, 0.81 mmol) were dissolved in t-BuOH (2 mL) and the mixture was
stirred under a N₂ atmosphere for 3 h. The reaction mixture was then diluted with water (50 mL)
and extracted with Et₂O (2 x 50 mL). The combined organic extracts were washed with 10%
NaOH solution (5 x 50 mL), dried (MgSO₄), and concentrated in vacuo to give a brown oil. ¹H-
NMR analysis of the crude material indicated that the major component of the mixture was the 2-
bromo isomer 541. No signals corresponding to the desired 3-bromo isomer 535 were evident in
the ¹H-NMR spectrum.

In a separate experiment, compound 543 (17 mg, 0.10 mmol) was reacted with NBS (35 mg,
0.20 mmol) and benzoyl peroxide (1 mg, 0.004 mmol) in CHCl₃ (3 mL) for 1 h under a N₂
atmosphere. The mixture was then transferred into a flask, which contained a slurry of KOAc
(98 mg, 1.0 mmol) in CHCl₃ (2 mL) and the resulting mixture was stirred at 45 °C for 2 h. The
mixture was diluted with water (50 mL) and extracted with Et₂O (3 x 50 mL). The organic
layers were combined, washed with 10% HCl solution (50 mL), brine (50 mL), dried (MgSO₄),
and evaporated under reduced pressure to give a brown residue. The only identifiable signals in
¹H-NMR spectrum corresponded to the 2-bromo isomer 541 and naphtho[b]furan (536).

7.3.10 Chlorination of 1-Acetyl-2-hydroxynaphthalene (550).

7.3.10.1 With Sulfuryl Chloride.

To a solution of 1-acetyl-2-hydroxynaphthalene (550) (100 mg, 0.537 mmol) dissolved in
CH₂Cl₂ (2 mL), H₂O (11 μL, 0.59mmol), and MeOH (23 μL, 0.59 mmol), was added SO₂Cl₂ (53
μL, 0.65 mmol). The mixture was refluxed under a N₂ atmosphere for 1 h and subsequently
quenched with H₂O (20 mL). The solution was extracted with Et₂O (20 mL), washed with H₂O
(2 x 20 mL), and dried (MgSO₄). Concentration of the organic phase afforded a greenish yellow
oil. Only a trace amount of the desired product 551 was evident in the crude ¹H-NMR spectrum.
7.3.10.2 With Hexachloro-2,4-cyclohexadienone.

Hexachloro-2,4-cyclohexadienone (111 mg, 0.371 mmol) was added to a solution of 1-acetyl-2-hydroxynaphthalene (550) (69 mg, 0.37 mmol) in absolute ethanol (3 mL) and the mixture was refluxed under a nitrogen atmosphere for 15 h. The solvent was removed in vacuo to give a brown residue. $^1$H-NMR analysis showed that the major component of mixture was unreacted starting material 550 as well a minor amount (<30%) of the desired $\alpha$-chloroketone 551 as evidenced by a singlet at 4.8 ppm corresponding to H-12. The product was not stable to column chromatography.

7.3.11 Preparation of Naphtho[2,1-b]furan-3(2H)-one (549) via $\alpha$-Bromination and Subsequent Cyclization of 1-Acetyl-2-hydroxynaphthalene (550).

7.3.11.1 Preparation of 1-Acetyl-2-(t-butyldimethylsilyloxy)naphthalene (552).

To a solution of 1-acetyl-2-hydroxynaphthalene (550) (21.9 g, 0.117 mol) in Et$_3$N (75 mL, 0.54 mol) and CH$_2$Cl$_2$ (500 mL) was added TBSCl (19.4 g, 0.129 mmol). The mixture was stirred at rt for 18 h before it was quenched with H$_2$O (500 mL). The mixture was then stirred for 1h, extracted with Et$_2$O (3 x 500 mL), and the pooled organic extracts were washed with 10% HCl solution (2 x 500 mL) and H$_2$O (2 x 500 mL). The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure to give 31.4 g (89%) of the TBS ether 552 as a light yellow oil. It had: $^1$H-NMR (200 MHz) $\delta$ 0.28 (s, 6H, H-13), 1.02 (s, 9H, H-15), 2.68 (s, 3H, H-12), 7.10 (d, $J$=12 Hz, 1H, H-3), 7.47 (m, 2H), 7.76 (m, 2H), 7.78 (d, $J$=12 Hz, 1H, H-4). This material was used in the next step without further purification.
7.3.11.2 Preparation of 1-[(1-trimethylsilyl)oxy]ethenyl-2-[(t-butyldimethylsilyl)oxy]-naphthalene (553).

To a solution of silyl ether 552 (31.4 g, 0.105 mol) in CH₂Cl₂ (600 mL) and Et₃N (73 mL, 0.52 mol) at 0 °C was added TMSOTf (24 mL, 0.13 mol). The mixture was warmed to rt and stirring was continued for 1 h under a N₂ atmosphere. The mixture was diluted with CHCl₃ (100 mL), washed with brine (2 x 300 mL), dried (Na₂SO₄), and evaporated to dryness under reduced pressure to give crude enol ether 553 in quantitative yield: ¹H-NMR (200 MHz) δ 0.18 (s, 9H, H-16), 0.27 (s, 6H, H-13), 1.09 (s, 9H, H-15), 4.39 (s, 1H, H-12), 4.74 (s, 1H, H-12), 7.07 (d, J=1 Hz, 1H, H-3), 7.45 (m, 2H), 7.71 (m, 2H), 8.08 (d, J=1 Hz, 1H, H-4). Trimethylsilyl enol ether 553 was used directly in the subsequent step.

7.3.11.3 Preparation of 1-(2-bromoacetyl)-2-[(t-butyldimethylsilyl)oxy]naphthalene (554).

In a flask equipped with a dropping funnel, TMS enol ether 553 (38.9 g, 0.105 mol) was dissolved in CCl₄ (450 mL) and cooled to 0 °C. A solution of bromine (5.66 mL, 0.119 mol) in CCl₄ (100 mL) was placed in the dropping funnel and 20 mL of this solution was added to the reaction mixture, and after warming to rt, the remaining 80 mL of the bromine solution was added over a 30 min period. The mixture was stirred for a further 30 min, diluted with H₂O (200 mL), and the layers were separated. The aqueous layer was extracted with CHCl₃ (2 x 100 mL) and the combined organic layers were washed with Na₂S₂O₃ solution (200 mL) and H₂O (2 x 200 mL). The organic fraction was dried (Na₂SO₄) and concentrated in vacuo to furnish 39.5 g of
compound 554 as a light orange oil. Crude α-bromoketone 554 had: \(^1\)H-NMR (200 MHz) \(\delta 0.29\) (s, 6H, H-13), 1.05 (s, 9H, H-15), 4.58 (s, 2H, H-12), 7.08 (d, \(J=11\) Hz, 1H, H-3), 7.50 (m, 2H), 7.78 (m, 2H), 7.85 (d, \(J=11\) Hz, 1H, H-4).

7.3.11.4 Cyclization of α-Bromoketone 554.

To a solution of compound 554 (39.7 g, 0.105 mol) in THF (400 mL) at 0°C was slowly added TBAF (1.0 M solution in THF, 110 mL, 0.110 mol) under a N\(_2\) atmosphere. The mixture was allowed to stir at 0°C for 10 minutes and at rt for 15 minutes. The dark purple solution was then quenched with NH\(_4\)Cl solution (100 mL) and the THF was removed in vacuo. The remaining residue was extracted with Et\(_2\)O (3 x 100 mL) and the combined Et\(_2\)O layers were washed with brine (100 mL), H\(_2\)O (3 x 150 mL), dried (MgSO\(_4\)), and evaporated under reduced pressure. The crude product was purified by column chromatography (20:1) to give 15.1 g (72% from compound 552) of cyclized ketone 549 as a light yellow solid: mp 133 °C (CH\(_2\)Cl/1/6, lit\(^{225}\) 133 °C); IR (KBr) 1688 (C=O) cm\(^{-1}\); \(^1\)H-NMR (200 MHz) \(\delta 4.77\) (s, 2H, H-2), 7.24 (dd, \(J=7.8, 1.0\) Hz, 1H, H-9), 7.47 (dt, \(J=7.6, 0.9\) Hz, 1H, H-8), 7.66 (dt, \(J=7.6, 1.0\) Hz, 1H, H-7), 7.82 (d, \(J=9.0\) Hz, 1H, H-12), 8.05 (d, \(J=9.0\) Hz, 1H, H-11), 8.75 (dd, \(J=8.2, 0.9\) Hz, 1H, H-6); \(^13\)C-NMR (50 MHz) ppm 75.5 (CH\(_2\)), 113.5 (C), 113.9 (CH), 123.1 (CH), 125.4 (CH), 126.4 (CH), 129.1 (C), 129.2 (C), 129.8 (CH), 139.7 (CH), 176.6 (C, C-13), 199.9 (C=O, C-3); mass spectrum, \(m/z\) (relative intensity, %) 184 (74, M\(^+\)), 155 (87), 126 (100). Exact mass caled for C\(_{12}\)H\(_8\)O\(_2\): 184.0524. Found: 184.0520.

7.3.12 Preparation of Naphtho[2,1-b]furan-3(2H)-one (549) via Friedel-Crafts Acylation of 2-Naphthoxyacetic Acid (555).

Ketone 549 could also be prepared directly from 2-naphthoxyacetic acid (555) using Eaton’s reagent.\(^{228}\) Distilled methanesulfonic acid (8.75 mL, 136 mmol) was added to a flask which contained phosphorus pentoxide (1.30 g, 9.13 mmol) and the mixture was stirred under a N\(_2\)
atmosphere at 40 °C until all of the P2O5 had dissolved. In a separate flask, 2-naphthoxyacetic acid (555) (241 mg, 1.19 mmol) was weighed out and freshly prepared Eaton reagent (vide supra) (5 mL) was added. The reaction was stirred for 12 h under an atmosphere of nitrogen, quenched with H2O (100 mL), and extracted with Et2O (2 x 100 mL). The combined Et2O extracts were dried (MgSO4) and concentrated under reduced pressure to afford a brown oil. Column chromatography (20:1) furnished 150 mg (63%) of ketone 549, which was identical (TLC, 1H-NMR) to the product obtained in section 7.3.11.4.

For large scale preparations of ketone 549 a two-step procedure from 2-naphthoxyacetic acid (555) was employed. Thus, 2-naphthoxyacetic acid (20.1 g, 99.3 mmol) in dry benzene (1 L) was treated with pyridine (80 μL, 0.99 mmol) and SOCl2 (14.4 mL, 199 mmol) at reflux under a N2 atmosphere for 2 h. The solution was cooled, concentrated in vacuo, and the resulting crude acid chloride was taken up into C6H6 (500 mL) and cooled to 0 °C. To the solution was then added AlCl3 (19.8 g, 149 mmol) and the resulting solution was stirred for 12 h at ambient temperature. The mixture was quenched with brine (200 mL) and extracted with benzene (2 x 100 mL). The combined organic extracts were then washed with water (2 x 100 mL), filtered through neutral alumina, and concentrated under reduced pressure to afford 17.2 g (95%) of compound 549 as a pale orange solid, which was clean by 1H-NMR analysis. It had spectroscopic properties (1H-NMR and 13C-NMR) in excellent agreement with those reported for ketone 549 prepared by a different route (see section 7.3.11.4).

7.3.13 Preparation of (±)-3,3'-Binaphtho[2,1-b]furan (556) via an in Situ Stille Coupling.


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To a solution of of ketone 549 (458mg, 2.49 mmol) in THF (20 mL) under a N2 atmosphere at -78 °C was added LHMDS•Et2O (629 mg, 2.61 mmol). The solution was stirred for 5 min
and then N-phenyltrifluoromethanesulfonimide (933 mg, 0.261 mmol) was added. The dark purple mixture was warmed to 0 °C and was stirred for 2 h. The THF was removed under reduced pressure and the residue was taken up into hexanes (100 mL), washed with brine (4 x 50 mL), dried (Na₂SO₄), and concentrated in vacuo to give an orange oil. The crude triflate was filtered through a pad of basic alumina (elution with hexanes) and evaporated under reduced pressure to give 704 mg (90%) of compound 548: ¹H-NMR (200 MHz) δ 7.54-7.70 (m, 3H), 7.83 (d, J=9.4 Hz, 1H), 7.97 (s, 1H, H-2), 7.99 (d, J=8.0 Hz, 1H), 8.37 (d, J=8.2 Hz, 1H). Triflate 548 was used in the subsequent coupling without any further purification.

7.3.13.2 Stille Coupling of Triflate 548.

To a mixture of triflate 548 (883 mg, 2.79 mmol), hexamethylditin (460 mg, 1.40 mmol), BHT (5 mg, 0.02 mmol), and lithium chloride (177 mg, 4.19 mmol) in 1,4-dioxane (5mL) was added Pd(PP₃)₄ (162 mg, 5 mol%). The mixture was refluxed under a N₂ atmosphere for 48 h and then was cooled to rt, diluted with water (50 mL), and extracted with Et₂O (3 x 50 mL). The combined Et₂O layers were washed with NaHCO₃ solution (3 x 100 mL), brine (3 x 100 mL), and H₂O (100 mL). The organic phase was dried (MgSO₄) and evaporated under reduced pressure to give a light yellow solid. The crude material was further purified by exhaustive radial chromatography (4 mm rotor, 30:1) to afford 293 mg (63%) of biaryl 556. It had: mp 292-294 °C (CH₂Cl₂/hexanes); IR (KBr) 2850, 1436 cm⁻¹; ¹H-NMR (200 MHz) δ 7.09 (ddd, J=8.4, 7.0, 1.3 Hz, 1H, H-7 or H-8), 7.35 (ddd, J=8.4, 6.7, 1.0 Hz, 1H, H-7 or H-8), 7.75 (d, J=8.3 Hz, 1H, H-12), 7.84 (m, 2H, H-6 and H-9), 7.86 (s, 1H, H-2), 7.94 (d, J=8.3 Hz, 1H, H-11); ¹³C-NMR (50 MHz) ppm 112.1 (C), 112.6 (CH, C-12), 113.9 (C), 123.3 (CH), 124.5 (CH), 126.3 (CH), 126.4 (CH), 128.4 (C), 128.6 (CH), 130.8 (C), 142.8 (CH, C-2), 153.5 (C, C-13); mass spectrum, m/z (relative intensity, %) 334 (100, M⁺), 305 (31), 276 (32), 138 (18). Exact mass
calcd for C_{24}H_{14}O_{2}: 334.0994. Found: 334.0970. Anal. calcd for C_{24}H_{14}O_{2}: C, 86.20; H, 4.22. Found: C, 85.96; H, 4.04.

7.3.14 Preparation of (±)-3,3'-Binaphtho[2,1-b]furan (556) via a McMurry Coupling of Ketone 549.

In a 1 L 3-neck round bottom flask equipped with an addition funnel was placed activated zinc dust (29.3 g, 0.448 mol) and DME (300 mL). The mixture was cooled to -78 °C and to it was carefully added TiCl_{4} (23.9 mL, 0.218 mol) dropwise via syringe over a 30 min period. The resulting blue mixture was warmed to reflux and starting naphthoketone 549 (10.0 g, 54.4 mmol in 100 mL DME) was added dropwise over a 20 min period. The resulting mixture was heated to reflux under a N₂ atmosphere for 18 h. The cooled mixture was then filtered through a coarse sintered glass funnel and the filtrate was concentrated under reduced pressure. The resulting orange gummy residue was then dissolved in C₆H₆ (300 mL) and treated with DDQ (6.17 g, 27.2 mmol) at reflux under a N₂ atmosphere for 4 h. The cooled mixture was then quenched with Na₂S₂O₃ solution (100 mL) and extracted with Et₂O (3 x 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated to afford the crude title compound. The product was readily purified by flash chromatography (100:1) to give analytically pure biaryl 556 (7.13 g, 78%), which was identical (TLC, \(^1\)H-NMR) to the sample prepared in section 7.3.13.2.

7.3.15 Preparation of (±)-2,2'-Bis(diphenylphosphinyl)-3,3'-binaphtho[2,1-b]furan (560).

3,3'-Binaphtho[2,1-b]furan (556) (0.593 g, 1.78 mmol) in dry Et₂O (30 mL) was lithiated with i-ButLi (1.7 M solution in hexanes, 2.6 mL, 4.4 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and 2 h at rt under a N₂ atmosphere. To the mixture was then added freshly distilled diphenylphosphinic chloride (0.85 mL, 4.4 mmol) and the resulting white slurry was stirred overnight at room temperature. The reaction mixture was quenched with water and extracted
with CHCl₃ (3 x 50 mL). The combined organic extracts were washed with 10% NaHCO₃ solution (50 mL), water (50 mL), and brine (50 mL). The organic phase was then dried (MgSO₄) and concentrated in vacuo to afford a light yellow solid residue. The crude material was purified by column chromatography (3:1 CH₂Cl₂/EtOAc → 19:1 CH₂Cl₂/MeOH) to afford 1.15 g (88%) of the title compound 560 as a white solid: mp 289-290 °C (CH₂Cl₂/hexanes); IR (KBr) 2924, 1437, 1120 cm⁻¹; ¹H-NMR (400 MHz) δ 6.96 (dt, J=7.7, 3.1 Hz, 2H), 7.06 (t, J=7.6 Hz, 1H), 7.23 (m, 3H), 7.36 (m, 2H), 7.46 (d, J=8.3 Hz, 1H), 7.53 (d, J=7.3 Hz, 1H), 7.56 (d, J=7.3 Hz, 1H), 7.64 (d, J=9.0 Hz, 1H), 7.72 (m, 2H), 7.83 (d, J=9.1 Hz, 1H), 7.87 (d, J=8.1 Hz, 1H); ¹³C-NMR (50 MHz) ppm 112.6 (CH), 121.5 (d, J=8 Hz, C, C-4), 122.7 (CH), 124.6 (C), 124.8 (CH), 126.9 (CH), 127.6 (d, J=13 Hz, CH), 128.1 (d, J=13 Hz, CH, C-3), 128.7 (CH), 129.9 (d, J=31 Hz, C, C-14 or C-18), 130.8 (C), 131.9 (d, J=3 Hz, CH), 132.0 (CH), 132.1 (d, J=35 Hz, C, C-14 or C-18), 132.1 (CH), 145.8 (d, J=128 Hz, C, C-2), 155.5 (d, J=8 Hz, C, C-13); ³¹P-NMR (162 MHz) ppm +16.5; mass spectrum, m/z (relative intensity, %) 533 (100, M⁺-P(O)Ph₂), 201 (54). Exact mass calcd for C₄₈H₃₂P₂O₄: 734.1778. Found: 734.1731.

7.3.16 Preparation of (±) 2,2'-Bis(diphenylphosphino)-3,3'-binaphtho[2,1-b]furan (509).

![Diagram](image_url)

3,3'-Binaphtho[2,1-b]furan (556) (3.4 g, 10.2 mmol) in dry Et₂O (130 mL) was lithiated with t-BuLi (2.0 M solution in hexanes, 11.2 mL, 22 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h under a N₂ atmosphere. Freshly distilled chlorodiphenylphosphine (4.0 mL, 22 mmol) was added to the mixture and the resulting white slurry was stirred overnight at room temperature. The reaction mixture was quenched with water and extracted with CHCl₃ (3 x 125 mL). The combined organic extracts were washed with 10% NaHCO₃ solution (100 mL), water (100 mL), and brine (100 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo to afford a light brown solid residue, which was purified by crystallization from CHCl₃/MeOH to
afford 6.49 g (91%) of the title compound 509: mp 228-229 °C; IR (KBr) 3052, 1433 cm⁻¹; ¹H-NMR (400 MHz) δ 7.04 (td, J=7.4, 1.0 Hz, 1H), 7.24-7.14 (m, 6H), 7.35-7.30 (m, 3H), 7.37 (td, J=8.1, 1.5 Hz, 2H), 7.62 (d, J=8.3 Hz, 1H), 7.76 (d, J=9.1 Hz, 1H), 7.84 (d, J=9.0 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H); ¹³C-NMR (100 MHz) ppm 113.3 (CH), 122.9 (d, J=3 Hz, C), 123.4 (CH), 125.0 (CH), 126.9 (CH), 127.0 (d, J=35 Hz, C, C-14 or C-18), 127.8 (CH), 128.6 (CH), 128.6 (d, J=2 Hz, CH), 128.7 (d, J=8 Hz, CH), 128.8 (d, J=27 Hz, C, C-14 or C-18), 129.0 (CH), 131.2 (C), 133.9 (d, J=2 Hz, CH), 134.1 (CH), 134.2 (d, J=2 Hz, CH), 135.5 (C), 136.2 (C), 153.4 (dd, J=36, 3 Hz, C, C-2), 156.7 (d, J=2 Hz, C, C-13); ³¹P-NMR (162 MHz) δ -32.3; mass spectrum, m/z (relative intensity, %) 625 (1, M⁺-Ph), 517 (37), 408 (79), 183 (100). Exact mass calcd for C₄₈H₃₂P₂O₂: 702.1878. Found: 702.1841.

7.3.17 Trichlorosilane Reduction of Phosphine Oxide 560.

Phosphine oxide 560 (791 mg, 1.08 mmol) was dissolved in a mixture of xylenes (25 mL) and Et₃N (3.61 mL, 25.9 mmol). To the solution was added SiCl₃H (2.18 mL, 21.6 mmol) and the resulting mixture was heated to 100 °C under nitrogen for 1 h and 150 °C for 3 h. The mixture was then cooled to 65 °C and 30% NaOH solution (60 mL) was added dropwise and the mixture was vigorously stirred for 1 h at 65 °C. The cooled reaction mixture was extracted with CHCl₃ (3 x 100 mL), dried (MgSO₄), and concentrated in vacuo. The product was purified by recrystallization from CHCl₃/MeOH to give 750 mg (99%) of phosphine 509, which was identical in all respects (TLC, ¹H-NMR, ¹³C-NMR) to a sample prepared by a different route (see section 7.3.15).
7.3.18 Preparation of (±)-Dichloro[2,2'-Bis(diphenylphosphino)-3,3'-binaphtho[2,1-b]furan]-palladium (II) (561).

(±)-2,2'-Bis(diphenylphosphino)-3,3'-binaphtho[2,1-b]furan (509) (300 mg, 0.427 mmol) and bis(acetonitrile)dichloropalladium(II) (111 mg, 0.427 mmol) were stirred in CH₂Cl₂ (20 mL) at rt for 15 h. The solution was concentrated in vacuo and the residue was purified by recrystallization from acetone/Et₂O to give 349 mg (93%) of palladium adduct 561 as orange crystals: mp 312-314 °C; IR (KBr) 3056, 1095, 999, 690 cm⁻¹; ¹H-NMR (400 MHz) δ 6.59 (m, J=6.9 Hz, 2H), 6.82 (t, J=7.3 Hz, 1H), 7.08 (t, J=7.6 Hz, 1H), 7.27-7.52 (m, 6H), 7.65 (d, J=7.5 Hz, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.77 (d, J=9.1 Hz, 1H), 7.91 (d, J=8.1 Hz, 1H), 8.11 (d, J=7.6 Hz, 1H), 8.15 (d, J=7.6 Hz, 1H); ¹³C-NMR (100 MHz) ppm 112.6 (CH, C-12), 122.0 (d, J=2 Hz, C, C-4), 123.8 (dd, J=7, 6 Hz, C, C-3), 124.3 (dd, J=62, 4 Hz, C, C-14 or C-18), 125.8 (CH), 126.8 (dd, J=68, 5 Hz, C, C-14 or C-18), 127.8 (CH), 128.1 (C, C-5 or C-10), 128.3 (t, J=6 Hz, CH, C-16 or C-20), 128.5 (t, J=6 Hz, CH, C-16 or C-20), 128.9 (CH), 129.2 (CH), 131.2 (d, J=2 Hz, C, C-5 or C-10), 131.6 (CH, C-17 or C-21), 132.0 (CH, C-17 or C-21), 134.3 (t, J=5 Hz, CH, C-15 or C-19), 136.3 (t, J=7 Hz, CH, C-15 or C-19), 147.4 (d, J=73 Hz, C, C-2), 158.1 (dd, J=4, 3 Hz, C, C-13); ³¹P-NMR (162 MHz) ppm +11.3; FAB-MS, m/z (relative intensity, %) 901 (9, M⁺Cl₂)+Na⁺, 878 (9, M⁺Cl₂).

7.4 Experiments Pertaining to Chapter Four.

Silver hydrogen dibenzoyl-L-tartrate,²⁴⁴b silver (1S)-(+-)10-camphorsulfonate,²⁴⁵ 2-chloro-2,2'-bis[8R,9R]-N,N'-dimethyl-1,3-diazahexahydro-2-phosphinoindane (581),²⁴⁹,²⁵⁰ N,N'-dimethyl-1,2-diphenylethlenediamine (584),²⁵²,²⁵³ (1S)-camphor-10-sulfonyl azide (593),²⁵⁹
2,2′-bis(diphenylphosphino)-3,3′-bibenzo[h]thiophene (525),\(^{220}\) (S)-2-[2-(diphenylphosphino)-phenyl]-4,5-dihydro-4-(2-methylpropyl)-oxazole (602),\(^{265}\) and (S)-7,7′dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (607)\(^{266}\) were prepared according to known literature procedures.

7.4.1 Procedure for the Attempted Resolution of Phosphine Oxide 560 via Complexation with (2R,3R)-(-)-2,3-O-Dibenzoyltartaric Acid (519), Table 4.1, Entry 1.

To a hot solution of phosphine oxide 560 (374 mg, 0.509 mmol) in chloroform (9 mL) was added a warm solution of (-)-DBTA (519) (182 mg, 0.509 mmol) in ethyl acetate (6 mL). The mixture was refluxed for 15 minutes and then left to stand overnight at ambient temperature. The mixture was filtered and the white precipitate thus obtained was washed with cold ethyl acetate. The H-NMR spectrum of the precipitate showed only unreacted starting material 560. Moreover, H-NMR analysis of the concentrated mother liquor showed only phosphine oxide 560 and unreacted resolving agent 519.

Entries 2-9 were performed in a similar fashion. Minor modifications to the reaction parameters are specified in Table 4.1.

7.4.2 Procedure for the Attempted Resolution of Phosphine Oxide 560 via Complexation with (1S)-(+)−10-Camphorsulfonic Acid Monohydrate (517).

A solution of phosphine oxide 560 (400 mg, 0.544 mmol) and (+)-CSA•H2O (517) (136 mg, 0.544 mmol) in ethyl acetate (10 mL) was heated to reflux. Acetic acid (3.3 mL) was then added dropwise and heating was continued until a clear solution was obtained. The mixture was slowly cooled to 0 °C and the crystals thus obtained were removed by filtration and washed with cold
ethyl acetate. The $^1$H-NMR spectrum of the solid showed only unreacted resolving agent 517. In addition, concentration of the mother liquor in vacuo gave a white solid, which was shown by $^1$H-NMR analysis to be uncomplexed phosphine oxide 560 and unreacted resolving agent 517.

In a separate experiment, the above procedure was repeated using 5 equivalents of (+)-CSA•H$_2$O (517). Thus, reaction of phosphine oxide 560 (800 mg, 1.09 mmol) and resolving agent 517 (1.36 g, 5.44 mmol) gave a white solid upon cooling to 0 °C. The solid was shown to be unreacted (1S)-(+)-CSA•H$_2$O by $^1$H-NMR spectroscopy. The mother liquor was concentrated under reduced pressure to give 1.32 g (99 %) of CSA bound complex 563 as a white solid. It had: $^1$H-NMR (200 MHz) δ 0.98 (s, 3H, H-8 or H-9), 1.95 (s, 3H, H-8 or H-9), 1.47 (m, 1H), 1.95-2.47 (m, 5H), 2.55 (ddd, $J$=16.8, 3.8, 1.6 Hz, 1H, H-3), 3.08 (d, $J$=13.5 Hz, 1H, H-10), 3.46 (d, $J$=13.5 Hz, 1H, H-10), 5.70 (br s, 1H, OH), 7.04 (dt, $J$=7.2, 2.9 Hz, 2H), 7.10 (d, $J$=7.8 Hz, 1H), 7.15-7.30 (m, 2H), 7.35-7.58 (m, 6H), 7.61-7.72 (m, 3H), 7.90 (dd, $J$=7.8, 5.1 Hz, 2H); $^{31}$P-NMR (81 MHz) ppm +19.7. Complex 563 could not be purified by either recrystallization or column chromatography.

7.4.3 Attempted Resolution of (±)-BINAPFu (509) using (+)-Di-µ-chlorobis{2-[1-(dimethylamino)-ethyl]phenyl-C,N}dipalladium (564).

A mixture of phosphine 509 (170 mg, 0.242 mmol) and (+)-di-µ-chlorobis{2-[1-(dimethylamino)-ethyl]phenyl-C,N}dipalladium (564) (70 mg, 0.12 mmol) were mixed in methanol (5 mL) under a N$_2$ atmosphere and stirred at rt for 2 h. A solution of potassium hexafluorophosphate (58 mg, 0.31 mmol) in water (4 mL) was added to the mixture and the resultant bright yellow slurry was stirred for 12 h. The mixture was then filtered through a fine sintered glass funnel to give 240 mg (90%) of the diastereomeric mixture of PF$_6$ salts 569a and 569b. $^{31}$P NMR (81 MHz) ppm +3.1 (d, $J$=35 Hz, P-2 of 569b), 3.4 (d, $J$=35 Hz, P-2 of 569a),
21.6 (d, J=35 Hz, P-1 of 569b), 22.6 (d, J=35 Hz, P-1 of 569a), 177.3 (sept, J=711 Hz, PF₆). The two diastereomers could not be separated by recrystallization or chromatographic methods.

7.4.4 Procedure for the Attempted Resolution of (+)-BINAPFu (509) via Formation of Diastereomeric Phosphonium Salts, Table 4.2, Entry 1.

A mixture of phosphine (509) (13 mg, 0.018 mmol) and (S)-(+)citronellyl bromide (571) (7.7 mg, 0.035 mmol) in CCl₄ (1 mL) was refluxed for 16 h under an atmosphere of nitrogen. The mixture was cooled to rt and the solid thus obtained was isolated by filtration. Only unreacted phosphine 509 and citronellyl bromide (571) (TLC and ¹H-NMR) were recovered.

The other entries in Table 4.2 were conducted the same as in entry 1, except with the appropriate changes in starting halide and/or solvent. In all cases, only unreacted phosphine 509 (TLC and ¹H-NMR) was obtained.

7.4.5 Preparation of (+)-2,2'-Bis{3,3'-binaphtho[2,1-b]furandiphenylmethyl}phosphonium iodide (575).

To a solution of (+)-BINAPFu (509) (100 mg, 0.143 mmol) in CHCl₃ (5 mL) was added methyl iodide (2.0 mL, 32 mmol) and the mixture was heated under a N₂ atmosphere for 5 days. The solvents were removed in vacuo to afford 130 mg (93%) of bis-phosphonium salt 575 as a bright yellow powder: ¹H-NMR (400 MHz) δ 2.97 (d, J=13.4 Hz, 3H, H-14), 7.24-7.28 (m, 3H), 7.43-7.70 (m, 10H), 7.97 (d, J=9.2 Hz, 1H), 8.03 (d, J=8.2 Hz, 1H), 8.17 (d, J=9.3 Hz, 1H); ¹³C-NMR (100 MHz) ppm 12.1 (d, J=57 Hz, CH₃, C-14), 113.8 (CH, C-12), 115.6 (d, J=77 Hz, C, C-15 or C-19), 116.6 (d, J=77 Hz, C, C-15 or C-19), 120.9 (d, J=8 Hz, C, C-3), 121.6 (CH), 127.2 (C), 127.5 (CH), 128.2 (C), 128.4 (C), 129.4 (CH), 130.5 (CH), 130.66 (CH), 130.71 (CH), 131.0 (CH), 131.0 (CH), 131.8 (C), 133.8 (d, J=120 Hz, C, C-2), 133.5 (d, J=14 Hz, CH,
C-16 or C-20), 133.6 (d, J=14 Hz, CH, C-16 or C-20), 136.5 (dd, J=8, 3 Hz, CH, C-6), 158.4 (d, J=8 Hz, C, C-13); $^{31}$P-NMR (162 MHz) ppm +12.9.

7.4.6 Procedure for the Attempted Resolution of Bis-phosphonium Salt 575 via Reaction with Silver Hydrogen Dibenzoyl-L-tartrate (Ag-DBHT) or Silver (1S)-(+)10-Camphorsulfonate (Ag-CSA).

Phosphonium iodide 575 (93 mg, 0.095 mmol) was dissolved in methanol (5 mL) and Ag-DBHT$^{224b}$ (112 mg, 0.19 mmol) was added. The reaction was refluxed for 4 h under a N$_2$ atmosphere, filtered through Celite,$^{9}$ and concentrated in vacuo. A mixture of unidentifiable products ($^{31}$P-NMR) was observed.

In a separate experiment, phosphonium iodide 575 (68 mg, 0.069 mmol) and Ag-CSA$^{245}$ (25 mg, 0.069 mmol) were refluxed in methanol (5 mL) under nitrogen for 30 minutes. The mixture was filtered through Celite$^{9}$ and concentrated under reduced pressure to afford a complex mixture of products ($^{31}$P-NMR).

7.4.7 Preparation of Bis-P-Borane-(R$_{ax}^*$)-2,2'-bis[(8R,9R)-N,N'-dimethyl-1,3-diazahexahydro-2-phosphinoindan-2-yl]-3,3'-binaphtho[2,1-b]furan complex (582a) and Bis-P-Borane-(S$_{ax}^*$)-2,2'-bis[(8S,9S)-N,N'-dimethyl-1,3-diazahexahydro-2-phosphinoindan-2-yl]-3,3'-binaphtho[2,1-b]furan complex (582b).

To a solution of naphtho[2,1-b]furan (536) (0.173 g, 0.518 mmol) in Et$_2$O (5.0 mL) at -78 °C was added 2.05 equivalents of t-BuLi (1.7 M in hexanes, 0.62 mL, 1.1 mmol). The resulting mixture was warmed to 0 °C and stirred under an atmosphere of nitrogen for 1.5 h. To the vessel was then added enantiopure 2-chloro-2,2'-bis[8R,9R]-N,N'-dimethyl-1,3-diazahexahydro-2-phosphinoindane (581)$^{249,250}$ (0.219 g, 1.06 mmol). The reaction contents were allowed to warm
to rt over a 1 h period and subsequently left to stir for 24 h. To the vessel was then added borane-dimethyl sulfide complex (2.0 M solution in THF, 0.531 mL, 1.1 mmol) and the resulting mixture was left to react for a further 24 h. The reaction contents were then quenched with brine (50 mL) and extracted with CHCl₃ (3 x 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to afford a light yellow oil. The crude material was purified by column chromatography (15:1) to afford a 1:1 mixture of the title compounds (0.270 g, 74%). A small sample (~3 mg) of each pure diastereomer was obtained by exhaustive preparative high performance liquid phase chromatography (Nova-Pak C₁₈, 93:7 CH₃CN:H₂O, 1.0 mL/min, 320 nm detection). The first isomer to elute, compound 582a, was obtained as a colorless film exhibiting the following analytical data: IR (KBr) 2937, 2387 (BH₃), 1462, 1025 cm⁻¹; ¹H-NMR (400 MHz) δ -0.50-0.63 (bq, 3H, H-1), 1.10-1.62 (m, 4H), 1.89 (t, J=12.9 Hz, 2H), 2.00-2.13 (m, 2H), 2.19 (d, J=14.5 Hz, 3H, H-14 or H-15), 2.48 (td, J=10.4, 3.0 Hz, 1H, H-16 or H-21), 2.74 (d, J=12.8 Hz, 3H, H-14 or H-15), 3.18 (t, J=9.6 Hz, 1H, H-16 or H-21), 7.02 (t, J=7.0 Hz, 1H, H-7 or H-8), 7.32 (t, J=7.0 Hz, 1H, H-7 or H-8), 7.58 (d, J=7.8 Hz, 1H), 7.82 (d, J=9.1 Hz, 1H, H-11 or H-12), 7.90 (d, J=9.1 Hz, 1H, H-11 or H-12), 7.91 (d, J=7.8 Hz, 1H); ¹³C-NMR (100 MHz) ppm 24.7 (CH₂, C-18 or C-19), 24.8 (CH₂, C-18 or C-19), 29.0 (d, J=8 Hz, CH₂, C-17 or C-20), 29.3 (d, J=5 Hz, CH₂, C-17 or C-20), 30.4 (d, J=3 Hz, CH₃, C-14 or C-15), 32.6 (d, J=10 Hz, CH₃, C-14 or C-15), 65.8 (d, J=3 Hz, CH, C-16 or C-21), 68.4 (CH, C-16 or C-21), 113.4 (CH, C-12), 122.8 (C, C-5 or C-10), 122.9 (C, C-5 or C-10), 123.5 (CH), 125.1 (CH), 126.4 (d, J=19 Hz, CH, C-3), 126.8 (CH), 128.9 (CH), 129.3 (CH), 131.3 (C, C-4), 150.4 (d, J=30 Hz, C, C-2), 155.5 (d, J=4 Hz, C, C-13); ³¹P-NMR (162 MHz) ppm +94.1 (q, J=71 Hz); FAB-MS, m/z (relative intensity, %) 725 (48, M+Na⁺). Compound 582b, also obtained as a colorless film, had the following properties: IR (KBr) 2935, 2390 (BH₃), 1461, 1003 cm⁻¹; ¹H-NMR (400 MHz) δ -0.48 (qd, J=12.3, 3.6 Hz, 1H), 0.20-1.20 (bq, 3H, H-1), 0.78-0.97 (m, 2H), 1.28 (d, J=8.6 Hz, 1H), 1.39 (d, J=9.8 Hz, 2H), 1.65 (d, J=8.9 Hz, 1H), 2.10 (td, J=12.0, 3.2 Hz, 1H, H-16 or H-21), 2.26 (m, 1H), 2.36 (d, J=13.1 Hz, 3H, H-14 or H-15), 2.62 (d, J=14.2 Hz, 3H, H-14 or H-15), 7.13 (t, J=8.0 Hz, 1H, H-7 or H-8), 7.36 (t, J=7.1 Hz, 1H, H-7 or H-8), 7.55 (d, J=8.3 Hz, 1H, H-6 or H-9), 7.88 (ABq, J=9.2 Hz, 2H, H-11 and H-12), 7.94 (d, J=8.1 Hz, 1H, H-6 or H-9); ¹³C-NMR (100 MHz) ppm 23.7 (CH₂, C-18 or C-19), 24.1 (CH₂, C-18 or C-19), 27.3 (d, J=5 Hz, CH₃, C-17 or C-20), 28.2 (d, J=8 Hz, CH₂, C-17 or C-20), 30.3 (d,
$J=2$ Hz, CH$_3$, C-14 or C-15), 32.8 (d, $J=10$ Hz, CH$_3$, C-14 or C-15), 64.1 (d, $J=3$ Hz, CH, C-16 or C-21), 68.2 (CH, C-16 or C-21), 113.5 (CH, C-12), 123.1 (d, $J=5$ Hz, C, C-4), 123.2 (d, $J=9$ Hz, C, C-3), 125.3 (CH), 127.1 (CH), 128.7 (CH), 129.0 (C, C-5 or C-10), 129.5 (CH), 131.5 (C, C-5 or C-10), 150.3 (d, $J=40$ Hz, C, C-2), 155.5 (d, $J=6$ Hz, C, C-13); $^{31}$P-NMR (162 MHz) ppm +98.7 (q, $J=74$ Hz); FAB-MS, m/z (relative intensity, %) 725 (7, M+Na$^+$).

7.4.8 Preparation of 2-Chloro-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidine (585).

![Structure of 585]

Under an argon atmosphere (1S,2S)-N,N-Dimethyl-1,2-diphenylethlenediamine (584) (1.59 g, 6.63 mmol) was dissolved in freshly distilled Et$_2$O (40 mL) and Et$_3$N (1.85 mL, 13.3 mmol). The reaction mixture was then cooled to $-40^\circ$C, phosphorus trichloride (0.578 mL, 6.63 mmol) was added, and the resultant thick white slurry was stirred for 30 min at $-40^\circ$C, for 1 h at 0 $^\circ$C, and for 24 h at room temperature. The slurry was filtered under an atmosphere of argon and the filtrate was concentrated under reduced pressure in an inert atmosphere to give a bright yellow solid residue. Crude phosphoramidous chloride 585 had: $^1$H-NMR (200 MHz) $\delta$ 2.55 (d, $J=19.5$ Hz, 3H, H-4), 4.28 (d, $J=7.4$ Hz, 1H, H-3), 7.11-7.40 (m, 5H); $^{13}$C-NMR (50 MHz) ppm 31.8 (d, $J=21$ Hz, CH$_3$, C-4), 78.1 (d, $J=11$ Hz, CH, C-3), 128.2 (CH), 128.7 (CH), 128.8 (CH), 137.1 (d, $J=2$ Hz, C, C-5); $^{31}$P-NMR (62 MHz) ppm +173.6. Compound 585 was used in the subsequent step without further purification.
7.4.9 Bis-P-Borane-(R\textsubscript{ax})-2,2'-bis[(4R,5R)-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl]-3,3'-binaphtho[2,1-b]furan complex (586a) and Bis-P-Borane-(S\textsubscript{ax})-2,2'-bis[(4R,5R)-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl]-3,3'-binaphtho[2,1-b]furan complex (586b).

To a solution of naphtho[6]furan (536) (0.245 g, 0.734 mmol) in Et\textsubscript{2}O (8.0 mL) at -78 °C was added 2.2 equivalents of t-BuLi (1.7 M in hexanes, 0.949 mL, 1.61 mmol). The resulting mixture was warmed to 0 °C and stirred under an atmosphere of nitrogen for 1.5 h. To the vessel was then added enantiopure diazaphospholidine reagent 585 (0.491 g, 1.61 mmol). The reaction contents were allowed to warm to rt over a 1 h period and subsequently left to stir for 3 h. To the vessel was then added borane-dimethyl sulfide complex (2.0 M solution in THF, 1.10 mL, 2.20 mmol) and the resulting mixture was left to react for a further 4 h. The reaction contents were then quenched with brine (50 mL) and extracted with CHCl\textsubscript{3} (3 x 75 mL). The combined organic extracts were dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo} to afford a light yellow solid residue. The crude material was purified by column chromatography (15:1) to afford a 1:1 mixture of the title compounds. Separation of the mixture was achieved by recrystallization from a binary mixture of CHCl\textsubscript{3} and hexanes. Under these conditions, compound 586a crystallized diastereomerically pure as long white needles (0.304 g, 46%) characterized by the following analytical data: mp 123-124 °C; IR (KBr) 2869, 2392 (BH\textsubscript{3}), 1455, 1147 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (300 MHz) δ -0.32-0.84 (bs, 3H, H-1), 2.02 (d, J=11.3 Hz, 3H, H-14 or H-15), 2.71 (d, J=13.3 Hz, 3H, H-14 or H-15), 4.00 (d, J=8.7 Hz, 1H, H-16 or H-21), 4.80 (d, J=8.7 Hz, 1H, H-16 or H-21), 7.02-7.45 (m, 12H), 7.74 (d, J=7.9 Hz, 1H), 7.84-8.10 (m, 3H); \textsuperscript{13}C-NMR (75 MHz)
ppm 31.8 (d, J=3 Hz, CH₃, C-14 or C-15), 32.7 (d, J=11 Hz, CH₃, C-14 or C-15), 75.1 (d, J=3 Hz, CH, C-16 or C-21), 76.3 (CH, C-16 or C-21), 112.7 (CH, C-12), 122.4 (C, C-17 or C-23), 122.5 (C, C-17 or C-23), 122.8 (CH), 124.8 (CH), 126.2 (C, C-5), 126.9 (CH), 127.7 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 131.1 (C, C-10), 137.6 (d, J=9 Hz, C, C-3), 138.5 (d, J=4 Hz, C, C-4), 151.6 (d, J=26 Hz, C, C-2), 155.0 (d, J=3 Hz, C, C-13); ³¹P-NMR (81 MHz) ppm +98.7 (bs); FAB-MS, m/z (relative intensity, %) 899 (1, M+H⁺). Borane adduct 586b was obtained isomerically pure after flash chromatographic (15:1) purification of the mother liquor. The following analytical data was recorded for this compound: mp 138-140 °C (CHCl₃/hexanes); IR (KBr) 2869, 2390 (BH₃), 1455, 1146 cm⁻¹; ¹H-NMR (400 MHz) δ -0.32-1.00 (bs, 3H, H-1), 2.11 (d, J=13.7 Hz, 3H, H-14 or H-15), 2.86 (d, J=11.1 Hz, 3H, H-14 or H-15), 4.15 (d, J=8.7 Hz, 1H, H-16 or H-21), 4.61 (d, J=8.7 Hz, 1H, H-16 or H-21), 6.99 (t, J=7.2 Hz, 1H), 7.12-7.23 (m, 2H), 7.25-7.34 (m, 4H), 7.35-7.50 (m, 5H), 7.70 (t, J=8.2 Hz, 1H), 7.91-8.03 (m, 3H); ¹³C-NMR (100 MHz) ppm 31.8 (d, J=5 Hz, CH₃, C-14 or C-15), 33.4 (d, J=11 Hz, CH₃, C-14 or C-15), 75.1 (d, J=2 Hz, CH, C-16 or C-21), 76.4 (CH, C-16 or C-21), 113.3 (CH, C-12), 122.9 (C, C-17 or C-23), 123.0 (C, C-17 or C-23), 123.5 (CH), 125.2 (CH), 126.7 (C, C-5), 126.9 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.8 (CH), 129.3 (CH), 129.4 (CH), 131.5 (C, C-10), 137.6 (d, J=9 Hz, C, C-3), 138.6 (d, J=4 Hz, C, C-4), 151.3 (d, J=26 Hz, C, C-2), 155.6 (d, J=3 Hz, C, C-13); ³¹P-NMR (81 MHz) ppm +91.3 (bs); FAB-MS, m/z (relative intensity, %) 899 (4, M+H⁺).

### 7.4.10 Attempted Acid Promoted Cleavage of the Diamine Chiral Auxiliary from Isomerically Pure Borane Adduct 586a, Table 4.3, Entry 1.

To a solution of borane adduct 586b (29 mg, 0.032 mmol) in dry Et₂O (5 mL) at 0 °C was added HCl (1.0 M solution in Et₂O, 260 µL, 0.26 mmol) and the mixture was stirred for 1 h under argon. The resultant white slurry was filtered under argon and the clear filtrate was cooled to -40 °C. Phenyllithium (2.4 M solution in cyclohexane, 67 µL, 0.16 mmol) was added and the solution was stirred at -40 °C for 2 h and subsequently at room temperature for 2 h. The reaction was then quenched with with H₂O (5 mL) and extracted with CHCl₃ (3 x 10 mL). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure to give a brown gum. Only a very complex mixture of products (³¹P-NMR) was obtained from the residue. The white
solid filtered from the reaction was shown by $^1$H-NMR analysis to be $N,N$-dimethyl-1,2-
diphenylethylenediamine dihydrochloride.

The other entries in Table 4.3 were performed following the above procedure except with
minor modifications to the reaction temperature, the use of phenylmagnesium bromide in place
of phenyllithium and/or the employment of anhydrous HCl(g) instead of the 1.0 M ethereal
solution. In all cases $N,N$-dimethyl-1,2-diphenylethylenediamine dihydrochloride was isolated
after the hydrolysis step, and only complex mixtures of products ($^3$P-NMR) were observed for
the residue.

7.4.11 Preparation of $P$-Borane-1,3-Dimethyl-2-phenyl-1,3,2-diazaphospholidine complex
(589).

To a solution of 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (588) (0.500 g, 2.57 mmol)
in Et$_2$O (8.0 mL) at 0 °C was added borane-dimethyl sulfide complex (2.0 M solution in THF,
1.29 mL, 2.57 mmol) and the resulting mixture was left to react for 1 h. The reaction contents
were then quenched with brine (10 mL) and extracted with CHCl$_3$ (3 x 75 mL). The combined
organic extracts were dried (MgSO$_4$) and concentrated in vacuo to afford a light yellow oil. The
crude material was purified by radial chromatography (2 mm rotor, 9:1) to afford 471 mg (88%)
the title compound: bp 75-85 °C (0.08 mm Hg); mp 35-37 °C (CHCl$_3$/hexanes); IR (neat) 2855,
2363 (BH$_3$), 1435, 1148 cm$^{-1}$; $^1$H-NMR (200 MHz) δ 0.85 (bq, $J=94$ Hz, 3H, H-5), 2.56 (d,
$J=11.8$ Hz, 6H, H-6), 3.20 (d, $J=8.2$ Hz, 4H, H-7), 7.34-7.51 (m, 3H), 7.60-7.74 (m, 2H); $^{13}$C-
NMR (50 MHz) ppm 33.3 (d, $J=7$ Hz, CH$_3$, C-6), 50.9 (CH, C-7), 128.5 (d, $J=9$ Hz, CH, C-2 or
C-3), 131.2 (d, $J=11$ Hz, C, C-1), 131.3 (d, $J=11$ Hz, CH, C-2 or C-3), 131.5 (d, $J=2$ Hz, CH, C-
4); $^3$P-NMR (81 MHz) ppm +101.1 (q, $J=79$ Hz); mass spectrum, m/z (relative intensity, %) 208
(1, M$^+$), 194 (17, M$^+$-BH$_3$), 150 (41), 117 (100). Exact mass calcd for C$_{16}$H$_{18}$BN$_2$P: 208.1303.
Found: 208.1278.
7.4.12 Preparation of Borane-triphenylphosphine Complex (590).

![Diagram of 590]

A solution of borane adduct 589 (253 mg, 1.22 mmol) in dry Et₂O (5 mL) at 0 °C was prepared and HCl (g) was bubbled through for 1 minute. This resulted in the immediate formation of a white solid. The solution was stirred for 30 minutes, quenched with Et₃N (4 mL, 0.03 mol) and allowed to stir for a further 20 minutes. The white slurry was then filtered under argon to give a clear solution. This crude phosphorous dichloride was cooled to −40 °C, phenylmagnesium bromide (0.50 M solution in Et₂O, 24 mL, 12 mmol) was added, and the mixture was stirred for 3 h. The reaction was quenched with water (20 mL) and extracted with CHCl₃ (3 x 50 mL). The pooled organic extracts were washed with 10% HCl solution (50 mL), dried (MgSO₄), and concentrated in vacuo to afford 155 mg (46%) of borane-triphenylphosphine complex (590). The same borane complex was obtained in 96% from the reaction of triphenylphosphine with borane-methyl sulfide complex.

7.4.13 Preparation of (Sₘ)-[(i^)-10-camphorsulfonamidyl]-[3,3'-binaphtho[2,1-b][furan]-2,2'-diylbis[diphenylphosphinimine]] (594a) and (Rₘ)-[(i^)-10-camphorsulfonamidyl]-[3,3'-binaphtho[2,1-b][furan]-2,2'-diylbis[diphenylphosphinimine]] (594b).
(±)-BINAPFu \textbf{509} (2.65 g, 3.78 mmol) in THF (60 mL) was treated with (1S)-(+) camphor-10-sulfonyl azide\textsuperscript{259} \textbf{593} (1.95 g, 7.55 mmol) at reflux under a N\textsubscript{2} atmosphere for 12 h. The cooled mixture was then concentrated under reduced pressure to afford a 1:1 mixture of \textbf{594a} and \textbf{594b} in quantitative yield. The diastereomeric products were separated by flash chromatography (9:1 CHCl\textsubscript{3}/CH\textsubscript{3}CN). The first spot off the column, \textbf{594a}, was determined to be the S-axial isomer by single crystal X-ray analysis and afforded the following analytical data: mp 175-177 °C (CHCl\textsubscript{3}); [\alpha]\textsubscript{D}\textsuperscript{21} -72.1\textdegree (c 4.13, CHCl\textsubscript{3}); IR (KBr) 1745 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (200 MHz) \delta 0.53 (s, 3H, H-8 or H-9), 0.90 (s, 3H, H-8 or H-9), 1.07-1.50 (m, 2H), 1.54-1.94 (m, 4H), 2.18 (dt, J=16.0, 3.0 Hz, 1H) 2.26-2.51 (m, 2H), 6.88 (m, 2H), 7.17 (t, J=6.6 Hz, 1H), 7.38 (d, J=8.4 Hz, 1H) 7.44 (t, J=8.0 Hz, 1H), 7.52-7.97 (m, 11H); \textsuperscript{13}C-NMR (50 MHz) ppm 20.2 (CH\textsubscript{3}, C-8 or C-9), 20.4 (CH\textsubscript{3}, C-8 or C-9), 24.6 (CH\textsubscript{2}, C-5 or C-6), 27.3 (CH\textsubscript{2}, C-5 or C-6), 42.9 (CH, C-4), 47.8 (C, C-1 or C-7), 51.7 (d, J=4 Hz, CH\textsubscript{2}, C-10), 58.7 (C, C-1 or C-7), 112.5 (CH), 122.5 (d, J=8 Hz, C), 123.7 (CH), 126.3 (d, J=8 Hz, C, C-23 or C-27), 127.9 (d, J=15 Hz, C), 128.0 (CH), 128.5 (d, J=11 Hz, CH), 129.0 (CH), 129.3 (CH), 129.5 (d, J=10 Hz, CH), 129.9 (CH), 131.2 (C), 133.0 (d, J=1 Hz, C), 133.8 (CH), 133.9 (CH), 134.0 (CH), 134.1 (CH), 140.1 (d, J=154 Hz, C, C-11), 156.3 (d, J=10 Hz, C, C-22), 214.8 (C, C-2); \textsuperscript{31}P-NMR (81 MHz) ppm +5.7; mass spectrum, m/z (relative intensity, %) 531 (1, M\textsuperscript{+}-C\textsubscript{32}H\textsubscript{49}N\textsubscript{6}PS\textsubscript{2}); FAB-MS, m/z (relative intensity, %) 1161 (31, M\textsuperscript{+}), 531 (68). Compound \textbf{594b} gave the following analytical data: mp 229 °C (CHCl\textsubscript{3}, dec.); [\alpha]\textsubscript{D}\textsuperscript{21} +66.5\textdegree (c 1.55, CHCl\textsubscript{3}); IR (KBr) 1743 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}) \delta 0.45 (s, 3H, H-8 or H-9), 0.71 (s, 3H, H-8 or H-9), 1.49-1.08 (m, 2H), 1.93-1.60 (m, 4H), 2.21 (dt, J=16.0, 3.0, 1H), 2.59-2.32 (m, 2H), 6.89-6.71 (m, 2H), 7.11 (t, J=8.0, 1H), 7.70-7.29 (m, 7H), 7.78 (t, J=8.5, 4H), 7.93 (t, J=9.6, 2H); \textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) ppm 20.2 (CH\textsubscript{3}, C-8 or C-9), 20.4 (CH\textsubscript{3}, C-8 or C-9), 24.8 (CH\textsubscript{2}, C-5 or C-6), 27.2 (CH\textsubscript{2}, C-5 or C-6), 42.6 (CH, C-4), 47.6 (C, C-1 or C-7), 51.7 (d, J=3 Hz, CH\textsubscript{2}, C-10), 58.3 (C, C-1 or C-7), 112.6 (CH), 122.2 (d, J=8 Hz, C), 123.7 (CH), 125.7 (CH), 126.2 (d, J=74 Hz, C, C-23 or C-27), 127.4 (d, J=74 Hz, C, C-23 or C-27), 125.8 (CH), 127.8 (d, J=15 Hz, C), 128.3 (d, J=10 Hz, CH), 128.9 (C), 129.3 (d, J=9 Hz, CH), 129.6 (CH), 130.5 (CH), 131.4 (C), 132.9 (d, J=1 Hz, CH), 133.6 (d, J=1 Hz, CH), 133.7 (CH), 134.1 (d, J=3 Hz, CH), 140.0 (d, J=15 Hz, C, C-11), 156.5 (d, J=9 Hz, C, C-22), 215.0 (C, C-2); \textsuperscript{31}P-NMR (81 MHz,
To a solution of phosphinimine 594a (132 mg, 0.114 mmol) in THF (5 mL) was added lithium aluminum hydride (43 mg, 1.1 mmol) and the mixture was refluxed for 4 h. Water (5 mL) was added and reaction mixture was extracted with CHCl₃ (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO₄), and concentrated under reduced pressure to afford a yellow oil. The crude residue was purified by radial chromatography (2 mm rotor, 9:1) to give three major fractions. The first contained 20 mg (53%) of 3,3'-binaphtho[b]furan (556), which was identical (TLC and ¹H-NMR) to an authentic sample prepared by the method listed section 7.3.14. The second fraction contained 15 mg (26%) of monophosphine 595. The third fraction contained 15 mg (19%) of 2,2'-bis(diphenylphosphino)-3,3'-binaphtho[2,1-b]furan (509), which was identical (¹H-NMR, ³¹P-NMR, and TLC) to the racemic phosphine prepared by the method detailed in section 7.3.16. Chiral HPLC analysis (Chiralcel® OJ column, 95:5 methanol:ethanol, 0.5 mL/min) showed phosphine 509 to be enantiopure.

7.4.15 Attempted Aza-Wittig of Phosphinimine 594a, Table 4.4, Entry 1.

Carbon dioxide was bubbled through a solution of phosphinimine 594a (33 mg, 0.28 mmol) in THF (5 mL) for 4 h before the solvent was evaporated under reduced pressure. Only starting material (TLC, ¹H-NMR and ³¹P-NMR) was obtained. The use of acetone and a longer reaction
time, or carbon disulfide in place of carbon dioxide also resulted in the exclusive recovery of unreacted starting material (Table 4.4, entries 2 and 3).

7.4.16 Hydrolysis of Diastereomerically Pure Phosphinimines 594a and 594b.

Phosphinimine 594a (1.44 g, 1.24 mmol) in dioxane (50 mL) was treated with 3 M aqueous H₂SO₄ solution (35 mL) and the resulting mixture was heated to reflux for 12 h. The cooled mixture was then quenched with 10% NaOH solution (50 mL) and extracted with CHCl₃ (3 x 100 mL). The combined organic extracts were dried (MgSO₄), and concentrated in vacuo to afford the crude phosphine oxide. The product was purified by flash chromatography on basic alumina (1:1 hexanes/ethyl acetate → 9:1 CHCL/MeOH) to afford the desired S-phosphine oxide 560 in quantitative yield. It gave \([\alpha]_D^{19} -166.6^\circ\) (c 1.01, CHCl₃).

In an analogous manner R-phosphine oxide 560 was prepared in quantitative yield from phosphimine 594b (1.39 g, 1.20 mmol). It gave \([\alpha]_D^{19} +172.9^\circ\) (c 1.03, CHCl₃).

7.4.17 Trichlorosilane Reduction of S-Phosphine Oxide 560.

S-Phosphine oxide 560 (821 mg, 1.12 mmol) was dissolved in a mixture of xylenes (25 mL) and Et₃N (3.75 mL, 26.8 mmol). To the solution was added SiCl₃H (2.26 mL, 22.4 mmol) and the resulting mixture was heated to 100 °C under argon for 1 h. The mixture was heated to 150 °C for 3 h and subsequently cooled to 65 °C. To the vessel was then added dropwise 30% NaOH solution (60 mL). The resulting mixture was vigorously stirred for 1 h at 65 °C. The cooled reaction mixture was extracted with CHCl₃ (3 x 100 mL) and the combined organic phases were dried (MgSO₄) and concentrated in vacuo. The product was purified by flash chromatography (20:1) to afford the optically pure (S)-BINAPFu (785 mg, 100%): \([\alpha]_D^{19} -203.0^\circ\) (c 1.09, CHCl₃). Heating the enantiopure ligand in p-xylens at 150 °C for 7 days did not result in any racemization of the chiral axis as evidenced by optical rotation and HPLC analysis (Chiralcel® OJ, 95/5 MeOH/EtOH, 0.5 mL/min, 270 nm detection).

In a separate experiment R-phosphine oxide 560 (903 mg, 1.23 mmol) was reduced according to the above procedure to give a quantitative yield of (R)-BINAPFu 560: \([\alpha]_D^{19} +172.9^\circ\) (c 1.03, CHCl₃).
7.4.18 General Procedure for the Preparation of Phosphine Selenides.

The following procedure is based on a method reported by Allen and coworkers. To a 0.02 M solution of the starting phosphine in CHCl₃ is added 10 molar equivalents of Se dust (100 mesh). The resulting mixture is refluxed under an atmosphere of argon gas for 5 h. The cooled mixture is filtered through a pad of Celite® and the filtrings washed with a small volume of CHCl₃. Concentration of the filtrate under reduced pressure furnishes the crude phosphine selenide.

7.4.19 Preparation of (S₄₅)-2,2'-Bis(selenodiphenylphosphinyl)-3,3'-binaphtho[2,1-b]furan (598).

![Structure of 598]

Compound 598 was prepared according to the general method for the preparation of phosphine selenides (see section 7.4.18) starting with optically pure (-)-BINAPFu (509) (0.119 g, 0.170 mmol). The crude product was recrystallized from CH₃CN to furnish the analytically pure product (0.142 g, 97%). X-ray diffraction analysis of a single crystal thus obtained, using the Bijvoet method, showed the S-configuration for the biaryl axis. Phosphine selenide 598 gave the following analytical data: mp 176-178 °C (CH₃CN); IR (KBr) 2923, 1435, 1095, 1003 cm⁻¹; ¹H-NMR (400 MHz) δ 7.04-7.15 (m, 6H), 7.19-7.26 (m, 1H), 7.35 (t, J=8.0 Hz, 1H), 7.49 (d, J=8.2 Hz, 1H), 7.61 (d, J=9.1 Hz, 1H), 7.67-7.79 (m, 4H), 7.82 (d, J=9.1 Hz, 1H), 7.87(d, J=8.1 Hz, 1H); ¹³C-NMR (50 MHz) δ 112.9 (CH, C-11), 122.5 (C), 122.6 (C), 123.2 (CH), 124.9 (d, J=16 Hz, 1H), 125.4 (CH), 127.3 (CH), 128.1 (d, J=3 Hz, CH), 128.2 (CH), 128.3 (CH), 129.2 (d, J=3 Hz, CH), 129.2 (d, J=21 Hz, C, C-13 or C-17), 130.3 (d, J=30 Hz, C, C-13 or C-17), 131.2 (d, J=3 Hz, C), 131.8 (d, J=3 Hz, CH), 132.0 (d, J=3 Hz, CH), 133.1 (d, J=12 Hz, CH), 133.7 (d,
7.4.20 Preparation of 2,2'-Bis(selenodiphenylphosphinyl)-3,3'-bibenzo[b]thiophene (601).

![Chemical structure of 601]

Compound 601 was prepared according to the general procedure for the preparation of phosphine selenides (see section 7.4.18) starting with (±)-BITIANP (525) (0.042 g, 0.066 mmol). The crude product was recrystallized from CH3CN to furnish the analytically pure product (0.048 g, 92%). The product exhibited the following characteristics: mp 275-277 °C (CH3CN); IR (KBr) 2926, 1435, 1088, 1008 cm⁻¹; ¹H-NMR (400 MHz) δ 6.87 (t, J=7.2 Hz, 1H), 6.96 (d, J=8.1 Hz, 1H), 7.13-7.23 (m, 2H), 7.23-7.33 (m, 2H), 7.35-7.44 (m, 2H), 7.45-7.53 (m, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.79 (dd, J=14.2, 7.5 Hz, 2H, H-10 or H-14), 8.06 (dd, J=14.2, 7.2 Hz, 2H, H-10 or H-14); ¹³C-NMR (50 MHz) ppm 121.8 (CH, C-7), 124.7 (CH), 125.3 (CH), 126.8 (CH), 128.0 (d, J=13 Hz, CH), 128.5 (d, J=13 Hz, CH), 130.1 (d, J=76 Hz, C, C-1), 131.4 (d, J=17 Hz, C, C-9 or C-13), 131.9 (d, J=3 Hz, CH, C-11 or C-16), 132.1 (d, J=3 Hz, CH, C-11 or C-16), 132.2 (d, J=15 Hz, C, C-9 or C-13), 133.1 (d, J=12 Hz, CH), 133.9 (d, J=11 Hz, CH), 138.2 (dd, J=7, 3 Hz, C, C-2), 141.6 (d, J=6 Hz, C), 141.8 (d, J=12 Hz, C); ³¹P-NMR (162 MHz) ppm +22.9 (Jp,Se=754 Hz); mass spectrum, m/z (relative intensity, %) 529 (1, M⁺-PPh₂Se), 449 (5, M⁺-PPh₂Se₂), 185 (24, PPh₂), 149 (61), 83 (100). Exact mass calcd for C₄₉H₂₈P₂Se₂: 793.9438. Found: 793.9403.
7.4.21 Preparation of (S)-2-[2-(Selenodiphenylphosphinyl)phenyl]-4,5-dihydro-4-(2-methylpropyl)-oxazole (603).

Compound 603 was prepared according to the general procedure for the preparation of phosphine selenides (see section 7.4.18) starting with 0.056 g (0.145 mmol) of the parent phosphine 602. An analytical sample was obtained by recrystallization from CH$_3$CN (0.065 g, 96%). The product exhibited the following characteristics: mp 91-93 °C (CH$_3$CN); IR (KBr) 2932, 1432, 1108 cm$^{-1}$; $^1$H-NMR (400 MHz) $\delta$ 0.79 (s, 9H, H-11), 3.48 (t, $J$=9.0 Hz, 1H, H-8), 3.62 (t, $J$=9.8 Hz, 1H, H-9a), 3.83 (t, $J$=8.4 Hz, 1H, H-9b), 7.28-7.54 (m, 8H), 7.62-7.90 (m, 6H); $^{13}$C-NMR (50 MHz) ppm 26.1 (CH$_3$, C-11), 33.6 (C, C-10), 68.7 (CH, C-8), 76.2 (CH$_2$, C-9), 128.3 (d, $J$=13 Hz, CH), 130.2 (d, $J$=12 Hz, CH), 131.0 (d, $J$=1 Hz, CH), 131.1 (d, $J$=1 Hz, CH), 131.4 (d, $J$=1 Hz, CH), 132.0 (d, $J$=42 Hz, C), 132.1 (d, $J$=11 Hz, CH), 132.3 (d, $J$=6 Hz, C, C-2), 132.7 (d, $J$=61 Hz, C), 132.7 (d, $J$=11 Hz, CH), 132.8 (d, $J$=53 Hz, C), 134.8 (d, $J$=11 Hz, CH), 163.0 (d, $J$=3 Hz, C, C-7); $^{31}$P-NMR (162 MHz) ppm +38.1 ($^3$P-$^74$H) mass spectrum, m/z (relative intensity, $\%$) 467 (8, M$^+$($^{80}$Se)), 465 (6, M$^+$($^{80}$Se)), 387 (5, M$^+$-Se), 330 (61, M$^+$-C$_4$H$_9$Se), 302 (100). Exact mass calcd for C$_{25}$H$_{26}$NOP$_{80}$Se: 467.0917. Found: 467.0906.

7.4.22 Preparation of Bis-2,2'(selenodiphenylphosphinyl)-1,1'-binaphthalene (604).

Compound 604 was prepared according to the general procedure for the preparation of phosphine selenides (see section 7.4.18) starting with (S)-BINAP (0.035 g, 0.056 mmol). The
crude product was recrystallized from CH$_3$CN to afford the analytically pure product (0.041 g, 93%) with the following characteristics: mp 317-319 °C (CH$_3$CN); IR (KBr) 3047, 1434, 1092 cm$^{-1}$; $^1$H-NMR (400 MHz) $\delta$ 6.71 (td, $J$=7.1, 0.9 Hz, 1H, H-7 or H-8), 6.78 (d, $J$=8.4 Hz, 1H), 7.22 (qd, $J$=7.3, 3.1 Hz, 4H), 7.28-7.37 (m, 3H), 7.52 (dd, $J$=12.6, 8.7 Hz, 1H, H-3), 7.61-7.81 (m, 6H); $^{13}$C-NMR (100 MHz) ppm 126.3 (CH), 127.5 (d, $J$=76 Hz, C), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.2 (d, $J$=16 Hz), 128.3 (CH), 128.6 (d, $J$=12 Hz, CH), 130.0 (d, $J$=12 Hz, CH), 130.7 (d, $J$=75 Hz, C), 131.0 (d, $J$=3 Hz, CH, C-14 or C-18), 131.3 (d, $J$=3 Hz, CH, C-14 or C-18), 133.0 (d, $J$=11 Hz, CH), 133.9 (d, $J$=11 Hz, CH), 134.1 (C), 134.4 (d, $J$=2 Hz, C), 134.9 (d, $J$=78 Hz, C), 140.2 (C); $^{31}$P-NMR (162 MHz) ppm +33.8 ($^{1}J_{P,Se}$=738 Hz); mass spectrum, m/z (relative intensity, %) 517 (8, M$^{+}$-PSePh$_2$), 437 (100, M$^{+}$-PPh$_2$Se$_2$). Exact mass calcd for C$_{32}$H$_{22}$P$_8$Se (M$^{+}$-PSePh$_2$): 517.0496. Found: 517.0582.

7.4.23 Preparation of Bis-1,1’-(selenodiphenylphosphinyl)ferrocene (605).

![Image of compound 605]

Compound 605 was prepared according to the general procedure for the preparation of phosphine selenides (see section 7.4.18) starting with 1,1’-bis(diphenylphosphino)ferrocene (0.083 g, 0.150 mmol). The crude product was recrystallized from CH$_3$CN to furnish the analytically pure product (0.097 g, 91%). The product exhibited the following characteristics: mp 210-212 °C (CH$_3$CN); IR (KBr) 3064, 1435, 1173, 1097 cm$^{-1}$; $^1$H-NMR (200 MHz) $\delta$ 4.32 (dd, $J$=6.1, 2.1 Hz, 4H, H-2), 4.69 (dd, $J$=6.1, 1.3 Hz, 4H, H-3), 7.31-7.52 (m, 12H), 7.55-7.72 (m, 8H); $^{13}$C-NMR (50 MHz) ppm 133.0 (d, $J$=79 Hz, C, C-4), 131.9 (d, $J$=11 Hz, CH, C-6), 131.3 (d, $J$=3 Hz, CH, C-7), 128.2 (d, $J$=12 Hz, CH, C-5), 75.4 (d, $J$=10 Hz, CH, C-3), 75.3 (d, $J$=87 Hz, C, C-1), 74.4 (d, $J$=12 Hz, CH, C-2); $^{31}$P-NMR (81 MHz) ppm +28.5 ($^{1}J_{P,Se}$=735 Hz);
mass spectrum, \(m/z\) (relative intensity, %) 633 (7, \(M^+\text{-}^{80}\text{Se}\)), 631 (5, \(M^+\text{-}^{78}\text{Se}\)), 553 (100, \(M^+\text{-}\text{Se}_2\)).

Exact mass calcd for \(\text{C}_{22}\text{H}_{18}\text{FeP (M}^+\text{-PPh}_2\text{Se}_2)\): 497.1670. Found: 497.1657.

7.4.24 Preparation of 7,7'-Dimethoxy-bis-2,2'-selenodiphenylphosphinyl)-1,1'-binaphthalene (607).

Compound 607 was prepared according to the general procedure for the preparation of phosphine selenides (see section 7.4.18) starting with (S)-7,7'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (609) \(^{266}\) (0.021 g, 0.031 mmol). The crude product was purified by flash chromatography (3:1) to give (0.022 g, 84%) the analytically pure product (0.041 g, 93%) with the following properties: mp 238-240 °C (\(\text{CH}_3\text{CN}\)); IR (KBr) 2953, 1504, 1434, 1224 cm\(^{-1}\); \(^1\)H-NMR (400 MHz) \(\delta\) 3.94 (s, 3H, H-11), 6.62 (dd, \(J=7.5, 1.1\) Hz, 1H, H-7), 6.82-7.05 (m, 5H), 7.35-7.56 (m, 5H), 7.62-7.74 (m, 4H); \(^{13}\)C-NMR (100 MHz) ppm 55.4 (CH\(_3\), C-11), 107.5 (CH, C-7 or C-9), 120.1 (CH, C-7 or C-9), 128.0 (d, \(J=12\) Hz, CH), 128.1 (d, \(J=1\) Hz, CH), 128.2 (d, \(J=1\) Hz, CH), 128.4 (d, \(J=6\) Hz, CH), 128.8 (d, \(J=118\) Hz, C), 129.4 (CH), 130.0 (d, \(J=2\) Hz, C, C-5), 130.9 (d, \(J=3\) Hz, CH), 131.2 (d, \(J=3\) Hz, CH), 131.4 (d, \(J=75\) Hz, C), 133.1 (d, \(J=11\) Hz, CH), 133.8 (d, \(J=11\) Hz, CH), 134.6 (d, \(J=77\) Hz, C), 135.6 (d, \(J=12\) Hz, C, C-10), 138.4 (dd, \(J=8, 5\) Hz, C, C-1), 158.2 (C, C-8); \(^{31}\)P-NMR (162 MHz) ppm +33.4 (\(^{1}J_{\text{P-Se}}\) = 732 Hz); mass spectrum, \(m/z\) (relative intensity, %) 577 (1, \(M^+\text{-PSePh}_2\)), 497 (18, \(M^+\text{-PPh}_2\text{Se}_2\)), 466 (\(M^+\text{-PPh}_2\text{Se}_2\text{OCH}_3\), 39), 438 (63), 183 (100). Exact mass calcd for \(\text{C}_{34}\text{H}_{26}\text{PO}_2\) (\(M^+\text{-PPh}_2\text{Se}_2\)): 497.1670. Found: 497.1657.
7.5 Experiments Pertaining to Chapter Five.

2-Iodo-N-(cyclohexen-1-carbonyl)-N-methylaniline (614),\(^{284}\) 2-bromo-N-(cyclohexen-1-carbonyl)-N-methylaniline (666),\(^{284}\) [RuCl((R)-BINAP)(C\(_6\)H\(_6\))]Cl (674),\(^{286a}\) (-)-2,2'-bis(trifluoromethanesulfonyloxy)-1,1'-binaphthalene (683),\(^{291}\) and (±)-2,2'-dibromo-1,1'-binaphthalene (690)\(^{294}\) were prepared according to literature procedures. The synthesis of (1S,2R)-O-(t-butyldimethylsilyl)isobornyl-10-sulfonyl azide (693) is described in section 7.6.

7.5.1 Studies on the Asymmetric Heck Arylation of 2,3-Dihydrofuran.

7.5.1.1 General Arylation Procedure.

The following procedure, which corresponds to Table 5.2 entry 1, serves as an illustration of how the Heck arylation was generally performed. In a 2 dram screw-cap vial, equipped with a magnetic stirring bar, was placed either (R)-BINAP (0.019 g, 0.031 mmol) or (R)-BINAPFu (0.021 g, 0.030 mmol) followed by DIPEA (0.255 mL, 1.46 mmol) and dry C\(_6\)H\(_6\) (2.25 mL). A solution of Pd(OAc)\(_2\) (0.224 mL, 0.045 M solution in C\(_6\)H\(_6\)) was added and the head space of the vial was purged with argon. The vessel was tightly sealed and heated to 60 °C for 30 minutes. The catalyst solution was cooled to ambient temperature and charged with 2,3-dihydrofuran (0.189 mL, 2.5 mmol) and phenyl triflate (0.079 mL, 0.488 mmol). The vial was again purged with argon, sealed, and placed in a thermostatically controlled oil bath (30 °C) for 9 days. The crude reaction mixture was then diluted with Et\(_2\)O, washed with 10% HCl solution (2 x 25 mL), dried (MgSO\(_4\)), and filtered through a pad of Celite.\(^{®}\) The filtrate was analyzed by chiral CG (Cyclodex B column, 80 °C start temperature, 2 min initial hold time, 1 °C/min ramp rate, 160 °C final temperature, He carrier gas at 2.0 mL/min, FID detection) with the reaction components eluting in the following order: phenyl triflate (10.81 min), (S)-2-phenyl-2,3-dihydrofuran (26.57 min), (R)-2-phenyl-2,3-dihydrofuran (26.97 min), 2-phenyl-4,5-dihydrofuran (29.11 min), (S)-2-phenyl-2,5-dihydrofuran (31.51 min), (R)-2-phenyl-2,5-dihydrofuran (31.91 min). The reaction procedure was slightly modified for those experiments employing Pd\(_2\)(dba)\(_3\) as the palladium source. In these cases, the Pd\(_2\)(dba)\(_3\) could be weighed directly (0.009 g, 2 mol% Pd) and only required 4 mol% of the chiral diphosphine ligand. Time study experiments were performed...
using the above procedure with the exception that 4.0 mL reactor vials capped with Teflon-faced silicone septa were used as reaction vessels. Aliquots (0.1 mL) were taken at regular intervals, filtered through basic alumina with a small volume of Et₂O, and subsequently analyzed using the previously defined GC protocol.

7.5.1.2 Bond Migration Investigation.

The Heck arylation of 2,3-dihydrofuran (611) was conducted on a larger scale (3 mmol PhOTf), by minor modification to the general procedure, using a Pd₂dba₃/(5)-BINAP catalyst system in dioxane at 100 °C and DIPEA (3.0 equiv) for 7 days. The product mixture was worked up according to section 7.5.1 and purified by flash chromatography (98:2) to afford isomerically pure 2-phenyl-2,3-dihydrofuran (612) in 59% yield (0.258 g, 42% ee). In a 2 dram screw-cap sample vial, equipped with a stir bar, was measured out DIPEA (0.255 mL, 1.46 mmol), dioxane (2.5 mL), and trifluoromethanesulfonic acid (0.043 mL, 0.49 mmol). To the vessel was then added product 612 (75 μL) and the resulting mixture was heated to 100 °C for 9 days. The cooled mixture was then diluted with Et₂O, washed with 10% HCl solution (2 x 25 mL), dried (MgSO₄), and filtered through Celite®. Chiral CG analysis of the filtrate showed only unreacted compound 612 in 42% ee.

7.5.1.3 Heck Arylation Reaction of 2,3-Dihydrofuran (611) and 1-Naphthyl Triflate (646) Spiked with Isomerically Pure 2-Phenyl-2,3-dihydrofuran (612).

Pd₂dba₃ (0.007 g, 0.008 mmol), (S)-BINAPFu (0.021 g, 0.031 mmol), and DIPEA (0.266 mL, 1.53 mmol) were measured out into a 2 dram screw-cap sample vial equipped with a magnetic stirring bar. Dioxane (2.5 mL) was added and the head space of the vessel was purged with argon. The vial was tightly sealed and heated to 60 °C for 30 min. To the cooled catalyst mixture was then added 1-naphthyl triflate (0.100 mL, 0.508 mmol), 2,3-dihydrofuran (0.200 mL, 2.64 mmol), and isomerically pure 2-phenyl-2,3-dihydrofuran (0.015 g, 0.103 mmol, 42% ee S). The vial was again purged with argon, sealed, and placed in a thermostatically controlled oil bath (100 °C) for 7 days. The reaction mixture was then cooled to ambient temperature and extracted with Et₂O (2 x 25 mL). The combined organic extracts were washed with 10% HCl
solution (2 x 25 mL) and brine. The aqueous phase was dried (MgSO₄) and filtered through a pad of Celite®. Chiral CG analysis of the product mixture, as per the general procedure, showed a 97/3 mixture of compounds 612 (41% ee S) and 613 (2% ee, S), respectively. Employing a slightly modified temperature program was required to analyze the 1-naphthyl derived products 647-649 (100 °C start temperature, 2 min initial hold time, 1 °C/min ramp rate, 200 °C final temperature). The elution order was tentatively assigned as follows: 2-(1-naphthyl)-4,5-dihydrofuran (64.5 min), (S)-2-(1-naphthyl)-2,3-dihydrofuran (66.4 min), (R)-2-(1-naphthyl)-2,3-dihydrofuran (66.6 min), (S)-2-(1-naphthyl)-2,5-dihydrofuran (73.0 min), (R)-2-(1-naphthyl)-2,5-dihydrofuran (73.8 min). The product distribution was thus determined to be 85% compound 647 (24% ee S), 12% compound 648 (43% ee S), and 3% compound 649 (See Figure 5.8).

7.5.2 Investigation of the Asymmetric Heck Cyclization of 2-Haloanilides 614 and 666.

7.5.2.1 General Cyclization Procedure.

The following procedure, which corresponds to Table 5.3 entry 1, serves as an illustration of how the Heck cyclization of amides 614 and 666 was generally performed. In a 2 dram screw-cap vial, equipped with a magnetic stirring bar, was placed either (R)-BINAP (0.008 g, 0.013 mmol) or (S)-BINAPFu (0.009 g, 0.013 mmol) followed by Pd₂dba₃ (0.003 g, 0.002 mmol), Ag₃PO₄ (0.276 g, 0.659 mmol), and DMA (2.5 mL). The head space of the vial was purged with argon and the vessel was tightly sealed. The mixture was heated to 60 °C for 30 min and subsequently cooled to ambient temperature. To the catalyst solution was added amide 614 (0.075 g, 0.220 mmol). The vial was once again purged with argon, sealed, and placed in a thermostatically controlled oil bath (70 °C) for 18 h. The cooled mixture was quenched with brine and extracted with Et₂O (2 x 25 mL). The combined organic extracts were washed with 10% HCl solution (2 x 25 mL), dried (MgSO₄), and concentrated in vacuo to afford a light orange oil. ¹H-NMR analysis of the crude mixture (200 MHz) showed two new vinylic proton signals at 5.31 ppm (d, J=10.2 Hz, 1H) and 6.14 ppm (dt, J=10.2, 4.1 Hz, 1H) corresponding to the Δ²,₃ isomer 615a. Small multiplet resonances representing vinyl protons of the minor Δ³,₄ isomer 615b could also be distinguished at 5.63 ppm and 5.80 ppm. The crude material was purified by flash chromatography (15:1) to afford the clean Δ²,₃ isomer 615a as a colorless oil.
Addition of ca. 5-10 mol% Eu(hfc)$_3$ to a CDCl$_3$ solution of product 615a efficiently resolved the $N$-methyl signals at 200 MHz field strength. The low field signal was assigned to the $R$-configuration by comparison to Overman's results.$^{149a}$ Alternatively, the ee of product 615a could be assessed by chiral HPLC analysis (Chiralcel® OJ, 9:1 hexane/IPA, 1.0 mL/min, 254 nm UV detection; (S)-615a $T_R$=9.24 min, (R)-615a $T_R$=10.29 min.).

7.5.3 Investigation of the Asymmetric Hydrogenation of $\alpha$- and $\beta$-Ketoesters.

7.5.3.1 Catalyst Preparation.

In a 25 mL Schlenk vessel was placed commercially available benzeneruthenium(II) chloride dimer (673) (0.044 g, 0.087 mmol) and (R)-BINAPFu (0.128 g, 0.183 mmol). To the vessel was then added, via cannula, freshly distilled, freeze/thaw (x 3) degassed DMF (3 mL). The resulting red-brown solution was then heated to 100 °C under an atmosphere of argon for 30 min. The mixture was then cooled to 50 °C and the solvent was removed under reduced pressure (0.1 mm Hg) for 1 h. The resulting bright orange solid residue was used as a hydrogenation catalyst without purification and was conveniently stored in a nitrogen filled glove box at ambient temperature.

7.5.3.2 General Hydrogenation Procedure.

The following procedure, which corresponds to Table 5.6 entry 3, serves as an illustration of how the asymmetric hydrogenation reaction was performed. In a 10 mL Schlenk vessel was placed RuCl$_2$[($C_6$H$_6$)(R-BINAPFu)] (675) (0.007 g, 0.007 mmol), MeOH (5 mL), and methyl acetoacetate (0.700 mL, 6.49 mmol). The resulting mixture was degassed with three freeze/thaw cycles and quickly loaded into the Parr apparatus using a small glass insert equipped with a magnetic stirring bar. The apparatus was sealed and carefully purged with H$_2$ five times. The vessel was then pressurized to 100 atm H$_2$ and thermostatically heated to 100 °C for 40 h behind a blast shield. The cooled vessel (0 °C) was then carefully vented. The reaction mixture was concentrated in vacuo to afford the crude product, which by $^1$H-NMR analysis showed only methyl 3-hydroxybutanoate (676). A small aliquot (ca. 0.010 g) of the product was placed in dry
pyridine (0.5 mL) and treated with commercially available (S)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPA-Cl, 10 μL) at rt for 1 h. The resulting solution was then analyzed by GC (Cydex-B column, 130 °C start temperature, 5 min initial hold time, 1 °C/min ramp rate, 220 °C final temperature, He carrier gas at 2.0 mL/min, FID detection) with the (R,S)-ester eluting at \( T_R = 29.9 \) min and the (S,S)-isomer eluting at \( T_R = 30.9 \) min.

### 7.5.3.3 Enantiopurity Analysis of Hydrogenation Products.

Crude ethyl 3-hydroxybutanoate (677) was converted to the (S)-MTPA ester as outlined in the general procedure (section 7.5.3.2) and analyzed by GC (Cydex-B column, 130 °C start temperature, 5 min initial hold time, 1 °C/min ramp rate, 220 °C final temperature, He carrier gas at 2.0 mL/min, FID detection) with the (R,S)-ester eluting at \( T_R = 35.1 \) min and the (S,S)-diastereomer eluting at \( T_R = 35.6 \) min. Product configurational assignment was made by comparison to Noyori’s results.\(^{285}\)

Ethyl 3-hydroxy-4-chlorobutanoate (678) was treated with Ac\(_2\)O in dry pyridine to afford the corresponding acetate. This material was readily analyzed by GC to determine the enantiopurity of the parent alcohol (Cyclodex B column, 110 °C isothermal, He carrier gas at 2.0 mL/min, FID detection). Under these conditions, the \( R \)-acetate eluted at \( T_R = 29.7 \) min and the \( S \)-isomer eluted at \( T_R = 30.0 \) min. The configurational assignment was based on comparison to Noyori’s results.\(^{285}\)

Ethyl 3-hydroxy-3-phenylpropionate (679) was distilled (bp 105 °C, 1 mmHg) and analyzed by chiral HPLC analysis (Chiralcel® OB, 80/20 hexane/IPA, 1.0 mL/min, 254 nm UV detection). The \( S \)-configuration had a retention time of 7.34 min while the \( R \)-configuration eluted at 8.62 min. The configurational assignment was based on comparison to Noyori’s results.\(^{285d}\)

Crude methyl lactate (680) was distilled (bp 45-50 °C, 10 mmHg) and subsequently subjected to HPLC analysis (Chiralcel® OB, 90/10 hexane/IPA, 1.0 mL/min, 205 nm UV detection). Under these conditions, methyl (S)-lactate eluted at 8.48 min while the \( R \)-configuration had a retention time of 9.03 min. Assignment of the product stereochemistry was made by analysis of a commercially available sample of methyl (R)-(+) -lactate (680, >98% ee).
The diastereomeric purity of methyl 2-hydroxy-1-cyclopentanecarboxylate (681) was assessed by GC analysis (methyl silicone fused silica column 25 m x 0.53 mm (i.d.) x 3 μm (film thickness, 50 °C start temperature, 5 min initial hold time, 2 °C/min ramp rate, 150 °C final temperature, He carrier gas at 2.0 mL/min, FID detection). The trans-product had a retention time of 16.7 minutes while the cis-diestereomer eluted at 17.4 min. Stereochemical assignment of the product peaks in the GC was based on Noyori’s hydrogenation results.  

7.5.4 Synthesis, Resolution, and Characterization of 2,2′-Bis(di-2-furylphosphino)-1,1′-binaphthalene (TetFuBINAP).

7.5.4.1 Preparation of Chlorodi-2-furylphosphine (684).

The following preparation of chlorodi-2-furylphosphine (684) is based on an unpublished procedure kindly provided by Dr. M. Scalone (Hoffmann-La Roche). To a solution of furan (5.8 mL, 80 mmol) in Et₂O (50 mL) at -40 °C was added n-BuLi (1.50 M solution in hexanes, 43 mL, 65 mmol) under an argon atmosphere. The mixture was warmed to 10 °C and stirred for 2 h. In a 1 liter three-neck flask, equipped with an inert atmosphere filtering tube, was placed freshly distilled phosphorus trichloride (2.9 mL, 33 mmol) and Et₂O (300 mL). The PCI₃ solution was then cooled to -78 °C under argon and to it was added the 2-furyllithium slurry over a 1 h period using a wide bore cannula. The transfer vessel was rinsed with dry Et₂O (40 mL) and the washings were added to the reaction vessel. Upon complete addition, the temperature of the mixture was raised to -60 °C for 15 min and subsequently cooled back down to -78 °C for 1 h. The resulting mixture was then slowly warmed to rt over a 4 h period and stirred for 14 h. The reaction mixture was then filtered under an atmosphere of argon and the filtrate was concentrated in vacuo. The remaining thick yellow oil was transferred via cannula into a 50 mL single neck round bottomed flask using a small volume of dry Et₂O. The Et₂O was again removed under reduced pressure and the residual oil was fractionally distilled under high vacuum (0.2 mm Hg).
The product was collected between 100-120 °C as a clear colorless oil (3.5 g, 53%). $^1$H-NMR (200 MHz) δ 6.50 (m, 1H), 7.04 (m, 1H), 7.78 (m, 1H, H-4); $^{31}$P-NMR (81 MHz) ppm +14.4.

7.5.4.2 Preparation of (±)-2,2'-Bis(di-2-furylphosphino)-1,1'-binaphthalene (682).

(±)-2,2'-Dibromo-1,1'-binaphthalene (690)$^{294}$ (1.0076, 2.44 mmol) and 1,2-dibromoethane (50 µL, 0.58 mmol) in a mixture of dry toluene (20 mL) and THF (2 mL) were treated with excess magnesium powder (0.238 g, 9.78 mmol) at 85 °C for 5 hrs. The resulting Grignard slurry was cooled to rt and transferred via cannula into a vessel (-30 °C) containing solution of chlorodi(2-furyl)phosphine (684) (1.03 g, 5.13 mmol) in THF (5 mL). The reaction mixture was then warmed to rt over a 30 min and left to stir for 12 h under an argon atmosphere. The mixture was then quenched with NaHCO$_3$ solution and extracted with CHC$_3$ (3 x 100 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated in vacuo to afford a bright yellow solid residue. The crude material was purified by flash chromatography (25:1) to afford the title compound as a white amorphous powder (0.783 g, 55%). The product exhibited the following analytical properties: mp 190-191 °C; IR (KBr) 2922, 1454, 1006, 741 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 5.98 (m, 1H), 6.00 (m, 1H), 6.44 (m, 1H), 6.71 (d, J=3.3 Hz, 1H), 6.81 (d, J=8.5 Hz, 1H), 7.02 (t, J=7.7 Hz, 1H), 7.32 (m, 1H), 7.37 (t, J=7.5 Hz, 1H), 7.73 (m, 1H), 7.81 (d, J=8.7 Hz, 1H), 7.84 (d, J=8.2 Hz, 1H), 7.95 (d, J=8.6 Hz, 1H); $^{13}$C-NMR (100 MHz) ppm 110.6 (d, J=4 Hz, CH, C-13 or C-17), 111.2 (t, J=3 Hz, CH, C-13 or C-17), 121.3 (t, J=15 Hz, CH, C-12 or C-16), 121.4 (d, J=108 Hz, C, C-2), 122.1 (t, J=13 Hz, CH, C-12 or C-16), 126.5 (CH), 126.8 (CH), 127.2 (CH), 128.1 (CH), 128.7 (CH), 130.1 (CH), 133.1 (C, C-5 or C-10), 133.8 (C, C-5 or C-10), 142.9 (t, J=20 Hz, C, C-1), 147.3 (CH, C-14 or C-18), 147.8 (CH, C-14 or C-18), 150.4 (d, J=8 Hz, C, C-11 or C-15), 151.3 (t, J=5 Hz, C, C-11 or C-15); $^{31}$P-NMR (162 MHz) ppm
-58.6; mass spectrum, \( m/z \), (relative intensity, \%) 582 (0.2, \( M^+ \)), 515 (0.3, \( M^+ \)-Fu), 417 (100, \( M^+ \)-PFu\(_2\)). Exact mass calcd for \( C_{28}H_{18}O_2P \) (\( M^+ \)-PFu\(_2\)): 417.1044. Found 417.1027.

### 7.5.4.3 Preparation of \((S)_a\)-[(\(J,S,2R\))-\(O\)-(\(t\)-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-\[1,1'\-binaphthalene\]-2,2'-diylbis[di-2-furylphosphinimine] (694a) and \((R)_a\)-[(\(J,S,2R\))-\(O\)-(\(t\)-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-\[1,1'\-binaphthalene\]-2,2'-diylbis[di-2-furylphosphinimine] (694b).

To a solution of (±)-2,2'-bis(di-2-furylphosphino)-1,1'-binaphthyl (682) (0.791 g, 1.36 mmol) in THF (20 mL) was added (1\(S\), 2\(R\))-\(O\)-(\(t\)-butyldimethylsilyl)isobornyl-10-sulfonyl azide (693) (1.12 g, 2.99 mmol). The resulting solution was heated to reflux under an argon atmosphere for 24 h. The cooled solution was then concentrated under reduced pressure to afford the crude phosphinimine mixture. Separation of the diastereomeric products was achieved by flash chromatography (3:1 benzene/ethyl acetate) to afford 694a (0.86 g, 50%) and 694b (0.84 g, 49%). The first diastereomer to elute from the column, compound 694a, had: mp 250-252 °C; IR (KBr) 2926, 1456, 695 cm\(^{-1}\); \(^1\)H-NMR (400 MHz) \( \delta \) 0.05 (s, 3H, H-1 1 or H-12), 0.11 (s, 3H, H-11 or H-12), 0.71 (s, 3H, H-8 or H-9), 0.90 (s, 9H, H-14), 0.96 (s, 3H, H-8 or H-9), 1.12-1.35 (m, 2H), 1.48-1.76 (m, 4H), 1.90 (t, \( J=14 \) Hz, 1H, H-4), 2.36 (d, \( J=13.8 \) Hz, 1H, H-10a), 3.32 (d, \( J=13.8 \) Hz, 1H, H-10b), 4.01 (m, 1H, H-2), 6.16 (s, 1H), 6.34 (s, 1H), 6.61 (s, 1H), 6.90 (d, \( J=8.5 \) Hz, 1H), 7.03 (s, 1H), 7.11 (t, \( J=7.6 \) Hz, 1H), 7.45 (d, \( J=13.1 \) Hz, 2H), 7.50 (d, \( J=7.4 \) Hz, 1H), 7.86 (d, \( J=8.1 \) Hz, 1H), 7.92 (d, \( J=6.7 \) Hz, 1H), 8.20 (dd, \( J=13.8, 8.8 \) Hz, 1H); \(^{13}\)C-NMR (100 MHz) ppm: -4.1 (CH\(_3\), C-11 or C-12), -4.4 (CH\(_3\), C-11 or C-12), 18.4 (C, C-13), 20.7 (CH\(_3\), C-8
or C-9), 21.3 (CH₃, C-8 or C-9), 26.5 (CH₂, C-14), 27.7 (CH₂, C-5 or C-6), 28.9 (CH₂, C-5 or C-6), 42.7 (CH₂ C-3), 44.9 (CH, C-4), 48.9 (C, C-1 or C-7), 50.7 (C, C-1 or C-7), 53.8 (d, J=5 Hz, CH₂, C-10), 76.7 (CH, C-2), 111.7 (d, J=9 Hz, CH), 111.9 (d, J=9 Hz, CH), 124.3 (d, J=131 Hz, C, C-15), 126.3 (CH), 126.5 (CH), 127.0 (CH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.9 (CH), 129.1 (d, J=8 Hz, CH), 129.3 (d, J=6 Hz, CH), 134.0 (d, J=14 Hz, C, C-17), 135.0 (d, J=2 Hz, C, C-22), 139.8 (dd, J=10.6 Hz, C, C-16), 142.1 (d, J=148 Hz, C, C-25 or C-29), 142.7 (d, J=144 Hz, C, C-25 or C-29), 149.3 (d, J=8 Hz, CH, C-28 or C-32), 149.7 (d, J=8 Hz, CH, C-28 or C-32); ³¹P-NMR (162 MHz) ppm -17.1; mass spectrum, m/z, (relative intensity, %) 596 (2), 417 (65), 57 (100). Compound 694b exhibited the following properties: mp 241-243 °C; IR (KBr) 2925, 1456, 1123, 637 cm⁻¹; ¹H-NMR (400 MHz) δ -0.01 (s, 3H, H-11 or H-12), 0.00 (s, 3H, H-11 or H-12), 0.69 (s, 3H, H-8 or H-9), 0.85 (s, 9H, H-14), 0.95 (s, 3H, H-8 or H-9), 1.28-1.40 (m, 2H), 1.53-1.78 (m, 4H), 1.92 (t, J=14 Hz, 1H, H-4), 2.24 (d, J=13.8 Hz, 1H, H-10a), 3.16 (d, J=13.8 Hz, 1H, H-10b), 3.96 (m, 1H, H-2), 6.17 (s, 1H), 6.36 (s, 1H), 6.72 (s, 1H), 7.11 (d, J=7.7 Hz, 1H), 7.14 (s, 1H), 7.48-7.57 (m, 3H), 7.87 (d, J=8.1 Hz, 1H), 7.94 (d, J=7.0 Hz, 1H), 8.11 (dd, J=14.0, 8.8 Hz, 1H); ¹³C-NMR (100 MHz) ppm -4.5 (CH₃, C-11 or C-12), -4.2 (CH₃, C-11 or C-12), 18.3 (C, C-13), 20.7 (CH₃, C-8 or C-9), 21.3 (CH₃, C-8 or C-9), 26.5 (CH₃, C-14), 27.7 (CH₂, C-5 or C-6), 28.7 (CH₂, C-5 or C-6), 42.7 (CH₂, C-3), 44.9 (CH, C-4), 48.9 (C, C-1 or C-7), 50.7 (C, C-1 or C-7), 53.5 (d, J=5 Hz, CH₂, C-10), 76.6 (CH, C-2), 111.7 (d, J=7 Hz, CH), 111.8 (d, J=7 Hz, CH), 124.2 (d, J=134 Hz, C, C-15), 126.6 (CH), 126.8 (CH), 127.2 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.9 (d, J=13 Hz, CH), 129.0 (CH), 129.1 (d, J=13 Hz, CH), 134.1 (d, J=14 Hz, C, C-17), 135.0 (d, J=2 Hz, C, C-22), 140.1 (dd, J=10.6 Hz, C, C-16), 142.4 (d, J=143 Hz, C, C-25 or C-29), 142.5 (d, J=144 Hz, C, C-25 or C-29), 149.4 (d, J=8 Hz, CH C-28 or C-32), 149.7 (d, J=8 Hz, CH, C-28 or C-32); ³¹P-NMR (162 MHz) ppm -17.7; mass spectrum, m/z, (relative intensity, %) 596 (2), 449 (13), 417 (65), 57 (100).
7.5.4.4 Preparation of \((S_a,)-(\cdot)-2,2',\text{-Bis(di-2-furylphosphinyl})\)-1,1'-binaphthalene (695).

Diastereomerically pure phosphinimine 694a (1.01 g, 0.794 mmol) in THF (50 mL) was treated with 3M \(\text{H}_2\text{SO}_4\) (3.0 mL, 9.0 mmol) at reflux for 0.5 h. The resulting solution was quenched with \(\text{NaHCO}_3\) solution and concentrated under reduced pressure. The residual aqueous phase was extracted with \(\text{CHCl}_3\) (3 x 50 mL) and the combined organic extracts were dried (\(\text{MgSO}_4\)). Subsequent concentration and chromatographic purification (9:1 \(\text{CHCl}_3/\text{MeOH}\)) afforded the desired phosphine oxide as a white foam in near quantitative yield. Compound 695 displayed the following properties: IR (KBr) 3101, 1582, 1490, 800 cm\(^{-1}\); \(^1\)H-NMR (400 MHz, \(\text{THF-d}_8\)) \(\delta\) 6.34 (m, 1H), 6.57 (m, 1H), 6.72 (m, 1H), 7.00 (d, \(J=8.5\) Hz, 1H), 7.15 (m, 1H), 7.21 (t, \(J=7.6\) Hz, 1H), 7.86 (m, 2H), 7.58 (m, 2H), 8.05 (d, \(J=8.1\) Hz, 1H), 8.12 (d, \(J=7.7\) Hz, 1H); \(^{13}\)C-NMR (100 MHz, \(\text{THF-d}_8\)) ppm 108.7 (d, \(J=9\) Hz, CH); 108.9 (d, \(J=9\) Hz, CH), 120.9 (d, \(J=20\) Hz, CH), 121.9 (d, \(J=21\) Hz, CH), 124.4 (CH), 124.9 (CH), 125.2 (d, \(J=14\) Hz, CH), 125.7 (d, \(J=123\) Hz, C, C-2), 125.9 (CH), 126.0 (CH), 126.3 (d, \(J=14\) Hz, CH), 131.6 (d, \(J=13\) Hz, C, C-10), 132.8 (d, \(J=2\) Hz, C, C-5), 139.2 (dd, \(J=8.5\) Hz, C, C-1), 144.5 (d, \(J=79\) Hz, C, C-11 or C-15), 146.0 (d, \(J=80\) Hz, C, C-11 or C-15), 146.4 (d, \(J=8\) Hz, CH, C-14 or C-18), 146.6 (d, \(J=8\) Hz, CH, C-14 or C-18); \(^{31}\)P-NMR (162 MHz, \(\text{THF-d}_8\)) ppm +2.2; mass spectrum \(m/z\), (relative intensity, %) 614 (0.2, \(\text{M}^+\)), 547 (0.5, \(\text{M}^+-\text{Fu}\)), 433 (100, \(\text{M}^+-\text{P(O)Fu}_2\)). Exact mass calc for \(\text{C}_{28}\text{H}_{18}\text{O}_3\text{P}(\text{M}^+-\text{P(O)Fu}_2)\): 433.1038. Found 433.1057.

7.5.4.5 Preparation of \((S_a,)-(\cdot)-2,2',\text{-Bis(di-2-furylphosphino})\)-1,1'-binaphthalene (682).

(S)-phosphine oxide 695 (0.407 g, 0.663 mmol) in xylenes (25 mL) was treated with \(\text{Et}_3\text{N}\) (2.22 mL, 15.9 mmol) and \(\text{SiCl}_3\) (1.34 mL, 13.3 mmol) at 150 °C for 3 h. To the cooled mixture was then added 30% \(\text{NaOH}\) solution (25 mL) and the resulting mixture was stirred at
65 °C for 30 min. The mixture was then extracted with CHCl₃ (3 x 75 mL). The combined organic extracts were dried (MgSO₄), and concentrated under reduced pressure to afford a light yellow solid, which was purified by column chromatography (25:1) to give the title compound 682 (0.272 g, 70%). mp 190-191 °C; [α]D¹⁹ -78.3° (c 0.95, CHCl₃). Trichlorosilane reduction of (+)-phosphine oxide 695 furnished (R)-TetFuBINAP (682) in 77% yield ([α]D¹⁷ +77.5° (c 1.03, CHCl₃)). In both cases, the products exhibited NMR spectral characteristics consistent with those previously described (see section 7.5.4.2).

7.5.4.6 Preparation of (S₆₅)-2,2'-Bis(selenodi-2-furylphosphinyl)-1,1'-binaphthalene (696).

Compound 696 was prepared according to the general method for the preparation of phosphine selenides (see section 7.4.18) starting with optically pure (-)-TetFuBINAP (682) (0.022 g, 0.038 mmol). The product was obtained as a light yellow amorphous solid (0.023 g, 82%) displaying the following characteristics: mp 210-213 °C (CH₃CN); IR (KBr) 2952, 1564, 1312, 846 cm⁻¹; ¹H-NMR (400 MHz) δ 6.22 (m, 2H), 6.79 (td, J=2.3, 1.1 Hz, 1H), 6.98 (m, 2H), 7.14 (t, J=7.7 Hz, 1H), 7.36 (m, 1H), 7.40-7.50 (m, 2H), 7.74-7.88 (m, 3H); ¹³C-NMR (100 MHz) ppm 111.4 (d, J=10 Hz, CH), 111.5 (d, J=10 Hz, CH), 124.7 (d, J=22 Hz, CH), 124.9 (d, J=22 Hz, CH), 127.0 (CH), 127.8 (CH), 127.8 (d, J=87 Hz, C, C-2), 128.4 (2 x CH), 128.6 (d, J=15 Hz, CH), 129.2 (d, J=14 Hz, CH), 134.1 (d, J=13 Hz, C, C-10), 134.5 (d, J=3 Hz, C, C-5), 138.2 (d, J=6 Hz, C, C-1), 145.4 (d, J=114 Hz, C, C-11 or C-15), 145.8 (d, J=114 Hz, C, C-11 or C-15), 148.5 (d, J=7 Hz, CH, C-14 or C-18), 149.0 (d, J=7 Hz, CH, C-14 or C-18); ³¹P-NMR (162 MHz) ppm -4.5 (¹J_P,Se=767 Hz); mass spectrum m/z, (relative intensity, %) 742 (1, M⁺), 497 (17, M⁺-PFu₂Se), 430 (100). Exact mass calcd for C₂₈H₁₈O₂P₈₀Se (M⁺-P(Se)Fu₂): 497.0260. Found: 433.0281.
7.6 Experiments Pertaining to Chapter Six.

Cyclohexylmethylphenylphosphine\textsuperscript{305a} (703), cyclopentylmethylphenylphosphine\textsuperscript{307} (704), isopropylmethylphenylphosphine\textsuperscript{307} (705), chloro(diisopropylamino)phenylphosphine\textsuperscript{308} (706), chloromethylphenylphosphine\textsuperscript{309} (708), methyl-1-naphthylphenylphosphine\textsuperscript{309} (710), methyl-(2-methoxy-1-naphthyl)phenylphosphine\textsuperscript{310} (712), methyl-2-naphthylphenylphosphine\textsuperscript{311} (713), methyl-9-phenanthrylphenylphosphine\textsuperscript{312} (714), 4-biphenyl-1-naphthylphenylphosphine\textsuperscript{313} (715), sodium (1S,2R)-isobornyl-10-sulfonate\textsuperscript{318} (722), BITIANP\textsuperscript{220} (525), and MeOBIPHEP\textsuperscript{325} (498) were prepared according to known procedures and exhibited spectral properties consistent with those reported in the literature. \((R)-\text{Cyclohexylphenylphosphine oxide}\textsuperscript{319} (730), \((S)-\text{isopropylmethylphenyl phosphine oxide}\textsuperscript{320} (741), \text{methyl-1-naphthylphenylphosphine oxide}\textsuperscript{321} (742), \((S)-\text{methyl-(2-methyl-1-naphthyl)phenylphosphine oxide}\textsuperscript{322b} (743)\) \((S)-\text{methyl-(2-methoxy-1-naphthyl)phenylphosphine oxide}\textsuperscript{310} (744), \((S)-\text{methyl-2-naphthylphenylphosphine oxide}\textsuperscript{319} (745), \text{methyl-9-phenanthrylphenylphosphine oxide}\textsuperscript{312} (746), \) and \((R)-\text{4-biphenyl-1-naphthylphenylphosphine oxide}\textsuperscript{313} (747) exhibited physical and spectral properties consistent with those reported in the literature.

7.6.1 Preparation of Methyl(2-methyl-1-naphthyl)phenylphosphine (711).

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\text{711}
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To a solution of chloromethylphenylphosphine\textsuperscript{309} (708) (0.238 g, 1.5 mmol) in dry Et\textsubscript{2}O (10 mL) at -40 °C was added a freshly prepared solution of 2-methyl-1-naphthylmagnesium bromide (0.080 M solution in THF, 20 mL, 1.6 mmol). The resulting mixture was warmed to rt and stirred for a 3h period. The mixture was quenched with 10% HCl solution (50 mL) and extracted with Et\textsubscript{2}O (3 x 50 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), and concentrated under reduced pressure to afford a thick yellow oil. The product was purified by flash chromatography (19:1 hexanes:benzene) to afford the analytically pure title compound (0.246 g.
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Phosphine 711 exhibited the following characteristics: mp 190-191 °C (CHCl₃); IR (KBr) 2954, 1114, 748 cm⁻¹; ¹H-NMR (400 MHz) δ 1.94 (d, J=4.8 Hz, 3H, H-1), 2.80 (s, 3H, H-12), 7.20-7.54 (m, 8H), 7.88 (d, J=8.3 Hz, 2H), 8.38 (dd, J=8.5, 3.6 Hz, 1H); ¹³C-NMR (100 MHz) ppm 10.8 (d, J=17 Hz, CH₃, C-12), 24.3 (d, J=26 Hz, CH₃, C-1), 125.2 (CH), 126.4 (CH), 126.8 (d, J=2 Hz, CH), 128.1 (d, J=17 Hz, CH), 128.9 (d, J=4 Hz, CH), 129.4 (CH), 129.6 (d, J=15 Hz, CH), 129.9 (d, J=6 Hz, CH), 131.2 (CH), 131.8 (d, J=20 Hz, C, C-2 or C-13), 133.4 (d, J=3 Hz, C, C-6), 136.4 (d, J=7 Hz, C, C-11), 142.9 (d, J=13 Hz, C, C-3), 145.4 (d, J=22 Hz, C, C-2 or C-13); ³¹P-NMR (162 MHz) ppm -41.4; mass spectrum, m/z (relative intensity, %) 264 (26, M⁺), 263 (100, M⁺-H), 215 (13), 170 (7). Exact mass calcd for C₁₈H₁₇P: 264.1068. Found: 264.1066.

7.6.2 Procedure for the Attempted Ketalization of (1S)-10-Camphorsulfonic Acid (517), Table 6.1, Entry 1.

A mixture of (1S)-10-CSA•H₂O (517) (1.0 g, 4.0 mmol), ethylene glycol (245 μL, 4.4 mmol) and C₆H₆ (25 mL) was heated to 80 °C in a vessel fitted with a Dean-Stark trap for 12 h. The reaction mixture was then cooled to rt and the solvent was removed in vacuo. ¹H-NMR analysis of the resulting residue showed only unreacted starting materials.

The other entries in Table 6.1 were conducted the same manner as entry 1 with the appropriate changes in diol identity, equivalence ratio, solvent, and reflux period being made. In all cases, only unreacted starting materials were isolated as evidenced by ¹H-NMR analysis.

7.6.3 Preparation of (1S, 2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonyl Azide (693).

To a solution of sodium (1S,2R)-isobornyl-10-sulfonate 722 (5.56g, 21.7 mmol) in DMF (150 mL) and Et₃N (15 mL) was added TBSCl (10.84 g, 71.92 mmol). The resulting mixture was stirred for 3 h at rt and the solvents were removed in vacuo (55 °C, 0.05 mmHg). The residue was taken up into Et₂O, filtered through a pad of Celite, and concentrated under reduced
pressure to afford a thick orange oily residue. The crude silyl ether was dissolved in benzene (150 mL) and a catalytic quantity (5 drops) of DMF was added followed by SOCl₂ (9.5 mL, 0.13 mmol). The resulting solution was heated to reflux for 12 h, quenched with saturated brine (200 mL), and extracted with Et₂O (3 x 200 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated in vacuo to afford the desired product (7.76 g, 82% from compound 722). The crude sulfonyl chloride was dissolved in DMA (80 mL) and H₂O (40 mL). To the solution was added NaN₃ (4.54 g, 69.8 mmol) and the resulting mixture was heated to 60 °C for 12 h. The cooled mixture was then extracted with Et₂O (3 x 150 mL), washed with brine (100 mL), dried (MgSO₄), and concentrated to furnish a light yellow oil. The product was purified by column chromatography (15:1) to afford 6.13 g (70%) of azide 693 as a colorless oil: [α]D²⁰ -36.2° (c 5.5, CHCl₃); IR (KBr) 2954, 2131 (N₃) cm⁻¹; H-NMR (200 MHz) δ 0.08 (s, 3H, H-11 or H-12), 0.11 (s, 3H, H-11 or H-12), 0.89 (s, 3H, H-8 or H-9), 0.90 (s, 9H, H-14), 1.05 (s, 3H, H-8 or H-9), 1.06-1.47 (m, 3H), 1.49-1.86 (m, 3H), 1.88-2.10 (m, 1H, H-4), 3.12 (d, J=14.0 Hz, 1H, H-10a), 3.97 (d, J=14.0 Hz, 1H, H-10b), 4.06 (m, 1H, H-2); C-NMR (50 MHz) ppm -5.4 (CH₃, C-11 or C-12), -4.1 (CH₃, C-11 or C-12), 17.8 (C, C-13), 20.1 (CH₃, C-8 or C-9), 20.6 (CH₃, C-8 or C-9), 25.8 (CH₃, C-14), 27.2 (CH₂, C-5 or C-6), 28.6 (CH₂, C-5 or C-6), 41.9 (CH₂, C-3), 44.5 (CH, C-4), 49.3 (C, C-1 or C-7), 50.4 (C, C-1 or C-7), 54.9 (CH₂, C-10), 75.8 (CH, C-2); mass spectrum, m/z (relative intensity, %) 345 (1, M⁻-N₂), 288 (44), 115 (66), 73 (100). Exact mass calcd for C₁₂H₂₂N₃O₃SSi (M⁺-C₄H₉): 316.1151. Found: 316.1120.

7.6.4 General Procedure for the Preparation of Phosphinimines Using Azide 693.

To a solution of the tertiary phosphine (1.0 mmol) in dry THF (10 mL) is cautiously added a solution of azide 693 (1.1 mmol) in THF (5 mL) at ambient temperature. The mixture is then heated to 60 °C under an inert atmosphere for 12 h. Removal of the solvent under reduced pressure gives the crude phosphinimine mixture, which may be purified by fractional crystallization or flash chromatography.
7.6.5 Preparation of \((S_P)\)-\([(1S,2R)-O-(\text{Butyldimethylsilyl})\text{isobornyl}-10\text{-sulfonamidyl}]\text{-cyclohexylmethylphenylphosphinimine}\) (726a) and \((R_P)\)-\([(1S,2R)-O-(\text{Butyldimethylsilyl})\text{isobornyl}-10\text{-sulfonamidyl}]\text{-cyclohexylmethylphenylphosphinimine}\) (726b).

Phosphinimines 726a and 726b were prepared according to the general procedure (see section 7.6.4) using cyclohexylmethylphenylphosphine\(^{305a}\) 703 (1.07 g, 5.20 mmol) and azide 693 (2.04 g, 5.46 mmol). Separation of the product diastereomers was achieved by recrystallization from petroleum ether.

The first diastereomer to crystallize, compound 726a, was obtained as fine, colorless needles (1.39 g, 49%) and exhibited the following analytical data: \([\alpha]_D^{20} -39.7^\circ\) (c 0.86, CHCl\(_3\)); mp 175-177 °C (petroleum ether); IR (KBr) 2930, 1452, 1110 cm\(^{-1}\); \(^1\)H-NMR (200 MHz) \(\delta\) 0.06 (s, 3H, H-11 or H-12), 0.16 (s, 3H, H-11 or H-12), 0.82 (s, 3H, H-8 or H-9), 0.91 (s, 9H, H-14), 1.00 (s, 3H, H-8 or H-9), 1.07-1.90 (m, 15H), 2.04 (d, \(J=11.2\) Hz, 3H, H-19), 1.91-2.24 (m, 3H), 2.81 (d, \(J=13.8\) Hz, 1H, H-10a), 3.70 (dd, \(J=13.8, 2.0\) Hz, 1H, H-10a), 4.19 (m, 1H, H-2), 7.66-7.45 (m, 3H, H-21 and H-23), 7.72-7.90 (m, 2H, H-22); \(^{13}\)C-NMR (50 MHz) ppm -4.4 (CH\(_3\), C-11 or C-12), 20.3 (CH\(_3\), C-8 or C-9), 20.9 (CH\(_3\), C-8 or C-9), 25.0 (d, \(J=3\) Hz, CH\(_2\)), 25.1 (d, \(J=3\) Hz, CH\(_2\)), 25.6 (CH\(_2\)), 26.0 (CH\(_3\), C-14), 26.2 (CH\(_2\)), 27.4 (CH\(_2\)), 28.1 (CH\(_3\)), 38.7 (d, \(J=71\) Hz, CH, C-15), 42.2 (CH\(_2\), C-3), 44.6 (CH, C-4), 48.5 (C, C-1 or C-7), 50.4 (C, C-1 or C-7), 53.8 (d, \(J=5\) Hz, CH, C-10), 76.3 (CH, C-2), 127.7 (d, \(J=86\) Hz, C, C-20), 128.7 (d, \(J=12\) Hz, CH, C-21), 131.1 (d, \(J=9\) Hz, CH, C-22), 134.2 (d, \(J=3\) Hz, CH, C-23) \(^{31}\)P-NMR (81 MHz) ppm +23.3; mass spectrum, \(m/z\) (relative intensity, %) 551 (0.2, M\(^+\)), 536 (1, M\(^+\)-CH\(_3\)), 494 (53, M\(^+\)-C\(_4\)H\(_9\)), 268 (64), 73 (100). Exact mass calcd for C\(_{23}\)H\(_{41}\)NO\(_3\)PSSi (M\(^+\)-C\(_4\)H\(_9\)): 494.2314. Found: 494.2339.
Compound 726b was recovered from the mother liquor by recrystallization (1.30 g, 45%) as colorless prisms and exhibited the following characteristics: $[\alpha]_D^{20} -10.0^\circ$ (c 1.06, CHCl$_3$); mp 147-149 °C (petroleum ether); IR (KBr) 2930, 1452, 1110 cm$^{-1}$; $^1$H-NMR (200 MHz) $\delta$ 0.06 (s, 3H, H-11 or H-12), 0.14 (s, 3H, H-11 or H-12), 0.85 (s, 3H, H-8 or H-9), 0.87 (s, 9H, H-14), 0.99 (s, 3H, H-8 or H-9), 1.02-1.98 (m, 15H), 1.98-2.26 (m, 3H), 2.03 (d, $J=13$ Hz, 3H, H-19), 2.81 (d, $J=13.8$ Hz, 1H, H-10a), 3.67 (dd, $J=13.8$, 2.4 Hz, 1H, H-10b), 4.10 (m, 1H, H-2), 7.41-7.64 (m, 3H, H-21 and H-23), 7.70-7.82 (m, 2H, H-22); $^{13}$C-NMR (50 MHz) ppm -4.9 (CH$_3$, C-11 or C-12), -4.4 (CH$_3$, C-11 or C-12), 10.3 (d, $J=59$ Hz, CH$_3$, C-19), 17.9 (C, C-13), 20.3 (CH$_3$, C-8 or C-9), 20.9 (CH$_3$, C-8 or C-9), 25.0 (d, $J=3$ Hz, CH$_2$), 25.2 (d, $J=3$ Hz, CH$_2$), 25.6 (CH$_2$), 26.0 (CH$_3$, C-14), 26.2 (CH$_2$), 27.4 (CH$_2$), 28.3 (CH$_2$), 38.7 (d, $J=72$ Hz, CH, C-15), 42.2 (CH$_2$, C-3), 44.6 (CH, C-4), 48.5 (C, C-1 or C-7), 50.4 (C, C-1 or C-7), 53.9 (d, $J=5$ Hz, CH$_2$, C-10), 76.4 (CH, C-2), 127.7 (d, $J=86$ Hz, C, C-20), 128.7 (d, $J=12$ Hz, CH, C-21), 131.1 (d, $J=10$ Hz, CH, C-22), 132.3 (d, $J=3$ Hz, CH, C-23); $^{31}$P-NMR (81 MHz) ppm 23.2; mass spectrum, $m/z$ (relative intensity, %) 551 (0.2, M$^+$), 536 (1, M$^+$-CH$_3$), 494 (53, M$^+$-C$_4$H$_9$), 268 (64), 73 (100). Exact mass calcd for C$_{25}$H$_{41}$N$_3$O$_7$Si (M$^+$-C$_4$H$_9$): 494.2314. Found: 494.2365.

7.6.6 Preparation of ($R^p$)-[(1S,2R)-O-(r-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-cyclopentylmethylphenylphosphinimine (727a) and ($S^p$)-[(1S,2R)-O-(r-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-cyclopentylmethylphenylphosphinimine (727b).

Phosphinimines 727a and 727b were prepared according to the general procedure (see section 7.6.4) using cyclopentylmethylphenylphosphine$^{307}$ 704 (0.794 g, 4.14 mmol) and azide 693 (1.62 g, 4.34 mmol). Separation of the product diastereomers was achieved by recrystallization from petroleum ether. The first diastereomer to crystallize, compound 727a,
was obtained as colorless needles (1.06 g, 48%) and exhibited the following analytical data:
$[\alpha]_D^{20}$ -13.5$^\circ$ (c 2.46, CHCl$_3$); mp 151-153 $^\circ$C (petroleum ether); IR (KBr) 2932, 1439, 1111 cm$^{-1}$; $^1$H-NMR (400 MHz) $\delta$ 0.06 (s, 3H, H-11 or H-12); 0.14 (s, 3H, H-7 or H-8), 0.85 (s, 3H, H-9 or H-9), 0.88 (s, 9H, H-14), 1.00 (s, 3H, H-8 or H-9), 1.45-2.01 (m, 14H), 2.04 (d, $J=12.7$ Hz, 3H, H-18), 2.06-2.21 (m, 1H), 2.44-2.52 (m, 1H, H-4), 2.85 (d, $J=13.8$ Hz, 1H, H-10a), 3.69 (d, $J=13.8$, 1H, H-10b), 4.09-4.14 (m, 1H, H-2), 7.47-7.60 (m, 3H, H-20 and H-22), 7.78-7.85 (m, 2H, H-21); $^{13}$C-NMR (50 MHz) ppm -4.5 (CH$_3$, C-11 or C-12), -4.0 (CH$_3$, C-11 or C-12), 12.5 (d, $J=60$ Hz, CH$_3$, C-18), 18.3 (CH$_3$, C-8 or C-9), 20.7 (CH$_3$, C-8 or C-9), 21.4 (C, C-13), 26.4 (CH$_3$, C-14), 26.8 (CH$_2$), 26.8 (d, $J=21$ Hz, CH$_2$), 27.1 (d, $J=11$ Hz, CH$_2$), 27.8 (CH$_2$), 28.6 (CH$_2$), 39.1 (d, $J=75$ Hz, CH, C-15), 42.6 (CH$_2$, C-3), 45.0 (CH, C-4), 49.0 (C, C-1 or C-7), 50.9 (C, C-1 or C-7), 54.3 (d, $J=3$ Hz, CH$_2$, C-10), 76.8 (CH, C-2), 129.2 (d, $J=12$ Hz, CH, C-20), 129.5 (d, $J=100$ Hz, C, C-19), 131.5 (d, $J=9$ Hz, CH, C-21), 132.7 (CH, C-22); $^{31}$P-NMR (81 MHz) ppm +23.0; mass spectrum, m/z (relative intensity, %) 537 (0.2, M$^+$), 522 (1, M$^+$-CH$_3$), 480 (53, M$^+$-C$_4$H$_9$), 268 (64), 73 (100). Exact mass calcd for C$_{27}$H$_{45}$NO$_3$PSSi (M$^+$-CH$_3$): 522.2627. Found: 522.2633.

Compound 727b was recovered from the mother liquor by recrystallization (0.943 g, 42%) as colorless plates and exhibited the following characteristics: $[\alpha]_D^{20}$ -52.8$^\circ$ (c 2.47, CHCl$_3$); mp 152-154 $^\circ$C (petroleum ether); IR (KBr) 2956, 1462, 1111 cm$^{-1}$; $^1$H-NMR (400 MHz) $\delta$ 0.06 (s, 3H, H-11 or H-12), 0.15 (s, 3H, H-11 or H-12), 0.83 (s, 3H, H-7 or H-8), 0.90 (s, 9H, H-14), 1.00 (s, 3H, H-7 or H-8), 1.43-1.98 (m, 14H), 2.05 (d, $J=13.3$ Hz, 3H, H-18), 2.08-2.18 (m, 1H), 2.42-2.55 (m, 1H, H-4), 2.80 (d, $J=13.8$ Hz, 1H, H-10a), 3.69 (d, $J=13.8$ Hz, 1H, H-10b), 4.07-4.13 (m, 1H, H-2), 7.44-7.62 (m, 3H, H-20 and H-22), 7.77-7.83 (m, 2H, H-21); $^{13}$C-NMR (100 MHz) ppm -4.5 (CH$_3$, C-11 or C-12), -4.0 (CH$_3$, C-11 or C-12), 12.4 (d, $J=60$ Hz, CH$_3$, C-18), 18.3 (C, C-13), 20.7 (CH$_3$, C-8 or C-9), 21.3 (CH$_3$, C-8 or C-9), 26.4 (CH$_3$, C-14), 26.7 (d, $J=10$ Hz, CH$_2$), 26.8 (d, $J=10$ Hz, CH$_2$), 27.0 (CH$_2$), 27.1 (CH$_2$), 27.8 (CH$_2$), 28.6 (CH$_2$), 39.2 (d, $J=74$ Hz, CH, C-15), 42.6 (CH, C-4), 45.0 (CH$_2$), 49.0 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 54.3 (d, $J=5$ Hz, CH$_2$, C-10), 76.8 (CH, C-2), 129.2 (d, $J=12$ Hz, CH, C-20), 129.5 (d, $J=100$ Hz, C, C-19), 131.4 (d, $J=10$ Hz, CH, C-21), 132.7 (d, $J=3$ Hz, CH, C-22); $^{31}$P-NMR (81 MHz) ppm +24.4; mass spectrum, m/z (relative intensity, %) 537 (0.3, M$^+$), 522 (4, M$^+$-CH$_3$), 480 (99,
Phosphinimine 728a was prepared according to the general procedure (see section 7.6.4) from isopropylmethyl-phenylphosphine\(^\text{307}\) 705 (0.437 g, 2.63 mmol) and azide 693 (1.03 g, 2.76 mmol). Compound 728a was obtained diastereomerically pure as white needles (0.585 g, 43%) by crystallization from petroleum ether and displayed the following analytical data: \(\alpha\)\(^D\) -10.2\(^\circ\) \((c 0.84, \text{CHCl}_3)\); mp 149-150 °C (petroleum ether); IR (KBr) 2928, 1439, 1113 cm\(^{-1}\); \(^1\)H-NMR (200 MHz) \(\delta\) 0.03 (s, 3H, H-11 or H-12), 0.10 (s, 3H, H-11 or H-12), 0.82 (s, 3H, H-8 or H-9), 0.85 (s, 9H, H-14), 0.97 (s, 3H, H-8 or H-9), 1.00-1.28 (m, 6H), 1.33-1.80 (m, 6H), 2.01 (d, \(J=17.0\) Hz, 3H, H-17), 2.37 (m, 2H), 2.79 (d, \(J=18.0\) Hz, 1H, H-10a), 3.66 (d, \(J=18.0\) Hz, 1H, H-10b), 4.08 (m, 1H, H-2), 7.41-7.61 (m, 3H, H-19 and H-21), 7.64-7.85 (m, 2H, H-20); \(^{13}\)C-NMR (50 MHz) ppm -5.0 (CH\(_3\), C-1 1 or C-12), -4.9 (CH\(_3\), C-11 or C-12), 10.9 (d, \(J=59\) Hz, CH, C-15), 15.3 (d, \(J=8\) Hz, CH\(_3\), C-16), 17.8 (C, C-13), 20.1 (CH\(_3\), C-8 or C-9), 20.8 (CH\(_3\), C-8 or C-9), 25.9 (CH\(_3\), C-14), 27.2 (CH\(_2\)), 28.1 (CH\(_2\)), 42.1 (CH\(_2\), C-3), 44.5 (CH, C-4), 48.4 (C, C-1 or C-7), 50.3 (C, C-1 or C-7), 53.7 (d, \(J=5\) Hz, CH\(_2\), C-10), 76.2 (CH, C-2), 127.7 (d, \(J=104\) Hz, C, C-18), 128.6 (d, \(J=12\) Hz, CH, C-19), 131.0 (d, \(J=9\) Hz, CH, C-20), 132.2 (d, \(J=3\) Hz, CH, C-21); \(^{31}\)P-NMR (81 MHz) ppm +26.1; mass spectrum, \(m/z\) (relative intensity, %) 496 (3, M\(^+\)-CH\(_3\)), 454 (89, M\(^+\)-C\(_4\)H\(_9\)), 302 (32), 228 (100). Exact mass calcd for C\(_{25}\)H\(_{43}\)NO\(_3\)PSSi (M\(^+\)-CH\(_3\)): 496.2471. Found: 496.2443. The opposite P-stereoisomer could not be obtained from the mother liquor in pure form. Attempts to obtain an analytical sample through reverse phase HPLC techniques were unsuccessful and thus compound 728b was not characterized.
7.6.8 Preparation of \((R\text{r})-[1(5,2r)-O-(t-\text{Butyldimethylsilyl})\text{isobornyl}-10-\text{sulfonamidyl}]\)-methyl-1-naphthylphenylphosphinimine (729a) and \((S\text{r})-[1(5,2r)-O-(t-\text{Butyldimethylsilyl})\text{isobornyl}-10-\text{sulfonamidyl}]\)-methyl-1-naphthylphenylphosphinimine (729b).

Phosphinimines 729a and 729b were prepared according to the general procedure (see section 7.6.4) from methyl-1-naphthylphenylphosphate \(^309\) 710 (1.00 g, 4.00 mmol) and azide \(^{693}\) (1.57 g, 4.2 mmol). Separation of the product diastereomers was achieved by flash chromatography (2:1). The first diastereomer to elute from the column, compound 729a, was obtained as a colorless foam (1.14 g, 48%) and gave the following analytical data: \([\alpha]_D^{20} +18.2^o\) (c 1.80, CHCl\(_3\)); IR (KBr) 2927, 1439, 1141 cm\(^{-1}\); \(^1\)H-NMR (200 MHz) \(\delta\) 0.02 (s, 3H, H-11 or H-12), 0.10 (s, 3H, H-11 or H-12), 0.48 (s, 3H, H-8 or H-9), 0.81 (s, 3H, H-8 or H-9), 0.84 (s, 9H, H-14), 1.41-1.76 (m, 6H), 1.92-2.17 (m, 1H, H-4), 2.40 (d, \(J=13.9\) Hz, 1H, H-10a), 2.49 (d, \(J=13.3\) Hz, 3H, H-15), 3.45 (d, \(J=13.9\) Hz, 1H, H-10b), 4.09 (m, 1H, H-2), 7.31-7.67 (m, 6H), 7.77 (d, \(J=6.7\) Hz, 1H), 7.80 (d, \(J=8.2\) Hz, 1H), 7.90 (d, \(J=8.2\) Hz, 1H), 7.99-8.29 (m, 3H); \(^{13}\)C-NMR (50 MHz) ppm -4.9 (CH\(_3\), C-11 or C-12), -4.5 (CH\(_3\), C-11 or C-12), 16.5 (d, \(J=66\) Hz, CH\(_3\), C-15), 17.9 (C, C-13), 20.1 (CH\(_3\), C-8 or C-9), 20.6 (CH\(_3\), C-8 or C-9), 26.0 (CH\(_3\), C-14), 27.3 (CH\(_2\), C-5 or C-6), 28.3 (CH\(_2\), C-5 or C-6), 42.1 (CH\(_2\), C-3), 44.5 (CH, C-4), 48.4 (C, C-1 or C-7), 50.3 (C, C-1 or C-7), 53.7 (d, \(J=3\) Hz, CH\(_2\), C-10), 76.1 (CH, C-2), 124.2 (d, \(J=103\) Hz, C, C-16 or C-26), 124.7 (d, \(J=15\) Hz, CH), 126.0 (d, \(J=7\) Hz, CH), 126.5 (CH), 127.4 (CH), 128.2 (d, \(J=72\) Hz, C, C-16 or C-26), 129.0 (d, \(J=13\) Hz, CH, C-27), 129.3 (CH), 131.0 (d, \(J=11\) Hz, CH, C-28), 132.1 (d, \(J=9\) Hz, C, C-20 or C-25), 132.4 (d, \(J=3\) Hz, CH), 133.6 (d, \(J=10\) Hz, CH), 133.9 (d, \(J=9\) Hz, C, C-20 or C-25), 134.3 (d, \(J=3\) Hz, CH); \(^{31}\)P-NMR (81 MHz) ppm +12.6; mass spectrum, \(m/z\) (relative intensity, %) 595 (0.2, M\(^+\)), 580 (1, M\(^+\)-CH\(_3\)), 538 (33, M\(^+\)-C\(_4\)H\(_9\)),...
Compound **729b** was obtained as a white solid (1.09 g, 46%) displaying the following physical properties: \( [\alpha]_D^{20} +101.4^\circ \) (c 1.36, CHCl3); mp 183-184 °C (CH3CN); IR (KBr) 2955, 1440, 1122 cm\(^{-1}\); \( ^1\)H-NMR (200 MHz) \( \delta \) 0.03 (s, 3H, H-1 or H-12), 0.19 (s, 3H, H-11 or H-12), 0.30 (s, 3H, H-8 or H-9), 0.60 (s, 3H, H-8 or H-9), 0.91 (s, 9H, H-14), 1.16-1.90 (m, 7H), 1.97 (d, \( J=14.0 \) Hz, 1H, H-10a), 2.46 (d, \( J=13.3 \) Hz, 3H, H-15), 3.39 (d, \( J=14.0 \) Hz, 1H, H-10b), 3.90-4.10 (m, 1H, H-2), 7.30-7.66 (m, 6H), 7.68-7.97 (m, 3H), 8.02-8.28 (m, 3H); \( ^{13}\)C-NMR (50 MHz) ppm -5.0 (CH\(_3\), C-11 or C-12), -4.4 (CH\(_3\), C-11 or C-12), 16.6 (d, \( J=66 \) Hz, CH\(_3\), C-15), 17.9 (C, C-13), 19.8 (CH\(_3\), C-8 or C-9), 20.4 (CH\(_3\), C-8 or C-9), 26.1 (CH\(_3\), C-14), 27.2 (CH\(_2\), C-5 or C-6), 28.0 (CH\(_2\), C-5 or C-6), 42.0 (CH\(_2\), C-3), 44.3 (CH, C-4), 48.2 (C, C-1 or C-7), 50.2 (C, C-1 or C-7), 53.3 (CH\(_2\), C-10), 76.0 (CH, C-2), 124.1 (d, \( J=97 \) Hz, C, C-16 or C-26), 124.8 (d, \( J=15 \) Hz, CH), 126.2 (d, \( J=7 \) Hz, CH), 126.6 (CH), 127.5 (CH), 127.6 (d, \( J=102 \) Hz, C, C-16 or C-26), 129.0 (d, \( J=13 \) Hz, CH, C-27), 129.2 (CH), 131.0 (d, \( J=11 \) Hz, CH, C-28), 132.2 (d, \( J=9 \) Hz, C, C-20 or C-25), 132.4 (d, \( J=3 \) Hz, CH), 133.5 (d, \( J=10 \) Hz, CH), 133.9 (d, \( J=9 \) Hz, C, C-20 or C-25), 134.3 (d, \( J=3 \) Hz, CH); \( ^{31}\)P-NMR (81 MHz) ppm +12.9; mass spectrum, \( m/z \) (relative intensity, %) 595 (0.3, M\(^+\)), 580 (2, M\(^+\)-CH\(_3\)), 538 (39, M\(^+\)-C\(_4\)H\(_9\)), 264 (100). Exact mass calcd for C\(_{32}\)H\(_{43}\)NO\(_3\)PSSi (M\(^+\)-CH\(_3\)): 580.2471. Found: 580.2485. Anal. calcd for C\(_{33}\)H\(_{46}\)SO\(_3\)SiPN: C, 66.52; H, 7.78; N, 2.35. Found: C, 66.20; H, 7.70; N, 2.52.

7.6.9 Preparation of (S\(_P^*\))-([1S,2R]-O-(r-Butyldimethylsilylisobornyl-10-sulfonamidyl)-methyl-(2-methyl-1-naphthyl)-phenylphosphinimine (730a) and (R\(_P^*\))-([1S,2R]-O-(r-Butyldimethylsilylisobornyl-10-sulfonamidyl)-methyl-(2-methyl-1-naphthyl)-phenylphosphinimine (730b).
Phosphinimines 730a and 730b were prepared according to the general procedure (see section 7.6.4) from methyl-(2-methyl-1-naphthyl)phenylphosphine 711 (0.453 g, 1.72 mmol) and azide 693 (0.672 g, 1.80 mmol). Separation of the product diastereomers was achieved by flash chromatography (3:1). The first product to elute, compound 730a, was obtained as a colorless gum (0.435 g, 42%) exhibiting the following analytical data: $[\alpha]_D^{20} +32.0^\circ$ (c 2.71, CHCl$_3$); IR (KBr) 2930, 1440, 1118 cm$^{-1}$; $^1$H-NMR (400 MHz) $\delta$ -0.01 (s, 3H, H-11 or H-12), 0.05 (s, 3H, H-11 or H-12), 0.41 (s, 3H, H-8 or H-9), 0.78 (s, 3H, H-8 or H-9), 0.79 (s, 9H, H-14), 0.83-0.99 (m, 1H), 1.39-1.72 (m, 5H), 1.92-2.14 (m, 1H, H-4), 2.44 (d, J=13.8 Hz, 4H, H-15 with H-10a), 2.71 (s, 3H, H-26), 3.48 (d, J=13.8 Hz, 1H, H-10b), 4.09 (m, 1H, H-2), 7.14-7.49 (m, 6H), 7.62 (d, J=7.9 Hz, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.73 (d, J=8.2 Hz, 1H), 7.87 (d, J=8.4 Hz, 1H), 8.27 (d, J=8.8 Hz, 1H); $^{13}$C-NMR (100 MHz) ppm -4.5 (CH$_3$, C-11 or C-12), -4.1 (CH$_3$, C-11 or C-12), 18.2 (C, C-13), 20.5 (CH$_3$, C-8 or C-9), 21.0 (CH$_3$, C-8 or C-9), 23.8 (d, J=63 Hz, CH$_3$, C-15), 25.3 (CH$_3$, C-26), 26.4 (CH$_3$, C-14), 27.8 (CH$_2$, C-5 or C-6), 28.7 (CH$_2$, C-5 or C-6), 42.6 (CH$_2$, C-3), 45.0 (CH, C-4), 48.8 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 54.0 (d, J=3 Hz, CH$_2$, C-10), 76.6 (CH, C-2), 122.5 (d, J=95 Hz, C, C-16 or C-27), 125.9 (CH), 127.1 (CH), 127.2 (CH), 129.3 (d, J=16 Hz, CH), 129.3 (CH), 130.5 (d, J=11 Hz, CH), 131.0 (d, J=13 Hz, CH), 132.2 (d, J=3 Hz, CH), 132.9 (d, J=9 Hz, C), 134.0 (d, J=10 Hz, C), 134.1 (d, J=11 Hz, C, C-16 or C-27), 134.1 (d, J=3 Hz, CH), 144.8 (d, J=9 Hz, C); $^{31}$P-NMR (162 MHz) ppm +16.8; mass spectrum, m/z (relative intensity, %) 552 (10, M$^+$-C$_4$H$_9$), 477 (10, M$^+$-TBSOH) 326 (33), 278 (100). Exact mass calcd for C$_{30}$H$_{39}$NO$_3$PSSi (M$^+$-C$_4$H$_9$): 552.2158. Found: 552.2174.

Phosphinimine 730b was obtained as a white crystalline solid (0.513 g, 49%) with the following properties: $[\alpha]_D^{20} -115.1^\circ$ (c 1.36, CHCl$_3$); IR (KBr) 2930, 1438, 1117 cm$^{-1}$; mp 146-148 °C (CH$_3$CN); $^1$H-NMR (400 MHz) $\delta$ 0.00 (s, 3H, H-11 or H-12), 0.17 (s, 3H, H-11 or H-12), 0.28 (s, 3H, H-8 or H-9), 0.57 (s, 3H, H-8 or H-9), 0.88 (s, 9H, H-14), 1.27-1.67 (m, 6H), 1.74-1.92 (m, 1H, H-4), 2.05 (d, J=13.8 Hz, H-10a), 2.42 (d, J=13.3 Hz, 3H, H-15), 2.74 (s, 3H, H-26), 3.38 (d, J=13.8 Hz, 1H, H-10b), 4.01 (m, 1H, H-2), 7.13-7.48 (m, 6H), 7.50-7.71 (m, 2H), 7.74 (d, J=7.9 Hz, 1H), 7.89 (d, J=8.2 Hz, 1H), 8.27 (d, J=8.6 Hz, 1H); $^{13}$C-NMR (100 MHz) ppm -4.6 (CH$_3$, C-11 or C-12), -3.9 (CH$_3$, C-11 or C-12), 18.3 (C, C-13), 20.5 (CH$_3$, C-8 or C-9), 21.0 (CH$_3$, C-8 or C-9), 24.4 (d, J=63 Hz, CH$_3$, C-15), 25.4 (CH$_3$, C-26), 26.5 (CH$_3$, C-14), 27.7 (CH$_2$, C-5 or C-6), 28.3 (CH$_2$, C-5 or C-6), 42.4 (CH$_2$, C-3), 44.8 (CH, C-4), 48.5 (C, C-1 or C-
7.6.10 Preparation of \((R_P)-[\{(1S,2R)-O-(t-\text{Butyldimethylsilyl})\text{isobornyl-10-sulfonamidyl}\}-\text{methyl-(2-methoxy-1-naphthyl)}\]-\text{phenylphosphinimine} (731a) and \((S_P)-[\{(1S,2R)-O-(t-\text{Butyldimethylsilyl})\text{isobornyl-10-sulfonamidyl}\}-\text{methyl-(2-methoxy-1-naphthyl)}\]-\text{phenylphosphinimine} (731b).

Phosphinimines 731a and 731b were prepared according to the general procedure (see section 7.6.4) from methyl-(2-methoxy-1-naphthyl)phenylphosphine\(^{310}\) 712 (0.269 g, 0.961 mmol) and azide 693 (0.376 g, 1.01 mmol). Separation of the product diastereomers was achieved by flash chromatography (3:1). The first product to elute, compound 731a, was obtained as a colorless oil (0.292 g, 49%) exhibiting the following analytical data: \([\alpha]_D^{20} +29.4^\circ\) (c 2.86, CHCl\(_3\)); IR (KBr) 2928, 1471, 1116 cm\(^{-1}\); \(^1\)H-NMR (400 MHz) \(\delta\) 0.02 (s, 3H, H-11 or H-12), 0.08 (s, 3H, H-11 or H-12), 0.49 (s, 3H, H-8 or H-9), 0.81 (s, 12H, H-14 and H-8 or H-9), 0.84-1.05 (m, 1H), 1.42-1.71 (m, 5H), 2.06 (m, 1H, H-4), 2.44 (d, \(J=13.8\) Hz, 1H, H-10a), 2.50 (d, \(J=14.4\) Hz, 3H, H-15), 3.42 (d, \(J=13.8\) Hz, 1H, H-10b), 3.87 (s, 3H, H-26), 4.10 (m, 1H, H-2), 7.28-7.51 (m, 6H), 7.67-7.80 (m, 3H), 8.02 (d, \(J=9.0\) Hz, 1H), 8.66 (m, 1H); \(^{13}\)C-NMR (100 MHz) ppm -4.5 (CH\(_3\), C-11 or C-12), -4.2 (CH\(_3\), C-11 or C-12), 18.2 (C, C-13), 20.5 (CH\(_3\), C-8
or C-9), 21.1 (CH₂, C-8 or C-9), 22.1 (d, J=64 Hz, CH₃, C-15), 26.4 (CH₃, C-14), 27.8 (CH₂, C-5 or C-6), 28.7 (CH₂, C-5 or C-6), 42.6 (CH₂, C-3), 45.0 (CH, C-4), 48.8 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 54.1 (d, J=3 Hz, CH₂, C-10), 56.8 (CH₃, C-26), 76.6 (CH, C-2), 105.8 (d, J=100 Hz, C, C-16), 113.5 (d, J=8 Hz, CH, C-18), 124.7 (CH), 126.8 (d, J=5 Hz, CH), 128.2 (CH), 129.1 (d, J=11 Hz, CH), 129.2 (CH), 130.0 (d, J=9 Hz, C, C-25), 130.6 (d, J=11 Hz, CH), 132.0 (d, J=3 Hz, CH), 133.7 (d, J=11 Hz, C, C-27), 134.8 (d, J=6 Hz, C, C-20), 137.0 (d, J=2 Hz, CH), 161.9 (d, J=4 Hz, C, C-17); ³¹P-NMR (162 MHz) ppm +16.8; mass spectrum, m/z (relative intensity, %) 625 (0.2, M⁺), 568 (4, M⁺-C₄H₉), 416 (31), 342 (100). Exact mass calcd for C₃₀H₃₉NO₄PSSi (M⁺-C₄H₉): 568.2107. Found: 568.2151.

Phosphinimine 731b was obtained as a white amorphous solid material (0.275 g, 46%) and exhibited the following characteristics: [α]D²₀ -103.9° (c 2.42, CHCl₃); mp 201-202 °C (CHCl₃); IR (CHCl₃); (KBr) 2928, 1471, 1114 cm⁻¹; ¹H-NMR (400 MHz) δ 0.04 (s, 3H, H-11 or H-12), 0.21 (s, 3H, H-11 or H-12), 0.34 (s, 3H, H-8 or H-9), 0.62 (s, 3H, H-8 or H-9), 0.91 (s, 9H, H-14), 1.32-1.67 (m, 6H), 1.75-1.91 (m, 1H, H-4), 2.01 (d, J=13.8 Hz, 1H, H-10a), 2.49 (d, J=14.6 Hz, 3H, H-15), 3.37 (d, J=13.8 Hz, 1H, H-10b), 3.97 (s, 3H, H-26), 4.05 (m, 1H, H-2), 7.28-7.35 (m, 3H), 7.36-7.51 (m, 3H), 7.70-7.84 (m, 3H), 8.06 (d, J=9.1 Hz, 1H), 8.43-8.52 (m, 1H); ¹³C-NMR (100 MHz) ppm -4.6 (CH₃, C-11 or C-12), -4.0 (CH₃, C-11 or C-12), 18.3 (C, C-13), 20.3 (CH₃, C-8 or C-9), 20.8 (CH₃, C-8 or C-9), 22.5 (d, J=65 Hz, CH₃, C-15), 26.4 (CH₃, C-14), 27.7 (CH₂, C-5 or C-6), 28.3 (CH₂, C-5 or C-6), 42.4 (CH₂, C-3), 44.8 (CH, C-4), 48.6 (C, C-1 or C-7), 50.6 (C, C-1 or C-7), 53.7 (d, J=2 Hz, CH₂, C-10), 57.0 (CH₃, C-26), 76.6 (CH, C-2), 108.0 (d, J=100 Hz, C, C-16), 113.6 (d, J=8 Hz, CH, C-18), 124.8 (CH), 127.0 (d, J=6 Hz, CH), 128.2 (CH), 129.1 (CH), 129.2 (CH), 129.9 (d, J=9 Hz, C, C-25), 130.8 (d, J=11 Hz, CH), 132.1 (d, J=3 Hz, CH), 133.2 (d, J=11 Hz, C, C-27), 134.7 (d, J=6 Hz, C, C-20), 136.9 (d, J=2 Hz, CH), 162.1 (d, J=4 Hz, C, C-17); ³¹P-NMR (162 MHz) ppm +16.7; mass spectrum, m/z (relative intensity, %) 625 (0.2, M⁺), 568 (16, M⁺-C₄H₉), 416 (8), 342 (84), 294 (100). Exact mass calcd for C₃₀H₃₉NO₄PSSi (M⁺-C₄H₉): 568.2107. Found: 568.2062. Anal. calcd for C₃₄H₄₈NO₄PSSi + CHCl₃: C, 56.41; H, 6.63; N, 1.88. Found: C, 56.21; H, 6.88; N, 1.90.
7.6.11 Preparation of (R)-[(1S,2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-methyl-2-naphthylphenylphosphinimine (732a) and (S)-[(1S,2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-methyl-2-naphthylphenylphosphinimine (732b).

Phosphinimines 732a and 732b were prepared according to the general procedure (see section 7.6.4) from methyl-2-naphthylphenylphosphine \textsuperscript{311} 713 (0.246 g, 0.982 mmol) and azide \textsuperscript{693} (0.384 g, 1.03 mmol). Separation of the product diastereomers was achieved by fractional crystallization from a binary mixture of CHCl\textsubscript{3} and petroleum ether. The first product to crystallize, compound 732a, was obtained as long colorless needles (0.241 g, 41%) with the following analytical data: $[\alpha]_D^{20}$ -35.5° (c 2.57, CHCl\textsubscript{3}); mp 87-88 °C (CHCl\textsubscript{3}/petroleum ether); IR (KBr) 2926, 1436, 1110 cm\textsuperscript{-1}; $^1$H-NMR (400 MHz) δ 0.06 (s, 3H, H-11 or H-12), 0.16 (s, 3H, H-11 or H-12), 0.69 (s, 3H, H-8 or H-9), 0.90 (s, 9H, H-14), 0.93 (s, 3H, H-8 or H-9), 1.39-1.79 (m, 6H), 2.02-2.16 (m, 1H, H-4), 2.44 (d, J=13.4 Hz, 3H, H-15), 2.59 (d, J=13.8 Hz, 1H, H-10a), 3.63 (d, J=13.8 Hz, 1H, H-10b), 4.13 (m, 1H, H-2), 7.44-7.54 (m, 2H), 7.54-7.73 (m, 4H), 7.74-7.87 (m, 2H), 7.89 (d, J=8.0 Hz, 1H), 7.93 (d, J=8.3 Hz, 2H), 8.42 (d, J=14.8 Hz, 1H); $^{13}$C-NMR (100 MHz) ppm -4.5 (CH\textsubscript{3}, C-11 or C-12), -4.0 (CH\textsubscript{3}, C-11 or C-12), 15.3 (d, J=65 Hz, CH\textsubscript{3}, C-15), 18.3 (C, C-13), 20.6 (CH\textsubscript{3}, C-8 or C-9), 21.1 (CH\textsubscript{3}, C-8 or C-9), 26.4 (CH\textsubscript{3}, C-14), 27.7 (CH\textsubscript{2}, C-5 or C-6), 28.7 (CH\textsubscript{2}, C-5 or C-6), 42.6 (CH\textsubscript{2}, C-3), 45.1 (CH, C-4), 48.8 (C, C-1 or C-7), 50.9 (C, C-1 or C-7), 54.3 (d, J=4 Hz, CH\textsubscript{2}, C-10), 76.8 (CH, C-2), 126.1 (d, J=12 Hz, CH), 126.8 (d, J=107 Hz, C, C-16 or C-26), 127.6 (CH), 128.2 (CH), 129.0 (CH), 129.2 (d, J=13 Hz, CH), 129.2 (CH), 129.4 (d, J=7 Hz, CH), 130.3 (d, J=104 Hz, C, C-16 or C-26), 131.9 (d, J=11 Hz, CH), 132.9 (d, J=14 Hz, C, C-18), 132.9 (d, J=3 Hz, CH), 134.1 (d, J=9 Hz, CH), 135.4 (d, J=2 Hz, C, C-23); $^{31}$P-NMR (162 MHz) ppm +15.0; mass spectrum, m/z (relative intensity, %) 595 (0.1, M\textsuperscript{+}), 580 (0.4, M\textsuperscript{+}-CH\textsubscript{3}), 538 (10, M\textsuperscript{+}-C\textsubscript{4}H\textsubscript{9}), 312 (100). Exact mass calcd for C\textsubscript{29}H\textsubscript{37}NO\textsubscript{3}PSSi (M\textsuperscript{+}-C\textsubscript{4}H\textsubscript{9}): 538.2001. Found: 538.2051.
Phosphinimine 732b was obtained diastereomerically pure by concentration of the mother liquor in vacuo (0.271 g, 46%). This compound exhibited the following physical characteristics: $[\alpha]_D^{20} +15.9^\circ$ (c 3.55, CHCl$_3$); IR (KBr) 2952, 1434, 1111 cm$^{-1}$; $^1$H-NMR (400 MHz) $\delta$ 0.06 (s, 3H, H-11 or H-12), 0.16 (s, 3H, H-11 or H-12), 0.61 (s, 3H, H-8 or H-9), 0.90 (s, 12H, H-14 and H-8 or H-9), 0.92-1.08 (m, 1H), 1.45-1.77 (m, 5H), 2.05 (m, 1H, H-4), 2.43 (d, $J=13.4$ Hz, 3H, H-15), 2.52 (d, $J=13.8$ Hz, 1H, H-10a), 3.62 (d, $J=13.8$ Hz, 1H, H-10b), 4.12 (m, 1H, H-2), 7.46-7.53 (m, 2H), 7.55-7.68 (m, 4H), 7.74-7.84 (m, 2H), 7.99 (m, 3H), 8.45 (d, $J=14.8$ Hz, 1H); $^{13}$C-NMR (100 MHz) ppm -4.5 (CH$_3$, C-11 or C-12), -4.0 (CH$_3$, C-11 or C-12), 15.4 (d, $J=65$ Hz, CH$_3$, C-15), 18.3 (C, C-13), 20.6 (CH$_3$, C-8 or C-9), 21.1 (CH$_3$, C-8 or C-9), 26.4 (CH$_3$, C-14), 27.7 (CH$_2$, C-5 or C-6), 28.7 (CH$_2$, C-5 or C-6), 42.6 (CH$_2$, C-3), 45.0 (CH, C-4), 48.9 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 54.1 (d, $J=3$ Hz, CH$_2$, C-10), 76.7 (CH, C-2), 126.1 (d, $J=12$ Hz, CH), 126.6 (d, $J=107$ Hz, C, C-16 or C-26), 127.7 (CH), 128.3 (CH), 129.1 (CH), 129.3 (d, $J=13$ Hz, CH), 129.3 (CH), 129.5 (d, $J=4$ Hz, CH), 129.9 (d, $J=105$ Hz, C, C-16 or C-26), 131.9 (d, $J=11$ Hz, CH), 132.9 (d, $J=8$ Hz, C, C-18), 133.0 (d, $J=3$ Hz, CH), 134.2 (d, $J=10$ Hz, CH), 135.3 (d, $J=3$ Hz, C, C-23); $^{31}$P-NMR (162 MHz) ppm +15.3; mass spectrum, m/z (relative intensity, %) 580 (0.4, M$^+$-CH$_3$), 538 (7, M$^+$-C$_4$H$_9$), 312 (100). Exact mass calcd for C$_{29}$H$_{37}$NO$_3$PSSi (M$^+$-C$_4$H$_9$): 538.2001. Found: 538.1974.

7.6.12 Preparation of (R$_P^+$)-[(1S,2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-methyl-9-phenanthrylphenylphosphinimine (733a) and (S$_P^+$)-[(1S,2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-methyl-9-phenanthrylphenylphosphinimine (733b).
Phosphinimines $733a$ and $733b$ were prepared according to the general procedure (see section 7.6.4) from methyl-9-phenanthrylphenylphosphine$^{312}$ 714 (0.99 g, 3.30 mmol) and azide 693 (1.29 g, 3.46 mmol). Separation of the product diastereomers was achieved by flash chromatography (4:1). The first diastereomer to elute from the column, compound $733a$, was obtained as a colorless film (1.00 g, 46%) and gave the following analytical data: $[\alpha]_D^{20} +6.6^\circ$ (c 5.45, CHCl$_3$); mp 183-184 °C (CH$_3$CN); IR (KBr) 2953, 1439, 1114 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 0.04 (s, 3H, H-1 or H-12), 0.13 (s, 3H, H-11 or H-12), 0.52 (s, 3H, H-8 or H-9), 0.82 (s, 3H, H-8 or H-9), 0.84 (s, 3H, H-14), 0.98 (m, 1H), 1.30-1.82 (m, 5H), 2.08 (m, 1H, H-4), 2.45 (d, $J=13.8$ Hz, 1H, H-10a), 2.58 (d, $J=13.3$ Hz, 3H, H-15), 3.48 (d, $J=13.8$ Hz, 1H, H-10b), 4.12 (m, 1H, H-2), 7.28-7.89 (m, 9H), 8.01 (d, $J=7.0$ Hz, 1H), 8.08 (d, $J=7.5$ Hz, 1H), 8.58 (d, $J=17.0$ Hz, 1H), 8.68-8.72 (m, 2H); $^{13}$C-NMR (100 MHz) ppm -4.4 (CH$_3$, C-11 or C-12), -4.0 (CH$_3$, C-11 or C-12), 16.9 (d, $J=65$ Hz, CH$_3$, C-15), 18.3 (C, C-13), 20.5 (CH$_3$, C-8 or C-9), 21.1 (CH$_3$, C-8 or C-9), 26.4 (CH$_3$, C-14), 27.8 (CH$_2$, C-5 or C-6), 28.8 (CH$_2$, C-5 or C-6), 42.6 (CH$_2$, C-3), 45.0 (CH, C-4), 48.8 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 54.3 (d, $J=3$ Hz, CH$_2$, C-10), 76.6 (CH, C-2), 123.1 (CH), 123.2 (d, $J=103$ Hz, C, C-16 or C-30), 124.0 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 129.0 (d, $J=25$ Hz, C), 129.5 (d, $J=13$ Hz, CH, C-31), 129.6 (C), 130.2 (C), 130.2 (d, $J=14$ Hz, C), 130.7 (CH), 132.0 (d, $J=94$ Hz, C, C-16 or C-30), 132.4 (d, $J=9$ Hz, CH, C-32), 132.8 (d, $J=2$ Hz, C), 133.0 (d, $J=3$ Hz, CH), 137.7 (d, $J=9$ Hz, CH), $^{31}$P-NMR (162 MHz) ppm +15.2; mass spectrum, $m/z$ (relative intensity, %) 630 (0.2, M$^+$-CH$_3$), 588 (4, M$^+$-C$_4$H$_9$), 362 (91), 314 (100). Exact mass calcd for C$_{33}$H$_{39}$N$_3$O$_3$PSSi (M$^+$-C$_4$H$_9$): 588.2158. Found: 588.2211.

Phosphinimine $733b$ eluted second from the column to give a colorless film (0.92 g, 43%) with the following physical properties: $[\alpha]_D^{20} -76.0^\circ$ (c 1.14, CHCl$_3$); mp 224-225 °C (CHCl$_3$); IR (KBr) 2926, 1441, 1111 cm$^{-1}$; $^1$H-NMR (200 MHz) δ 0.06 (s, 3H, H-11 or H-12), 0.22 (s, 3H H-11 or H-12), 0.28 (s, 3H, H-8 or H-9), 0.67 (s, 3H, H-8 or H-9), 0.94 (s, 3H H-14), 1.16-1.99 (m, 7H), 2.13 (d, $J=14.0$ Hz, 1H, H-10a), 2.57 (d, $J=13.3$ Hz, 3H, H-15), 3.48 (d, $J=14.0$ Hz, 1H, H-10b), 4.10 (m, 1H, H-2), 7.36-7.94 (m, 9H), 8.04 (d, $J=7.9$ Hz, 1H), 8.13 (d, $J=8.2$ Hz, 1H), 8.56 (d, $J=17.1$ Hz, 1H), 8.72 (t, $J=6.9$ Hz, 2H); $^{13}$C-NMR (50 MHz) ppm -5.0 (CH$_3$, C-11 or C-12), -4.4 (CH$_3$, C-11 or C-12), 16.7 (d, $J=67$ Hz, CH$_3$, C-15), 18.0 (C, C-13), 19.9 (CH$_3$, C-8 or C-9), 20.4 (CH$_3$, C-8 or C-9), 26.1 (CH$_3$, C-14), 27.2 (CH$_2$, C-5 or C-6), 28.0 (CH$_2$, C-5 or
C-6), 42.0 (CH₂, C-3), 44.4 (CH, C-4), 48.2 (C, C-1 or C-7), 50.2 (C, C-1 or C-7), 54.5 (CH₂, C-10), 76.1 (CH, C-2), 122.6 (CH), 122.8 (d, J=98 Hz, C, C-16 or C-30), 123.4 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.6 (C), 129.1 (d, J=13 Hz, CH, C-31), 129.5 (d, J=8 Hz, C), 129.7 (CH), 129.8 (C), 130.4 (CH), 130.9 (d, J=11 Hz, C), 131.0 (d, J=11 Hz, CH, C-32), 131.7 (d, J=69 Hz, C, C-16 or C-30), 132.5 (d, J=3 Hz, CH), 137.0 (d, J=9 Hz, CH); ³¹P-NMR (81 MHz) δ 13.2; mass spectrum, m/z (relative intensity, %) 630 (0.2, M⁺-CH₃), 588 (4, M⁺-C₄H₉), 362 (83), 314 (100). Exact mass calcd for C₃₃H₃₉NO₃PSSi (M⁺-C₄H₉): 588.2158. Found: 588.2131.

7.6.13 Preparation of (R)-[(1S,2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-4-biphenyl-1-naphthylphenylphosphinimine (734a) and (S)-[(1S,2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamidyl]-4-biphenyl-1-naphthylphenylphosphinimine (734b).

Phosphinimines 734a and 734b were prepared according to the general procedure (see section 7.6.4) from 4-biphenyl-1-naphthylphenylphosphine ³¹³ 715 (0.200 g, 0.515 mmol) and azide 693 (0.202 g, 0.541 mmol). Separation of the product diastereomers was achieved by flash chromatography (8:1). The first diastereomer to elute, compound 734a, was obtained as a white foam (0.170 g, 45%) which exhibited the following analytical data: [α]D²⁰ +13.7° (c 0.83, CHCl₃); IR (KBr) 2954, 1438, 1116 cm⁻¹; ¹H-NMR (400 MHz) δ 0.08 (s, 3H, H-11 or H-12), 0.20 (s, 3H, H-11 or H-12), 0.49 (s, 3H, H-8 or H-9), 0.87 (s, 3H, H-8 or H-9), 0.91 (s, 9H, H-14), 0.92-1.06 (m, 1H), 1.42-1.77 (m, 5H), 1.93-2.11 (m, 1H, H-4), 2.40 (d, J=13.8 Hz, 1H, H-10a), 3.60 (d, J=13.8 Hz, 1H, H-10b), 4.13 (m, 1H, H-2), 7.31-7.63 (m, 11H), 7.63-7.76 (m, 3H), 7.84-8.03 (m, 5H), 8.10 (d, J=8.1 Hz, 1H), 8.31 (d, J=8.5 Hz, 1H), ¹³C-NMR (100 MHz) ppm -
Phosphinimine 734b was obtained as a colorless film (0.167 g, 46%) with the following characteristics: $[\alpha]_D^{20}$ = -36.3° (c 1.44, CHCl$_3$); mp 90-92 °C (CH$_2$CN); IR (KBr) 2953, 1439, 1116 cm$^{-1}$; $^1$H-NMR (400 MHz) $\delta$ 0.07 (s, 3H, H-1 or H-12), 0.19 (s, 3H, H-11 or H-12), 0.49 (s, 3H, H-8 or H-9), 0.82 (s, 3H, H-8 or H-9), 0.90 (s, 9H, H-14), 0.95-1.08 (m, 1H), 1.42-1.73 (m, 5H), 1.94-2.00 (m, 1H, H-4), 2.41 (d, $J=13.8$ Hz, 1H, H-10a), 3.59 (d, $J=13.8$ Hz, 1H, H-10b), 4.12 (m, 1H, H-2), 7.34-7.56 (m, 8H), 7.56-7.63 (m, 3H), 7.64-7.76 (m, 3H), 7.84-8.02 (m, 5H), 8.10 (d, $J=8.1$ Hz, 1H), 8.32 (d, $J=8.5$ Hz, 1H); $^{13}$C-NMR (100 MHz) ppm -4.5 (CH$_3$, C-11 or C-12), -4.1 (CH$_3$, C-11 or C-12), 18.3 (C, C-13), 20.5 (CH$_3$, C-8 or C-9), 21.0 (CH$_3$, C-8 or C-9), 26.5 (CH$_3$, C-14), 27.7 (CH$_2$, C-5 or C-6), 28.6 (CH$_2$, C-5 or C-6), 42.6 (CH$_2$, C-3), 45.0 (CH, C-4), 48.8 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 54.0 (d, $J=4$ Hz, CH$_2$, C-10), 76.7 (CH, C-2), 124.5 (d, $J=98$ Hz, C), 125.1 (CH, d, $J=15$ Hz, CH), 127.0 (CH), 127.7 (CH), 127.77 (d, $J=8$ Hz, CH), 127.82 (d, $J=109$ Hz, C), 127.9 (d, $J=7$ Hz, CH), 128.0 (CH), 128.7 (CH), 129.2 (d, $J=13$ Hz, CH), 129.3 (d, $J=121$ Hz, C), 129.4 (CH, C-20 or C-21), 129.8 (CH), 132.9 (d, $J=3$ Hz, CH), 133.5 (d, $J=9$ Hz, C, C-27 or C-32), 133.6 (d, $J=11$ Hz, CH), 133.8 (d, $J=11$ Hz, CH), 134.5 (d, $J=9$ Hz, C, C-27 or C-32), 134.7 (d, $J=3$ Hz, CH), 136.7 (d, $J=12$ Hz, CH), 140.0 (C, C-19), 145.6 (d, $J=3$ Hz, C, C-18); $^{31}$P-NMR (162 MHz) ppm +13.7; mass spectrum, m/z (relative intensity, %) 602 (1, M$^+$-OTBS), 580 (1), 524 (27), 450 (75), 402 (81), 41 (100). Exact mass calcd for C$_{40}$H$_{43}$NO$_3$PSSi (M$^+$-C$_4$H$_9$): 676.2471. Found: 676.2468.
7.6.14 General Procedure for the Hydrolysis of Isomerically Pure (1S, 2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamidyl Phosphinimines to Give Enantiomerically Pure Phosphine Oxides and (1S, 2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonamide (737).

The isomerically pure phosphinimine starting material (1.0 mmol) in p-dioxane (20 mL) is treated with 3M H₂SO₄ solution (7 mL) and the resulting mixture is heated to 100 °C for 3 h. The cooled reaction mixture is quenched with NaHCO₃ solution and extracted with CHCl₃ (3 x 50 mL). The combined organic extracts are then dried (MgSO₄) and concentrated in vacuo to afford the crude mixture of the desired phosphine oxide and (1S,2R)-O-(t-butyldimethylsilyl)isobornyl-10-sulfonamide (737). Compound 737 can ordinarily be removed from the phosphine oxide product by flash chromatography using a 1:1 eluent mixture of hexanes and ethyl acetate. The phosphine oxide, which typically remains at the baseline, can be flushed from the column using 9:1 CHCl₃/MeOH as the eluent. The sulfonamide byproduct 737 exhibits the following characteristics: mp 113-115 °C (CHCl₃); IR (KBr) 3430 (NH st), 3371 (NH), 2929, 1385 (S=O), 1089 cm⁻¹; ¹H-NMR (400 MHz) δ 0.07 (s, 3H, H-11 or H-12), 0.10 (s, 3H, H-11 or H-12), 0.87 (s, 3H, H-8 or H-9), 0.90 (s, 9H, H-14), 1.02 (s, 3H, H-8 or H-9), 1.02-1.13 (m, 1H), 1.30-1.42 (m, 1H), 1.62-1.80 (m, 4H), 1.90-2.03 (m, 1H, H-4), 2.96 (d, J=14.0 Hz, 1H, H-10a), 3.77 (d, J=14.0 Hz, 1H, H-10b), 4.05 (m, 1H, H-2), 4.62 (s, 2H, H-15); ¹³C-NMR (50 MHz) ppm -4.8 (CH₃, C-11 or C-12), -3.7 (CH₃, C-11 or C-12), 18.3 (C, C-13), 20.5 (CH₃, C-8 or C-9), 21.1 (CH₃, C-8 or C-9), 26.3 (CH₃, C-14), 27.6 (CH₂, C-5 or C-6), 28.8 (CH₂, C-5 or C-6), 42.3 (CH₂, C-3), 44.9 (CH, C-4), 49.3 (C, C-1 or C-7), 50.6 (C, C-1 or C-7), 54.0 (CH₂, C-10), 76.4 (CH, C-2); mass spectrum, m/z (relative intensity, %) 290 (1, M⁺-C₄H₉), 226 (27), 135 (100). Exact mass calcd for C₁₂H₂₄NO₃SSi (M⁺-C₄H₉): 290.1246. Found: 290.1236.
7.6.15 Preparation of \((R^p)^*\)-Cyclopentylmethylphenylphosphine oxide (739).

Phosphine oxide 739 was prepared from isomerically pure phosphinimine 727b (0.30 g, 0.56 mmol) according to the general hydrolysis procedure (see section 7.6.14). The product thus obtained (0.108 g, 93%) was characterized by the following analytical data: \([\alpha]_D^{20^0} +33.3^0\) (c 1.62, MeOH); IR (KBr) 2960, 1438, 1167, 752 cm\(^{-1}\); \(^1\)H-NMR (200 MHz) \(\delta\) 1.44-1.75 (m, 6H), 1.66 (d, \(J=12.4\) Hz, 3H, H-4), 1.74-1.96 (m, 2H), 2.11-2.27 (m, 1H, H-1), 7.41-7.51 (m, 3H, H-6 and H-8), 7.63-7.72 (m, 2H, H-7); \(^{13}\)C-NMR (50 MHz) ppm 15.2 (d, \(J=69\) Hz, CH\(_3\), C-4), 26.7 (d, \(J=1\) Hz, CH\(_2\), C-3), 27.1 (d, \(J=9\) Hz, CH\(_2\), C-2), 40.0 (d, \(J=74\) Hz, CH, C-1), 128.9 (d, \(J=11\) Hz, CH, C-6), 130.7 (d, \(J=9\) Hz, CH, C-7), 131.8 (d, \(J=3\) Hz, CH, C-8), 134.2 (d, \(J=94\) Hz, C, C-5); \(^{31}\)P-NMR (81 MHz) ppm +40.1; mass spectrum, \(m/z\) (relative intensity, %) 208 (11, M\(^+\)), 167 (100), 140 (78), 125 (43). Exact mass calcd for C\(_{12}\)H\(_{17}\)O\(_P\): 208.1017. Found: 208.1029.

7.6.16 Preparation of \((R^p)^*\)-Methyl(2-methyl-1-naphthyl)phenylphosphine oxide (742).

Phosphinimine 730b (0.318 g, 0.523 mmol) was subjected to the hydrolysis conditions outlined in the general procedure (see section 7.6.14) to give phosphine oxide 742 in 94% yield (0.138 g). The product had the following properties: \([\alpha]_D^{20^0} +19.6^0\) (c 1.55, MeOH); mp 190-191 °C (CHCl\(_3\)); IR (KBr) 2921, 1176, 749 cm\(^{-1}\); \(^1\)H-NMR (400 MHz) \(\delta\) 2.29 (d, \(J=12.9\) Hz, 3H, H-1), 2.78 (d, \(J=1\) Hz, 3H, H-12), 7.32-7.53 (m, 5H), 7.64-7.73 (m, 3H), 7.84 (d, \(J=7.8\) Hz, 1H), 7.93 (d, \(J=8.4\) Hz, 1H), 8.54 (d, \(J=8.6\) Hz, 1H); \(^{13}\)C-NMR (100 MHz) ppm 19.9 (d, \(J=73\) Hz, CH\(_3\), C-1), 24.2 (d, \(J=5\) Hz, CH\(_3\), C-12), 125.1 (d, \(J=96\) Hz, C, C-2 or C-13), 125.7 (CH), 126.1 (CH), 127.0 (CH), 129.2 (d, \(J=1\) Hz, CH), 129.3 (d, \(J=12\) Hz, CH), 130.0 (d, \(J=10\) Hz, CH),
To a solution of racemic BINAPFu (509) (0.242 g, 0.345 mmol) in DME (2.5 mL) was added a solution of azide 693 (0.284 g, 0.759 mmol) in 7.5 mL DME. The resulting mixture was refluxed under a N\textsubscript{2} atmosphere for 12 h. The cooled mixture was then concentrated \textit{in vacuo} to afford a thick yellow oil. Separation of the product diastereomers was achieved by column chromatography (3:1). The first isomer to elute from the column, compound 747\textsubscript{a}, was obtained as white solid (0.224 g, 49%), which gave the following analytical data: mp 196-198 °C (CH\textsubscript{3}CN/H\textsubscript{2}O); IR (KBr) 2954, 1437, 1120 cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (400 MHz) \(\delta\) -0.27 (s, 3H, H-11 or H-12), -0.10 (s, 3H, H-11 or H-12), 0.57 (s, 3H, H-8 or H-9), 0.70 (s, 9H, H-14), 0.79 (s, 3H, H-8 or H-9), 1.28-1.37 (m, 2H), 1.38-1.63 (m, 4H), 1.70-1.86 (m, 1H, H-4), 2.01 (d, J=13.6 Hz, 1H, H-10a), 2.83 (d, J=13.6 Hz, 1H, H-10b), 3.85 (m, 1H, H-2), 6.72-6.87 (m, 2H), 7.03-7.15 (m, 1H), 7.29-7.43 (m, 1H), 7.44-7.70 (m, 7H), 7.78-7.90 (m, 5H); \textsuperscript{13}C-NMR (100 MHz) ppm -4.7 (CH\textsubscript{3}, C-11 or C-12), -4.3 (CH\textsubscript{3}, C-11 or C-12), 18.1 (C, C-13), 20.5 (CH\textsubscript{3}, C-8 or C-9), 21.1
(CH₃, C-8 or C-9), 26.4 (CH₂, C-14), 27.8 (CH₂, C-5 or C-6), 29.0 (CH₂, C-5 or C-6), 42.8 (CH₂, C-3), 44.8 (CH, C-4), 48.8 (C, C-1 or C-7), 50.6 (C, C-1 or C-7), 53.4 (d, J=5 Hz, CH₂, C-10), 76.4 (CH, C-2), 112.7 (CH, C-25), 122.2 (d, J=8 Hz, C), 123.6 (CH), 125.9 (CH), 127.0 (d, J=105 Hz, C, C-27 or C-31), 127.2 (d, J=15 Hz, C), 128.0 (CH), 128.1 (d, J=10 Hz, CH), 128.3 (d, J=105 Hz, C, C-27 or C-31), 129.0 (C), 129.2 (CH), 129.3 (CH), 130.2 (CH), 131.2 (C), 132.8 (d, J=3 Hz, CH), 133.3 (d, J=3 Hz, CH), 133.9 (d, J=12 Hz, CH), 134.1 (d, J=10 Hz, CH), 140.8 (d, J=151 Hz, C, C-15), 156.1 (d, J=9 Hz, C, C-26); ³¹P-NMR (162 MHz) ppm +4.9; FAB-MS, m/z (relative intensity, %) 1393 (2, M+H⁺).

Phosphinimine 747b was obtained as a pale yellow solid (0.198 g, 43%), which was recrystallized from CH₃CN/H₂O as long white needles with the following properties: mp 176-178 °C (CH₃CN/H₂O); IR (KBr) 2954, 1438, 1118 cm⁻¹; ¹H-NMR (400 MHz) δ 0.05 (s, 3H, H-11 or H-12), 0.11 (s, 3H, H-11 or H-12), 0.35 (s, 3H, H-8 or H-9), 0.81 (s, 3H, H-8 or H-9), 0.91 (s, 9H, H-14), 1.07-1.78 (m, 7H), 1.99 (d, J=13.3 Hz, 1H, H-10a), 2.85 (d, J=13.3 Hz, 1H, H-10b), 3.90 (m, 1H, H-2), 6.56-6.77 (m, 2H), 7.04 (t, J=7.1 Hz, 1H), 7.30-7.47 (m, 4H), 7.51 (td, J=7.3, 3.2 Hz, 2H), 7.59 (td, J=6.9, 1.7 Hz, 1H), 7.66 (d, J=9.1 Hz, 1H), 7.71 (d, J=8.2 Hz, 1H), 7.78 (d, J=7.4 Hz, 1H), 7.81 (d, J=7.5 Hz, 1H), 7.87 (d, J=9.1 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H); ¹³C-NMR (100 MHz) ppm -4.2 (2CH₃, C-11 and C-12), 18.4 (C, C-13), 20.5 (CH₃, C-8 or C-9), 20.9 (CH₃, C-8 or C-9), 26.7 (CH₃, C-14), 27.6 (CH₂, C-5 or C-6), 29.5 (CH₂, C-5 or C-6), 42.7 (CH₂, C-3), 44.9 (CH, C-4), 48.8 (C, C-1 or C-7), 50.7 (C, C-1 or C-7), 54.3 (d, J=2 Hz, CH₂, C-10), 76.6 (CH, C-2), 113.1 (CH, C-25), 122.1 (d, J=8 Hz, C), 123.8 (CH), 125.8 (CH), 126.3 (d, J=107 Hz, C, C-27 or C-31), 126.9 (d, J=16 Hz, C), 127.8 (CH), 127.8 (d, J=105 Hz, C, C-27 or C-31), 128.0 (d, J=9 Hz, CH), 128.9 (C), 129.1 (d, J=14 Hz, CH), 129.5 (CH), 130.0 (CH), 131.2 (C), 132.6 (d, J=3 Hz, CH), 133.2 (d, J=3 Hz, CH), 133.7 (d, J=12 Hz, CH), 134.1 (d, J=12 Hz, CH), 140.9 (d, J=145 Hz, C, C-15), 156.1 (d, J=9 Hz, C, C-26); ³¹P-NMR (162 MHz) ppm +5.8; FAB-MS, m/z (relative intensity, %) 1393 (2, M+H⁺). Anal. calcd for C₈₀H₈₀N₂O₈P₅S₂Si₂ + 2H₂O: C, 67.20; H, 6.91; N, 1.96. Found: C, 67.36; H, 6.80; N, 2.01. In order to establish absolute stereochemistry, phosphinimine 747a (0.155 g, 0.111 mmol) was subjected to acid hydrolysis, according to the general procedure (see section 7.6.14) to afford (S)-2,2'-bis(diphenylphosphinyl)-3,3'binaptho[2,1-b]furan (560) (0.076 g, 93%) with α⁻²²D -170.4°.
7.6.18 Preparation of \((S_\alpha)-(S,2R)-O-(\text{t-Butyldimethylsilyl})\text{isobornyl-10-sulfonamidyl})\-
[3,3'-bibenzo[b]thiophene]-2,2'-diylbis[diphenylphosphinimine] (748a) and \((R_\alpha)-(R,2S)-O-\
(\text{t-Butyldimethylsilyl})\text{isobornyl-10-sulfonamidyl})-[3,3'-bibenzo[b]thiophene]-2,2'-diylbis[
\text{diphenylphosphinimine}] (748b).

\[\text{748a} \quad \text{748b}\]

To a solution of racemic BITIANP\(^{220}\) (525) (0.247 g, 0.389 mmol) in THF (2.5 mL) was
added a solution of azide 693 (0.320 g, 0.855 mmol) in 7.5 mL THF. The resulting mixture was
refluxed under a \(\text{N}_2\) atmosphere for 24 h. The cooled mixture was then concentrated \textit{in vacuo}
to afford a thick yellow oil. Separation of the product diastereomers was achieved by column
chromatography (3:1). The first isomer to elute from the column, compound 748a, was obtained
as white solid (0.240 g, 47%), which gave the following analytical data: \(\text{mp} 277-279\ ^\circ\text{C}\)
\((\text{CH}_3\text{CN}/\text{H}_2\text{O})\); \(\text{IR} (\text{KBr}) 2927, 1438, 1121, 1086\ \text{cm}^{-1}\); \(^1\text{H}-\text{NMR} (400 \text{MHz}) \delta -0.05 \text{ (s, 3H, H-
11 or H-12), -0.01 \text{ (s, 3H, H-11 or H-12), 0.67 \text{ (s, 3H, H-8 or H-9), 0.84 \text{ (s, 9H, H-14), 0.90 \text{ (s, 3H, H-8 or H-9), 1.38 \text{ (m, 1H), 1.62 \text{ (m, 5H), 2.02 \text{ (m, 1H, H-4), 2.17 \text{ (d, J=13.8 Hz, 1H, H-10a), 3.01 \text{ (d, J=13.8 Hz, 1H, H-10b), 3.95 \text{ (m, 1H, H-2), 7.00 \text{ (td, J=7.7, 3.2 Hz, 2H), 7.20 \text{ (t, J=7.4 Hz, 2H), 7.32 \text{ (d, J=8.2 Hz, 1H), 7.38 \text{ (t, J=7.5 Hz, 1H), 7.50 \text{ (td, J=7.5, 3.3 Hz, 2H), 7.60 \text{ (d, J=7.4 Hz, 2H), 7.63 \text{ (d, J=7.5 Hz, 1H), 7.75 \text{ (d, J=8.2 Hz, 2H), 7.78 \text{ (d, J=7.4 Hz, 1H); ^13\text{C-NMR} (100 MHz) ppm -4.4 \text{ (CH}_3, C-11 \text{ or C-12), -4.1 \text{ (CH}_3, C-11 \text{ or C-12), 18.3 \text{ (C, C-13), 20.8 \text{ (CH}_3, C-8 \text{ or C-9), 21.3 \text{ (CH}_3, C-8 \text{ or C-9), 26.5 \text{ (CH}_3, C-14), 27.7 \text{ (CH}_2, C-5 \text{ or C-6), 29.2 \text{ (CH}_2, C-5 \text{ or C-6), 42.8 \text{ (CH}_2, C-3), 44.9 \text{ (CH, C-2), 48.9 \text{ (C, C-1 or C-7), 50.7 \text{ (C, C-1 or C-7), 53.5 \text{ (d, J=7 Hz, CH}_2, C-10), 76.7 \text{ (CH, C-2), 122.2 \text{ (d, J=2 Hz, CH), 125.6 \text{ (CH), 125.8 \text{ (CH), 127.7}}}
\]
(CH), 127.8 (d, J=123 Hz, C), 127.9 (d, J=102 Hz, C), 128.2 (d, J=13 Hz, CH), 129.1 (d, J=13 Hz, CH), 129.6 (d, J=104 Hz, C), 132.7 (d, J=124 Hz, C), 133.3 (d, J=3 Hz, CH, C-26 or C-30), 133.7 (d, J=12 Hz, CH), 133.9 (d, J=12 Hz, CH), 140.4 (dd, J=7, 2 Hz, C, C-16), 141.6 (d, J=13 Hz, C), 142.2 (d, J=7 Hz, C); $^{31}$P-NMR (162 MHz) ppm +8.1; FAB-MS, m/z (relative intensity, %) 1325 (2, M+H$^+$). Anal. calcd for C$_{72}$H$_{90}$N$_2$O$_6$P$_2$S$_4$Si$_2$ + H$_2$O: C, 64.35; H, 6.90; N, 2.08. Found: C, 64.57; H, 6.69; N, 2.18.

Phosphinimine 748b was obtained as a colorless solid (0.208 g, 40%) with the following properties: mp 220-222 °C (CH$_3$CN/H$_2$O); IR (KBr) 2927, 1438, 1122, 1086 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 0.05 (s, 3H, H-11 or H-12), 0.15 (s, 3H, H-11 or H-12), 0.52 (s, 3H, H-8 or H-9), 0.86 (s, 3H, H-8 or H-9), 0.92 (s, 9H, H-14), 1.21 (m, 1H), 1.35-1.70 (m, 6H), 2.01 (d, J=13.7 Hz, 1H, H-10a), 3.01 (d, J=13.7 Hz, 1H, H-10b), 3.94 (m, 1H, H-11 or H-12), 6.88 (td, J=7.7, 3.4 Hz, 2H), 7.14 (d, J=8.1 Hz, 1H), 7.18 (d, J=7.7 Hz, 1H), 7.25 (d, J=8.7 Hz, 1H), 7.31-7.42 (m, 3H), 7.51 (dt, J=7.6, 3.3 Hz, 2H), 7.57-7.63 (m, 1H), 7.74 (d, J=7.7 Hz, 2H), 7.77 (d, J=7.3 Hz, 1H); $^{13}$C-NMR (100 MHz) ppm -4.2 (CH$_3$, C-11 or C-12), -4.0 (CH$_3$, C-11 or C-12), 18.4 (C, C-13), 20.7 (CH$_3$, C-8 or C-9), 21.1 (CH$_3$, C-8 or C-9), 26.7 (CH$_3$, C-14), 27.7 (CH$_2$, C-5 or C-6), 29.4 (CH$_2$, C-5 or C-6), 42.8 (CH$_2$, C-3), 44.9 (CH, C-4), 48.9 (C, C-1 or C-7), 50.7 (C, C-1 or C-7), 54.1 (d, J=3 Hz, CH$_2$, C-10), 76.7 (CH, C-2), 122.4 (CH), 125.2 (CH), 125.4 (CH), 127.3 (d, J=104 Hz, C), 127.5 (CH), 127.8 (d, J=124 Hz, C), 128.0 (d, J=13 Hz, CH), 128.7 (d, J=100 Hz, C), 129.0 (d, J=13 Hz, CH), 132.5 (d, J=3 Hz, CH, C-26 or C-30), 133.3 (d, J=3 Hz, CH, C-26 or C-30), 133.3 (d, J=12 Hz, CH), 134.4 (d, J=11 Hz, CH), 140.0 (dd, J=8, 2 Hz, C, C-16), 141.3 (d, J=14 Hz, C), 142.3 (d, J=7 Hz, C); $^{31}$P-NMR (162 MHz) ppm +9.8; FAB-MS, m/z (relative intensity, %) 1325 (2, M+H$^+$). In order to establish absolute stereochemistry, phosphinimine 748a (0.110 g, 0.083 mmol) was subjected to acid hydrolysis, according to the general procedure, to afford (S)-2,2'-bis(diphenylphosphinyl)-3,3'-bibenzo[6]thiophene (526) (0.050 g, 91%) with $\alpha_D^{22}$ -324.2° (lit.$^{220}$ $\alpha_D^{25}$ -329.0°).

7.6.19 Reaction of (+)-BINAP (505) with (iS,2/?)-O-(t-Butyldimethylsilyl)isobornyl-lO-sulfonyl azide (693).

To a solution of racemic BINAP (505) (0.247 g, 0.397 mmol) in degassed toluene (10 mL) was added azide 693 (0.326 g, 0.873 mmol) and the mixture was heated to reflux under an argon atmosphere for 48 h. The cooled mixture was concentrated under reduced pressure to afford a
thick yellow oil. $^{31}$P-NMR analysis of the crude material showed the complete consumption of starting material to yield four products 749-752 in an approximate 2:2:3:3 ratio. Subjecting the mixture to flash chromatography (4:1) afforded bis-phosphinimine products 749-750 in isomerically pure form along with a third fraction containing compounds 751-752.

![Diagrams of 749 and 750](image)

The first isomer to elute from the column, compound 749, was obtained as a colorless film (0.940 g, 18%) with the following properties: mp 176-178 °C (CHCl$_3$); IR (KBr) 2926, 1438, 1085 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 0.04 (s, 3H, H-11 or H-12), 0.10 (s, 3H, H-11 or H-12), 0.50 (s, 3H, H-8 or H-9), 0.91 (s, 3H, H-8 or H-9), 0.93 (s, 3H, H-14), 1.27 (m, 1H), 1.37-1.65 (m, 6H), 1.71 (d, $J$=13.6 Hz, 1H, H-10a), 2.78 (d, $J$=13.6 Hz, 1H, H-10b), 3.91 (m, 1H, H-2), 6.87-6.99 (m, 2H), 7.14 (t, $J$=7.1 Hz, 1H), 7.35-7.51 (m, 5H), 7.55 (td, $J$=7.9, 1.4 Hz, 2H), 7.69 (d, $J$=7.3 Hz, 2H), 7.72 (d, $J$=7.3 Hz, 2H), 7.82 (t, $J$=7.1 Hz, 2H); $^{13}$C-NMR (100 MHz) ppm -4.1 (CH$_3$, C-11 or C-12), -3.9 (CH$_3$, C-11 or C-12), 18.4 (C, C-13), 20.8 (CH$_3$, C-8 or C-9), 21.1 (CH$_3$, C-8 or C-9), 26.7 (CH$_3$, C-14), 27.7 (CH$_2$, C-5 or C-6), 29.7 (CH$_2$, C-5 or C-6), 43.0 (CH$_2$, C-3), 44.9 (CH, C-4), 48.9 (C, C-1 or C-7), 50.9 (C, C-1 or C-7), 53.8 (d, $J$=4 Hz, CH$_2$, C-10), 76.8 (CH, C-2), 124.2 (d, $J$=114 Hz, C), 127.3 (CH), 128.2 (d, $J$=13 Hz, CH), 128.5 (d, $J$=10 Hz, CH), 128.7 (CH), 128.7 (d, $J$=101 Hz, C), 128.8 (CH), 128.8 (d, $J$=14 Hz, CH), 129.0 (CH), 129.9 (d, $J$=14 Hz, CH), 130.9 (d, $J$=95 Hz, C), 131.9 (d, $J$=3 Hz, CH, C-27 or C-31), 132.5 (d, $J$=3 Hz, CH, C-27 or C-31), 133.9 (d, $J$=13 Hz, CH), 134.0 (d, $J$=11 Hz, CH), 134.4 (d, $J$=2 Hz,
Bis-phosphinimine 750 was obtained as a colorless amorphous solid (0.105 g, 20%) with the following characteristics: mp 148-151 °C (CHCl₃); IR (KBr) 2926, 1438, 1120, 1086 cm⁻¹; ¹H-NMR (400 MHz) δ -0.18 (s, 3H, H-1 or H-12), -0.05 (s, 3H, H-11 or H-12), 0.69 (s, 3H, H-8 or H-9), 0.81 (s, 3H, H-8 or H-9), 0.98 (s, 3H, H-14), 1.11-1.30 (m, 2H), 1.42-1.66 (m, 5H), 2.02 (d, J=13.8 Hz, 1H, H-10a), 2.70 (d, J=13.8 Hz, 1H, H-10b), 3.85 (m, 1H, H-10), 7.15 (td, J=8.9, 3.6 Hz, 4H), 7.23 (d, J=6.7 Hz, 1H), 7.40 (td, J=7.6, 3.1 Hz, 2H), 7.45-7.57 (m, 3H), 7.64-7.74 (m, 4H), 7.82 (l, J=8.4 Hz, 2H); ¹³C-NMR (100 MHz) ppm -4.2 (2CH₃, C-11 and C-12), 18.2 (C, C-13), 20.9 (CH₃, C-8 or C-9), 21.5 (CH₃, C-8 or C-9), 26.6 (CH₃, C-14), 27.7 (CH₂, C-5 or C-6), 29.2 (CH₂, C-5 or C-6), 43.1 (CH₂, C-3), 44.7 (CH, C-4), 49.1 (C, C-1 or C-7), 50.7 (C, C-1 or C-7), 53.3 (d, J=8 Hz, CH₂, C-10), 76.6 (CH, C-2), 124.3 (d, J=116 Hz, C), 127.4 (CH), 128.2 (CH), 128.5 (CH), 128.5 (d, J=6 Hz, CH), 128.6 (CH), 128.7 (d, J=96 Hz, C), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.5 (d, J=16 Hz, CH), 131.0 (d, J=98 Hz, C), 132.3 (d, J=3 Hz, CH), 133.7 (d, J=11 Hz, CH), 134.2 (d, J=12 Hz, CH), 134.3 (C), 134.8 (d, J=12 Hz, C), 143.2 (l, J=5 Hz, C, C-16); ³¹P-NMR (162 MHz) ppm +14.6; FAB-MS, m/z (relative intensity, %) 1313 (6, M+H⁺).

The third fraction obtained from the column contained a mixture of compounds 751 and 752. This mixture was separated by repeated preparative TLC (7:3 CHCl₃/CH₃CN). The less polar fraction, compound 751, was obtained as a colorless solid (0.118 g, 30%) and exhibited the following analytical data: mp 212-214 °C (CHCl₃); IR (KBr) 2951, 1437, 1118 cm⁻¹; ¹H-NMR
(400 MHz) δ 0.07 (s, 3H, H-11 or H-12), 0.13 (s, 3H, H-11 or H-12), 0.52 (s, 3H, H-8 or H-9), 0.89 (s, 3H, H-8 or H-9), 0.91 (s, 3H, H-14), 1.33-1.44 (m, 1H), 1.50-1.71 (m, 5H), 1.88-1.98 (m, 1H, H-4), 2.22 (d, J=13.4 Hz, 1H, H-10a), 3.45 (d, J=13.4 Hz, 1H, H-10b), 4.07 (m, 1H, H-2), 6.29 (d, J=8.5, Hz, 1H), 6.44 (td, J=8.5, 1.3 Hz, 1H), 6.65 (td, J=8.0, 3.6 Hz, 2H), 6.89 (td, J=8.4, 1.6 Hz, 1H), 7.05-7.25 (m, 7H), 7.36-7.71 (m, 13H), 7.73 (t, J=8.2 Hz, 2H), 7.97 (dd, J=8.4, 2.1 Hz, 1H), 8.19 (d, J=13.1 Hz, 1H), 8.22 (d, J=13.1 Hz, 1H), 8.33-8.45 (m, 2H); 13C-NMR (100 MHz) ppm -4.3 (CH3, C-11 or C-12), -4.2 (CH3, C-11 or C-12), 18.4 (C, C-13), 20.8 (CH3, C-8 or C-9), 21.1 (CH3, C-8 or C-9), 26.5 (CH3, C-14), 27.7 (CH2, C-5 or C-6), 29.0 (CH2, C-5 or C-6), 42.7 (CH2, C-3), 44.9 (CH, C-4), 48.8 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 53.8 (d, J=4 Hz, CH2, C-10), 76.9 (CH, C-2), 125.8 (CH), 126.5 (d, J=129 Hz, C), 127.3 (CH), 127.4 (CH), 127.7 (CH), 127.9 (d, J=6 Hz, CH), 128.0 (CH), 128.1 (d, J=5 Hz, CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.8 (d, J=115 Hz, C), 128.9 (CH), 129.6 (CH), 130.6 (d, J=13 Hz, CH), 131.1 (d, J=3 Hz, CH), 131.4 (d, J=3 Hz, CH), 131.5 (d, J=9 Hz, CH), 131.6 (d, J=98 Hz, C), 132.0 (d, J=3 Hz, CH), 132.4 (d, J=3 Hz, CH), 132.68 (d, J=12 Hz, C), 132.72 (d, J=9 Hz, CH), 133.1 (C), 133.5 (d, J=11 Hz, CH), 133.6 (d, J=101 Hz, C), 134.3 (d, J=11 Hz, CH), 134.6 (d, J=34 Hz, C), 134.7 (d, J=36 Hz, C), 134.9 (d, J=11 Hz, C), 141.4 (dd, J=8, 5 Hz, C-17 or C-28), 142.2 (dd, J=7, 5 Hz, C-17 or C-28); 31P-NMR (162 MHz) ppm +12.9 (P-15), +26.1 (P-26); FAB-MS, m/z (relative intensity, %) 984 (47, M+H+).

The less polar material, compound 752, was obtained as a colorless solid (0.107 mg, 27%) with the following properties: mp 189-191 °C (CHCl3); IR (KBr) 2926, 1437, 1117 cm⁻¹; 1H-NMR (400 MHz) δ -0.07 (s, 3H, H-11 or H-12), -0.01 (s, 3H, H-11 or H-12), 0.63 (s, 3H, H-8 or H-9), 0.83 (s, 9H, H-14), 0.98 (s, 3H, H-8 or H-9), 1.20-1.40 (m, 1H), 1.47-1.71 (m, 5H), 1.96-2.07 (m, 1H, H-4), 2.33 (d, J=13.9 Hz, 1H, H-10a), 2.98 (d, J=13.9 Hz, 1H, H-10b), 3.93 (m, 1H, H-2), 6.36 (d, J=8.5, Hz, 1H), 6.50 (t, J=7.5 Hz, 1H), 6.96 (td, J=7.6, 3.0 Hz, 2H), 7.08-7.26 (m, 7H), 7.28-7.57 (m, 10H), 7.58-7.98 (m, 7H), 8.07 (dd, J=12.7, 5.3 Hz, 2H); 13C-NMR (100 MHz) ppm -4.3 (CH3, C-11 or C-12), -4.2 (CH3, C-11 or C-12), 18.3 (C, C-13), 20.8 (CH3, C-8 or C-9), 21.4 (CH3, C-8 or C-9), 26.6 (CH3, C-14), 27.8 (CH2, C-5 or C-6), 29.0 (CH2, C-5 or C-6), 42.9 (CH2, C-3), 44.8 (CH, C-4), 49.0 (C, C-1 or C-7), 50.7 (C, C-1 or C-7), 53.6 (d, J=4 Hz, CH2, C-10), 76.8 (CH, C-2), 124.8 (C), 125.9 (CH), 127.7 (d, J=5 Hz, CH), 127.75 (d, J=7 Hz, CH), 127.84 (CH), 127.9 (CH), 128.0 (CH), 128.1 (d, J=4 Hz, CH), 128.2 (d, J=12 Hz,
CH), 128.3 (d, J=3 Hz, CH), 128.6 (CH), 128.7 (CH), 128.9 (d, J=12 Hz, CH), 129.2 (d, J=76 Hz, C), 129.6 (d, J=15 Hz, CH), 130.3 (d, J=97 Hz, C), 131.3 (d, J=3 Hz, CH), 131.7 (d, J=3 Hz, CH), 131.8 (d, J=4 Hz, CH), 131.9 (d, J=9 Hz, CH), 132.0 (d, J=24 Hz, C), 132.2 (d, J=3 Hz, CH), 132.8 (d, J=10 Hz, CH), 132.9 (d, J=8 Hz, C), 133.2 (C), 133.4 (d, J=63 Hz, C), 133.5 (d, J=9 Hz, CH), 134.1 (d, J=2 Hz, CH), 134.2 (d, J=3 Hz, CH), 134.5 (d, J=53 Hz, C), 134.6 (d, J=53 Hz, C), 134.8 (d, J=10 Hz, C), 142.6 (dd, J=7, 5 Hz, C-17 or C-28), 143.2 (dd, J=6, 4 Hz, C-17 or C-28); $^3$P-NMR (162 MHz) ppm +13.2 (P-15), +27.1 (P-26); FAB-MS, m/z (relative intensity, %) 984 (21, M+H$^+$).

7.6.20 Reaction of (±)-BIPHEP (498) with (1S,2R)-O-(t-Butyldimethylsilyl)isobornyl-10-sulfonyl azide (693).

To a solution of racemic MeOBIPHEP$^{325}$ (498) (0.304 g, 0.546 mmol) in degassed toluene (10 mL) was added azide 693 (0.448 g, 1.20 mmol). The mixture was then heated to reflux under an argon atmosphere for 48 h. The cooled mixture was concentrated under reduced pressure to afford a thick yellow oil. $^3$P-NMR analysis of the crude material showed the complete consumption of starting material to yield four products 749-752 in an approximate 2:2:3:3 ratio. Subjecting the mixture to exhaustive flash chromatography (4:1) afforded bis-phosphinimine product 753 and an inseparable mixture of the diastereomeric bis-phosphinimine 754, and mono-phosphine oxides 755 and 756. Compound 753 had: IR (KBr) 2928, 1470, 1110 cm$^{-1}$; $^1$H-NMR (400 MHz) δ 0.05 (s, 3H, H-11 or H-12), 0.08 (s, 3H, H-11 or H-12), 0.58 (s, 3H, H-8 or H-9), 0.88 (s, 3H, H-8 or H-9), 0.91 (s, 9H, H-14), 1.22-1.31 (m, 1H), 1.45-1.70 (m, 5H),
1.78-1.92 (m, 1H, H-4) 2.08 (d, J=13.5 Hz, 1H, H-10a), 3.29 (d, J=13.5 Hz, 1H, H-10b), 3.47 (s, 3H, H-21), 3.99 (m, 1H, H-2), 6.81 (d, J=8.1 Hz, 1H), 7.09 (td, J=7.5, 3.1 Hz, 2H) 7.15-7.32 (m, 3H), 7.40-7.55 (m, 3H), 7.58 (d, J=7.6 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H), 7.86 (d, J=7.1 Hz, 1H), 7.89 (d, J=7.1 Hz, 1H); $^{13}$C-NMR (100 MHz) ppm -3.9 (CH$_3$, C-11 or C-12), -4.3 (CH$_3$, C-11 or C-12), 18.4 (C, C-13), 20.9 (CH$_3$, C-8 or C-9), 21.4 (CH$_3$, C-8 or C-9), 26.6 (CH$_3$, C-14), 27.8 (CH$_2$, C-5 or C-6), 29.6 (CH$_2$, C-5 or C-6), 43.0 (CH$_2$, C-3), 44.9 (CH, C-4), 49.0 (C, C-1 or C-7), 50.8 (C, C-1 or C-7), 53.6 (d, J=5 Hz, CH$_2$, C-10), 55.5 (CH$_3$, C-21), 76.5 (CH, C-2), 113.9 (d, J=3 Hz, CH, C-18), 126.8 (d, J=114 Hz, C), 127.1 (d, J=13 Hz, CH), 128.4 (d, J=13 Hz, CH), 128.6 (d, J=7 Hz, CH), 128.9 (d, J=17 Hz, CH), 129.5 (dd, J=7, 4 Hz, C), 130.8 (d, J=81 Hz, C), 130.8 (d, J=117 Hz, C), 131.9 (d, J=3 Hz, CH), 132.4 (d, J=3 Hz, CH), 133.7 (d, J=11 Hz, CH), 134.6 (d, J=11 Hz, CH), 157.9 (d, J=16 Hz, C, C-17); $^{31}$P-NMR (162 MHz) ppm +14.0; FAB-MS, m/z (relative intensity, %) 1273 (5, M$^+$), 1216 (9, M$^+$-C$_4$H$_9$), 70 (100).


39. The NMR spectral data and physical properties of compound 82 were consistent with the literature. See reference 36.
41. Bis(pinacolato)diboron may be purchased from the Aldrich Chemical Company at a price of 1g/$53.20 CDN or 5g/$228.00 CDN.
44. The literature was searched to the end of 1999 by Chemical Abstracts. No attempt was made to cover the patent literature.
46. The value of 2.28 Å was taken to be an intermediate length for M-P bonds. See: Corbridge, D.E.C., The Structural Chemistry of Phosphorus, Elsevier, Amsterdam, 1974.
47. The van der Waals of radius of an H atom is 0.1 nm and for the F atom it is 0.14 nm. See: Lehninger, A.L; Nelson, D.L.; Cox, M.M. Principles of Biochemistry, 2nd Ed. 1993, Worth Publishers, New York, pp. 61.
48. The cone angle for TFP has not been reported in the literature. The author has used the procedure described by Tolman to arrive at the 133° figure reported herein. See reference 45a for details.


75. The mechanism of Cine substitution has traditionally been thought to involve a β-elimination of a Pd-H species as shown. However, recent evidence has suggested involvement of a Pd(0) carbene intermediate. See Farina, V.; Hossain, M.A. *Tetrahedron Lett.* 1996, 37, 6997.


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127. Tributyltin hydride may be generated *in situ* from (Bu$_3$Sn)$_2$O and polymethylhydrosiloxane (PHMS). See: (a) Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am.


152. The turn over number (TON) can be a useful factor in evaluating catalyst performance. In this study TON/h⁻¹ = [(moles of iodobenzene) × (% conversion)]/[(moles of catalyst added) × (hours of reaction)]


191. A substructure search of the Chemical Abstracts database revealed 79 phosphines containing a 2-furyl or substituted 2-furyl moiety. Only those structures which have been reported in the literature as ligands in metal-catalyzed reactions are included in the text.


209. Atomic coordinates and thermal parameters were obtained from the Cambridge Crystallographic Database; Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EKK, U.K.


214. Molecular modeling was conducted with the Spartan® graphical interface (version 4.1.1, Wavefunction, Inc., Irvine, California, **1996**) at the AM1 level of theory.


236. X-ray crystallographic analysis was performed by Dr. M. Parvez at the University of Calgary on a Enraf-Nonius CAD-4 diffractometer with graphite monochromated Cu-Kα radiation. The following crystal parameters were obtained: monoclinic P2₁/n (No. 14); a=16.673(5) Å, b=18.478(7) Å, c=13.702(3) Å; V=4134(2) Å³; Z=4; R=0.053; Rw=0.041.


248. Optical rotation analysis on the L-(-)-tartrate adduct, isolated during the resolution procedure, indicated that the complex was a single diastereomer [α_D^{25} = +11.6° (c 1.1, H_2O)]. See: Galsbøl, F.; Steebøl, P.; Søndergaard Sørensen, B. *Acta Chem Scand.* 1972, 26, 3605.


263. BITIANP was prepared with minor modification to the reported literature procedure. See reference 220.


265. Enantiopure phosphinoaryl oxazoline ligand was prepared by M.J. Burke according to literature procedure. See: Lloyd-Jones, G.C.; Butts, C.P. *Tetrahedron* 1998, 54, 901.


268. X-ray crystallographic analysis was performed by Dr. M. Parvez at the University of Calgary on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation. The following crystal parameters were obtained: monoclinic P2₁ (No. 4); a=9.842(4) Å; b=21.045(5) Å; c= 10.347(3) Å; V=2031(1) Å³; Z=2; R=0.0406; Rw=0.0915; Flack Parameter [Flack, H.D. *Acta Crystallogr.* 1983, *A39*, 876] = 0.006(19). Bijvoet analysis was performed. A refinement of the inverted structure was carried out and converged with R=0.0465, Rw=0.1043 with Flack parameter = 0.20(2) and was therefore rejected as the absolute configuration present in the crystal.

269. X-ray crystallographic analysis was performed by Dr. R. McDonald at the University of Alberta on a Bruker P4 diffractometer equipped with a SMART 1000 CCD area detector using graphite monochromated Mo-Kα radiation. The following crystal parameters were obtained: monoclinic P2₁ (No. 4); a=16.248(2) Å; b=11.0208(16) Å; c= 35.643(5) Å; V=6372.8(15) Å³; Z=4; R=0.0696; Rw=0.2355.


See experimental section for further details.


292. Dr M. Scalone (Hoffman-La Roche) is thanked for supplying an unpublished procedure for the preparation chlorodi-2-furylphosphine.


295. For the Synthesis of (1S,2R)-O-(t-butyldimethylsilyl)isobornyl-10-sulfonyl azide and its use in the resolution of axially stereogenic diphenolines, see Chapter 6.


301. Fairlie, D.P.; Bosnich, B. Organometallics 1988, 7, 946.


306. The phosphines shown in Figure 6.1 were prepared and resolved by P.D. Ramsden.


323. X-ray crystallographic analysis was performed by Dr. M. Parvez at the University of Calgary. The following crystal parameters were obtained: orthorhombic $P2_12_12_1$ (No. 19); $a=12.337(4)$ Å, $b=12.833(3)$ Å, $c=18.751(2)$ Å, $V=2969(1)$ Å$^3$; $Z=4$; $R=0.0459$; $wR=0.1208$; Flack parameter $=-0.03(2)$. Bijvoet analysis was performed. A refinement of the inverted structure was carried out and converged with $R=0.0543$, $wR=0.1427$ with Flack parameter $=1.03(3)$ and was therefore rejected as the absolute configuration present in the crystal.


