Asymmetric Palladium-Catalyzed Reactions for the Synthesis of Pyrrolidines and Other Heterocycles

by

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Dedication

To Mom and Dad
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Abbreviations

AIBN ........................................................................................................ azobisisobutyronitrile
Ar ........................................................................................................ aryl
BINAP .................................................................................................. 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bz ........................................................................................................ benzoyl
Boc ....................................................................................................... tert-butylxocarbonyl
Cbz ...................................................................................................... carboxybenzyl
Cy2\NMe ............................................................................................. N-methyl dicyclohexylamine
dba ....................................................................................................... dibenzylideneacetone
DEAD ................................................................................................. diethyl azodicarboxylate
DIAD ................................................................................................... diisopropyl azodicarboxylate
DIP-Cl ................................................................................................. diisopinocampheyl chloroborane
DMAP ................................................................................................. 4-dimethylaminopyridine
dpe-phos ........................................................................................... bis(2-diphenylphosphinophenyl)ether
dppb ..................................................................................................... 1,2-bis(diphenylphosphino)benzene
dppf ..................................................................................................... 1,1’-(diphenylphosphino)ferrocene
EDC ................................................................................................. 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EH ....................................................................................................... 2-ethylhexanoate
HOAc ................................................................................................. acetic acid
HMPA ................................................................................................. hexamethylphosphoramide
LAH ................................................................................................. lithium aluminum hydride
MOM ................................................................................................. methoxy methyl
Mts ................................................................................................. 2-mesitylsulfonyl
Mtx ................................................................................................. methotrexate
NaO\tAm ........................................................................................... sodium tert-pentoxide
NaO\tBu ........................................................................................... sodium tert-butoxide
NCS ................................................................................................. N-chlorosuccinimide
NK1…………………………………………………………………………...neurokinin 1
NMP………………………………………………………………..…
OAc………………………………………………………………..acetate
PCC………………………………………………………………..pyridinium chlorochromate
PDC………………………………………………………………..pyridinium dichromate
Ph……………………………………………………………………..phenyl
Red-Al……………………………………………………………..sodium bis-(2-methoxyethoxy)aluminum hydride
SPhos……………………………………………………………..2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
TMS………………………………………………………………..trimethylsilyl
TBS………………………………………………………………..tert-butyldiemethylsilyl
TEMPO………………………………………………………………(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA………………………………………………………………..trifluoroacetic acid
TFAA……………………………………………………………..trifluoroacetic anhydride
Tf2O………………………………………………………………trifluoromethanesulfonic anhydride
THF………………………………………………………………...tetrahydrofuran
TMG………………………………………………………………..1,1,3,3-tetramethyl guanidine
Ts……………………………………………………………………..4-toluencesulfonyl
Abstract

The synthesis of nitrogen-containing heterocycles is important due to the fact that many biologically active molecules contain these motifs. Over the past 10 years, the Wolfe group has developed efficient and highly diastereoselective Pd-catalyzed carboamination reactions for the synthesis of pyrrolidines, ureas, pyrazolidines, isoxazolidines, morpholines and benzodiazepines in good yields. These transformations involve syn-insertion of an alkene into a Pd–N bond of an intermediate Pd-amido species followed by C–C bond forming reductive elimination. However, enantioselective variants that involve syn-aminopalladation are rare, and only two reports of enantioselective syn-aminopalladation have appeared in the literature.

An enantioselective synthesis of 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidines via Pd-catalyzed alkene carboamination reactions of N-Boc-pent-4-enylamines and aryl or alkenyl bromides is described. These transformations generate enantiomerically enriched pyrrolidine products with up to 94% ee. The application of this method has been demonstrated for the concise asymmetric synthesis of phenanthroindolizidine alkaloid (−)-tylophorine. Studies on asymmetric Pd-catalyzed desymmetrization reactions for the formation of cis-2,5-disubstituted pyrrolidines are also described.

A new enantioconvergent route for the asymmetric synthesis of (+)-aphanorphine has been accomplished using an asymmetric carboamination/Friedel-Crafts alkylation strategy. Enantioselective Pd-catalyzed carboamination reaction of a racemic γ-
aminoalkene derivative provides a 1:1 mixture of enantiomerically enriched diastereomers. This mixture of diastereomers is then converted to one stereoisomer via Friedel-Crafts reaction, which generates a quaternary stereocenter. Three additional steps provide the natural product.

Lastly, studies on asymmetric Pd-catalyzed reactions for the enantioselective synthesis of imidazolidin-2-ones, isoxazolidines, pyrazolidines and tetrahydrofurans are described. Promising ligand scaffolds have been identified and promising leads are being followed up by current group members.
Chapter 1

Introduction

1.1 Introduction to Wolfe Group Chemistry

The syn-insertion of alkenes into palladium-nitrogen bonds has been implicated as a key step in a number of important metal-catalyzed processes including alkene carboaminations, diaminations, and oxidative aminations. Over the past few years, the Wolfe group has developed efficient Pd-catalyzed carboamination reactions for the synthesis of N-heterocycles such as pyrrolidines, isoxazolidines, pyrazolidines, imidazolidin-2-ones, piperidines, and morpholines (Table 1-1). The attractive features of this carboamination reaction are: 1) up to 2 stereocenters are generated with concomitant formation of a C N and C C bond; 2) good yields and diastereoselectivity; and 3) the facile generation of analogs by varying the aryl/alkenyl coupling partner.
1.2 Mechanistic Considerations

The Pd-catalyzed carboamination reaction proceeds via the catalytic cycle shown below in Scheme 1-1. Oxidative addition of an aryl halide to Pd(0) precatalyst I-1 generates palladium complex I-2. Pd(0) is either generated from Pd$_2$(dba)$_3$ or a Pd(II) source such as Pd(OAc)$_2$, which is reduced to Pd(0) in situ. Base-mediated deprotonation of the γ-amino alkene I-3 and subsequent transmetallation affords Pd-amido complex I-4. Coordination and syn-insertion of the alkene into the Pd N bond via I-5 generates Pd alkyl intermediate I-6. Finally, C C bond forming reductive elimination affords the desired pyrrolidine I-7 and regenerates the Pd(0) catalyst (Scheme 1-1).
Scheme 1-1. Representative Catalytic Cycle

The high diastereoselectivity of these reactions arise from minimization of $A^{(1,3)}$-strain and 1,3-diaxial interactions.\textsuperscript{1a,1b} For example, carboamination reaction of \textit{N}-Boc-pent-4-enylamine derivatives \textit{I}-8 and \textit{I}-15 proceed in good selectivity for \textit{cis}-2,5-disubstituted pyrrolidines and \textit{trans}-2,3-disubstituted pyrrolidines respectively (Scheme 1-2).\textsuperscript{2c} The conversion of \textit{I}-8 to \textit{cis}-2,5-disubstituted pyrrolidine \textit{I}-11 can be rationalized via transition state \textit{I}-9, which would generate \textit{I}-10 and reductive elimination generates pyrrolidine product \textit{I}-11. Cyclization through \textit{I}-9 is favored because transition state \textit{I}-12 suffers from $A^{(1,3)}$-strain between the C1-phenyl group and the \textit{N}-Boc protecting group. Alternatively, substrates \textit{I}-15 bearing allylic substituents provide \textit{trans}-2,3-disubstituted pyrrolidine products \textit{I}-18 via transition state \textit{I}-16, which orient the C3-methyl group in
the more favorable pseudo-equatorial position to minimize $A^{(1,3)}$-strain and 1,3-diaxial interactions.

**Scheme 1-2.** Stereochemical Rationale for Diastereoselectivity

1.3 Enantioselective Alkene Functionalization Reactions

Enantioselective variants that involve syn-aminopalladation of alkenes are rare and to this date, only a few asymmetric Pd-catalyzed aminopalladation reactions that likely proceed through syn-insertion have been reported. Enantioselective Pd-catalyzed carboamination reactions between aryl/alkenyl halides and alkenes bearing pendant nitrogen atoms have not been previously reported.

1.3.1 Enantioselective Diamination Reactions

In 2007, Shi reported the first catalytic asymmetric diamination of conjugated dienes and trienes for the synthesis of imidazolidin-2-ones. As shown below, treatment
of di-tert-butylaziridinone I-19 and conjugated diene I-20 with a catalyst system generated from Pd$_2$(dba)$_3$ and tetramethylpiperidine-derived phosphoramidite ligand I-L1, gave diamination product I-21 in 91% yield and 92% ee (Scheme 1-3). A variety of dienes and trienes were employed, and the diamination reaction was highly selective for the internal alkene of the diene or triene. The steric bulk of the nitrogen substituent on I-L1 was imperative for high reactivity and enantioselectivity. For example, the use of a dimethylamine derivative of I-L1 only provided < 1% conversion.

Scheme 1-3. Asymmetric Diamination of Conjugated Dienes and Trienes

This reaction is believed to proceed via oxidative addition of I-19 to Pd(0) to generate Pd(II) intermediate I-22, which undergoes syn-aminopalladation to afford allylpalladium complex I-23. Reductive elimination from I-23 provides I-21 and regenerates the Pd(0) catalyst. Mechanistic studies on Pd(0)-catalyzed diamination of conjugated dienes with Pd(PPh$_3$)$_4$ support the formation of a four-membered Pd(0) intermediate I-22.$^7c$

The imidazolidin-2-one products can be further manipulated for the synthesis of optically active diamine compounds (Scheme 1-4).$^{7a}$ From imidazolidin-2-one I-24, deprotection with TFA and hydrochloric acid, followed by basic workup yields diamine
I-26 without erosion of enantioselectivity. I-24 can also be oxidized to generate imidazolidin-2-one derivative I-27. Selective mono deprotection of I-27 provides opportunities to introduce other functional groups onto the nitrogen atom of I-28. Deprotection of I-27 with TFA and treatment with 2 N HCl yields functionalized diamine I-29 in nearly quantitative yield.

**Scheme 1-4. Deprotection and Further Elaboration of Cyclic Urea I-24**

Chiral N-heterocyclic carbene Pd(0) complexes have also been effective for asymmetric diamination reactions of conjugated dienes and trienes (Scheme 1-5). For example, treatment of di-tert-butylaziridinone I-30 and diene I-31 with NHC-Pd(0) complex afforded imidazolidin-2-one I-32 in 88% yield and 76% ee. As compared to the Pd-phosphoramidite catalyst system described above, NHC Pd(0) complexes can potentially serve as better catalysts, since these catalysts are potentially more stable and subtle changes to the N-heterocyclic carbene structure seem to effect reactivity and enantioselectivities to a greater degree.
Scheme 1-5. Chiral N-Heterocyclic Carbene Pd(0) Catalyzed Diamination

1.32 Enantioselective Oxidative Amidation

Stahl recently reported a highly enantioselective intramolecular Wacker-type oxidative cyclization of internal alkenyl sulfonamides using a (pyrox)Pd(II)(TFA)$_2$ catalyst and O$_2$ as the sole stoichiometric oxidant for the synthesis of enantioenriched pyrrolidines (Scheme 1-6). As shown below, substrates such as I-33 were converted to I-34 using a catalyst system of Pd(TFA)$_2$ and pyridine-oxazoline ligand $(S)$-I-L2 in good-to-excellent yields and high enantioselectivities. Preliminary computational studies have revealed that the reaction may proceed through a rate-limiting and enantio-determining transition state such as I-35, where the vinylic methyl group in I-35 is oriented downward, away from the phenyl group, which leads to differentiation of the two enantiotopic faces of the alkene in the insertion step.
Scheme 1-6. Asymmetric Aerobic Oxidative Amidation

Catalyst-controlled stereoselective cyclization was also demonstrated for a number of chiral substrates (Scheme 1-6). For example, treatment of chiral substrate I-36 with the (R)- or (S)-enantiomer of I-L2 provided cis-2,4-disubstituted pyrrolidine I-37 or trans-2,4-disubstituted pyrrolidine I-38 in good yield and high diastereoselectivity respectively.

1.33 Enantioselective Oxidative Cascade Cyclization

Yang and coworkers reported the first enantioselective oxidative tandem cyclization for the synthesis of indolines, which proceeds through a mechanism involving aminopalladation followed by carbopalladation of the second alkene. As shown below, 2-allylaniline derivative I-39 was converted to I-40 through the treatment of I-39 with a catalyst system composed of Pd(OAc)_2 and tert-butyl quinoline-oxazoline ligand I-L3 with molecular oxygen as the sole oxidant afforded indolines I-40 in good yield and high
ee (Scheme I-7). The oxidative cascade cyclization typically yielded one diastereomer and the olefin geometry of the substrate was discovered to control the relative stereochemistry of the product. In addition, the stereochemical outcome of I-40 supports syn-aminopalladation as the only mechanistic pathway that leads to the product.

**Scheme I-7.** Pd(II)/t-Bu-Quinoline-Oxazoline Catalyzed Cascade Cyclization

1.34 **Copper(II)-Catalyzed Intramolecular Carboamination of Alkenes**

Chemler reported the first catalytic and enantioselective Cu-catalyzed syn-aminocupration of unactivated alkenes for the synthesis of chiral cyclic sulfonamides. As shown in Scheme 1-8, exposure of various N-(arylsulfonyl)-pent-4-enylamines I-43 with a catalyst system of Cu(OTf)$_2$ and bisoxazoline ligand I-L4 provided I-44 in good yields and enantioselectivities. A copper(II) source of Cu(OTf)$_2$ provided higher enantioselectivities than Cu(EH)$_2$, due to better ligand chelation. MnO$_2$ oxidant was imperative for higher catalyst turnover. Furthermore, changing the solvent from toluene to trifluorotoluene decreased formation of hydroamination side product. These chiral
sulfonamides (I-44) can also be converted to 2-(aryl methyl)pyrrolidines via reductive deprotection of SO₂ under dissolving metal conditions.

**Scheme 1-8.** Enantioselective Cu(II)-Catalyzed Carboamination

The catalytic cycle and rationale for enantioselectivity is described below in Scheme 1-9.¹⁰ᵇ,¹¹ Treatment of N-(arylsulfonyl)-pent-4-enylamine I-46 with copper(II) catalyst I-45 affords aminocuprate intermediate I-47. Intermediate I-47 is converted to I-49 through a presumed rate and enantiodetermining syn-aminocupration via transition state I-48. In this transition state, steric interactions are minimized where the N-substituent is facing in the opposite direction of the closest oxazoline phenyl substituent. C-C bond formation occurs via homolysis of the unstable carbon-copper(II) I-49 bond to generate primary carbon radical intermediate I-50, which adds into the tethered aryl ring. Oxidation and rearomatization of the resulting aryl cation produces chiral sulfonamide I-51. The Cu(I) species (I-52) is reoxidized and transmetallation of the substrate regenerates active Cu(II) catalyst I-47.
Chemler and coworkers have obtained evidence in support of this mechanism by trapping radical intermediate I-50 with TEMPO for an enantioselective aminooxygenation reaction (Scheme 1-10). Treatment of I-53 with a catalyst system of Cu(OTf)₂, cis-4,5-disubstituted phenyl bisoxazoline derivative I-L5 and 3 equivalents of TEMPO provided I-54 in 97% yield and 86% ee. TEMPO alone could promote copper catalyst turnover.
Pyrrolidine products such as I-54 were converted to aminoalcohol I-55 by reduction with Zn, or amino aldehyde derivative I-56 by oxidation with m-CPBA.

**Scheme 1-10.** Enantioselective Copper-Catalyzed Intramolecular Aminooxygenation

1.4 Other Enantioselective Pd-Catalyzed Reactions that Involve Alkene-Aminopalladation

There are several other synthetically useful enantioselective alkene aminopalladation reactions that proceed via anti-aminopalladation or an aminopalladation mechanism that has not been stereochemically defined. These reactions are attractive methods for the enantioselective synthesis of N-heterocycles such as imidazolidin-2-ones, oxazolidinones, amides, and β-amino acid derivatives.

A non-oxidative approach toward the asymmetric synthesis of N-heterocycles is Pd(II)-catalyzed alkene aminopalladation involving substrates bearing allylic acetates. In contrast to oxidative amination reactions described in Scheme 1-6, these transformations are terminated by β-elimination of the allylic acetate. These reactions no longer require oxidant, but substrates become more complex. Nonetheless, treatment of I-57 with catalytic amount of FOP catalyst affords ureas, amides and oxazolidinones (I-58) in high...
yield and enantioselectivities. Aminopalladation of I-57 proceeds through Pd alkyl intermediate I-59 and subsequent β-acetoxy elimination provides N-heterocycles I-58 and regenerates the active catalyst (Scheme 1-11).\(^\text{12}\)

**Scheme 1-11. Pd-Catalyzed Asymmetric Aminopalladation**

![Scheme 1-11](image)

Sasai and coworkers have reported a highly enantioselective aminocarbonylation reaction for the synthesis of bicyclic β-amino acid. A catalyst system of [Pd(MeCN)\(_4\)](BF\(_4\))\(_2\) and spiro bisisoxazoline ligand I-L6 was effective for the conversion of I-60 to I-61 in 89% yield and 88% ee (Scheme 1-12).\(^\text{13}\) The authors propose a mechanism that involves coordination of the alkene and nucleophilic attack to generate alkylpalladium complex I-62. CO insertion provides acylpalladium intermediate I-63, in which ring closure via nucleophilic trapping of I-63 by the tethered tosylamide yields I-61 and Pd(0), which is reoxidized by benzoquinone to regenerate the Pd(II) catalyst. However, the reaction requires low temperatures and long reaction times (ca. 7 days), there is potential for other spiro bisisoxazoline ligands to be employed as effective ligands for enantioselective oxidative cyclization reactions.
1.5 Summary

Over the past few years, the syn-insertion of alkenes into palladium-nitrogen bonds has been an important method for the synthesis of N-heterocycles. However, asymmetric variants are rare and there are only a few reports of enantioselective alkene functionalization reactions that proceed via syn-aminopalladation or other aminopalladation mechanisms. Our recent success in diastereoselective palladium-catalyzed carboamination reactions prompted us to explore an asymmetric variant. The following chapters in this thesis will describe the following: 1) our development of an asymmetric Pd-catalyzed carboamination reaction for the synthesis of 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidines; 2) preliminary studies on asymmetric Pd-catalyzed desymmetrization reactions; 3) the enantioconvergent synthesis of (+)-aphanorphine via Pd-catalyzed carboamination reaction; and 4) preliminary studies on asymmetric Pd-catalyzed reactions for the synthesis of biologically relevant 5-membered heterocycles.
References:


6 For a review on the reduction of Pd(OAc)$_2$ to Pd(0) in palladium-catalyzed Heck and cross-coupling reactions see: Amatore, C.; Jutand, A. *Acc. Chem. Res.* 2000, 33, 314.


8 McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* ASAP.


Chapter 2

Enantioselective Synthesis of 2-Substituted Pyrrolidines via Asymmetric Pd-Catalyzed Carboamination Reactions

2.1 Introduction

2-(Arylmethyl)pyrrolidines are prominent features of many natural products such as phenanthroindolizidine alkaloid tylophorine (II-1), homoharringtonine (II-2), preussin (II-3), and 3-benzomorphan aphanorphine (II-4), which exhibit anti-tumor, anti-leukemia, anti-fungal and analgesic activity respectively (Figure 2-1).¹

Figure 2-1. 2-(Arylmethyl)pyrrolidine Containing Natural Products

![Figure 2-1. 2-(Arylmethyl)pyrrolidine Containing Natural Products](image)

The 2-(arylmethyl)pyrrolidine motif is found in pharmaceutical leads II-5, and their absolute stereochemistry can have striking effects on biological activity.² For example, the $R$-enantiomer of pyrrolidine II-5 is a potent 5-HT₆ agonist, whereas the $S$-enantiomer displays antagonistic activity (Figure 2-2). 5-HT₆ serotonin receptors have been
implicated in anxiety, depression, cognition, and learning. Binding studies have also shown a high affinity of this receptor for certain anti-psychotic and anti-depressant drugs.

**Figure 2-2. 5-HT<sub>6</sub> Receptor-Active Compounds**

2-(Arylmethyl)pyrrolidines have also served as organocatalysts for enantioselective Michael additions. For example, Kotsuki and coworkers have developed chiral pyrrolidine catalyst (R)-II-L1 that contain an attached pyridine base, which facilitates enamine formation from ketone II-6 and acts as a proton shuttle. The pyridinium ring also effectively shields one side of the enamine forcing the nitroolefin acceptor II-7 to approach from the nonshielded side, providing highly enantioselective and diastereoselective formation of Michael adducts such as II-8 (Scheme 2-1).

**Scheme 2-1. Chiral Pyrrolidine/Pyridine Catalysts for Asymmetric Michael Addition Reactions**

\[
\text{II-6} \quad \text{II-7} \quad 10 \text{ mol } \% \text{ II-L1} \\
\text{CHCl}_{3}, \text{rt} \\
95\% \text{ yield, } 99\% \text{ ee syn/anti (98:2)}
\]

Acid = 2,4-dinitrobenzenesulfonic acid
Due to the importance of enantiomerically enriched 2-(arylmethyl)pyrrolidines in natural products, pharmaceutical leads, and organocatalysts, methods to synthesize 2-(arylmethyl)pyrrolidines are of interest to the synthetic community.

2.2 Recent Methods for the Asymmetric Synthesis of 2-(Arylmethyl)pyrrolidines

One of the most common methods for the synthesis of enantioenriched 2-(arylmethyl)pyrrolidines involves the addition of Grignard reagents to proline derivatives followed by reduction of the ketone (Scheme 2-2).\textsuperscript{6} Commercially available D-proline II-9 can be protected with ethyl trifluoroethanoate and converted to the mixed anhydride II-10 in 65% yield. Treatment of II-10 with various Grignard reagents followed by hydrogenolysis in acidic EtOH affords 2-(arylmethyl)pyrrolidines II-11 in low to moderate yields.

**Scheme 2-2.** Synthesis of 2-(Arylmethyl)pyrrolidines via Grignard Reactions


Jackson and coworkers have recently developed a new method for the synthesis of 2-(arylmethyl)pyrrolidines involving \textit{in situ} trapping of \textit{N}-Boc-2-pyrrolidinylmethylzinc iodide with aryl iodides (Scheme 2-3).\textsuperscript{7} Treatment of \textit{N}-Boc-prolinol (II-12) with PPh\textsubscript{3}, I\textsubscript{2} and imidazole produces alkyl iodide II-13 in 89% yield. \textit{N}-Boc-2-pyrrolidinylmethylzinc iodide is generated in situ from II-13, which undergoes Negishi coupling with an aryl iodide in the presence of catalytic Pd\textsubscript{2}(dba)\textsubscript{3} and SPhos to afford \textit{N}-Boc-2-(arylmethyl)pyrrolidines II-14 in low to good yields. Attempts to generate the proline-derived zinc reagent separately were unsuccessful, as the reagent underwent rapid
elimination to give the corresponding \( \gamma \)-amino alkene. The variable yields of 2-(arylmethyl)pyrrolidines II-14 are due to the instability of these alkyl zinc reagents and substrate-dependent rates of Negishi cross-coupling.

Scheme 2-3. Negishi Cross-Coupling for the Enantioselective Synthesis of 2-(Arylmethyl)pyrrolidines

As previously discussed in Chapter 1, Chemler has developed a copper-catalyzed carboamination reaction of \( N \)-sulfonyl alkenes II-15 for the synthesis of chiral sulfonamides II-16, which can be desulfonylated to provide the corresponding 2-(arylmethyl)pyrrolidines in good yields and enantioselectivities (Scheme 2-4). These reactions are rare examples of enantioselective carboamination involving alkene insertion into a Cu–N bond.

Scheme 2-4. Enantioselective Copper-Catalyzed Intramolecular Carboamination

Over the past few years, our group has developed a practical and efficient method for the diastereoselective synthesis of substituted pyrrolidines via Pd-catalyzed carboamination reactions between aryl/alkenyl bromides and \( \gamma \)-aminoalkene derivatives, which proceed in good yields and high diastereoselectivity. Our success in this endeavor prompted us to investigate an asymmetric variant of these transformations that would
generate enantiomerically enriched 2-(arylmethyl)pyrrolidines in a concise manner. The rest of Chapter 2 will describe our studies on the enantioselective synthesis of 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidines via asymmetric Pd-catalyzed carboamination reactions.

2.3 Project Goals and Previous Studies

As shown below in Scheme 2-5, our goal was to couple amine II-17 with an aryl or alkenyl halide for the synthesis of enantioenriched 2-(arylmethyl)pyrrolidines II-18. To accomplish this task, we needed to address the following: 1) identify a chiral ligand that would induce asymmetry in the C-N bond forming step (syn-aminopalladation); 2) optimize the reaction conditions for high yields and enantioselectivities; and 3) demonstrate utility through application of the asymmetric carboamination reaction toward the synthesis of a natural product.

Scheme 2-5. Synthetic Strategy

\[
\begin{align*}
\text{II-17} & \quad + \quad \text{R}^1-\text{X} \\
\text{PG} & \quad \text{NH} \\
\text{Base, Solvent, Temp} & \quad \text{Pd}, \text{L}^* \\
\rightarrow & \quad \text{II-18}
\end{align*}
\]

2.3.1 Previous Studies by Dr. Qifei Yang

Preliminary work on asymmetric Pd-catalyzed carboamination reactions was initially conducted by Dr. Qifei Yang, who was a former post-doctoral researcher in the Wolfe group. After a brief survey of ligands, Dr. Yang found that treatment of N-Phenyl-pent-4-enylamine II-19 and 2-bromonaphthalene with a catalyst system composed of Pd\(_2\)dba\(_3\) and (S)-Quinap facilitated formation of pyrrolidine II-20 in 30% yield and 10% ee (Scheme 2-6).\(^\text{10}\) The reaction was a proof of concept that asymmetric induction, albeit
low, could be achieved through the use of a chiral ligand. We wanted to explore this reaction in greater detail by examining the coupling of N-Boc-pent-4-enylamine derivatives with a variety of other chiral ligands.

Scheme 2-6. Previous Studies by Dr. Qifei Yang

2.4 Substrate Synthesis

A variety of substituted N-Boc-pent-4-enylamines were synthesized according to literature procedures.\textsuperscript{9f} 4-penten-1-ol derivatives (II-21\textsuperscript{23}) were converted to N-Boc-pent-4-enylamines (II-24a\textsuperscript{26}) via nucleophilic displacement of the alcohol, hydrazine monohydrate cleavage of the phthalimide and Boc protection of the free amine. N-Boc-pent-4-enylamines (II-24a\textsuperscript{26}) were obtained in good yields ranging from 69-81\% yield (Scheme 2-7).

Scheme 2-7. Synthesis of N-Boc-pent-4-enylamine Derivatives

2,2-dimethyl- and 2,2-diethoxy-N-Boc-pent-4-enylamines II-24b and II-24c were synthesized according to a procedure developed by Michael and coworkers.\textsuperscript{11} Deprotonation of 2,2-disubstituted nitrile (II-27 and II-28) with LDA produced the
corresponding lithium carbanion, which was allowed to react with allyl bromide to produce alkenyl derivatives II-29 and II-30 in good yield. LAH reduction of the nitrile followed by addition of Boc₂O provided 2,2-disubstituted N-Boc-pent-4-enylamines II-24b and II-24c in moderate yield (Scheme 2-8).

**Scheme 2-8.** Synthesis of 2,2-Dimethyl- and 2,2-Diethoxy-N-Boc-pent-4-enylamines

![Synthetic pathway](image)

2.5 **Optimization Studies: Ligand Screen/Ligand Synthesis**

In our initial experiments, we examined the coupling of N-Boc-pent-4-enylamine II-24a with 2-bromonaphthalene (Table 2-1). It was our hope that with the appropriate chiral ligand and reaction conditions, II-31a would be formed with some degree of asymmetric induction. Our prior studies with achiral catalysts indicated that chelating ligands with relatively large bite angles (e.g., dpe-phos or dppb)⁹e provided satisfactory yields of racemic products. Thus, we examined a series of chiral bis-phosphines for the carboamination reaction (Table 2-1). Unfortunately, ligands such as (S)-BINAP (II-L3) or (S)-PHANEPHOS (II-L7), which possess bite angles similar to dpe-phos and dppb, provided poor yields of II-31a, low enantioselectivities, or both. Other bis-phosphines such as (S,S)-BDPP (II-L9) and (R,R)-NORPHOS (II-L11) provided similar results. In summary, bidentate bis-phosphine ligands provided low conversion and enantioselectivity of pyrrolidine II-31a.
Table 2-1. Bidentate Phosphine Ligand Screen$^{a,b,c}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-L3</td>
<td>(S)-BINAP</td>
<td>10%</td>
<td>26%</td>
</tr>
<tr>
<td>II-L4</td>
<td>(S)-Tol-BINAP</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>II-L5</td>
<td>(S)-SEGPHOS</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>II-L6</td>
<td>(R,R)-DIOP</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>II-L7</td>
<td>(S)-PHANEPHOS</td>
<td>63%</td>
<td>-10%</td>
</tr>
<tr>
<td>II-L8</td>
<td>CTH-(R)-3,5-xylyl-PHANEPHOS</td>
<td>54%</td>
<td>20%</td>
</tr>
<tr>
<td>II-L9</td>
<td>(S,S)-BDPP</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>II-L10</td>
<td>(S,S)-CHIRAPHOS</td>
<td>56%</td>
<td>5%</td>
</tr>
<tr>
<td>II-L11</td>
<td>(R,R)-NORPHOS</td>
<td>33%</td>
<td>-7%</td>
</tr>
<tr>
<td>II-L12</td>
<td>catAsium D(R)</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>II-L13</td>
<td>(R,R)-Me-DuPhos</td>
<td>Decomposition</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtBu, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, toluene (0.15 M), 110 °C, 14 h. $^b$ Enantiomeric excess was determined by chiral HPLC analysis. $^c$ Negative ee values indicate the opposite enantiomer is formed.
A majority of the ferrocene-derived ligands examined provided no trace of pyrrolidine product (II-31a), as decomposition of the starting material was often observed (Table 2-2). However, Josiphos-derived ligands II-L17 and II-L20 provided II-31a in good yield. A comparison of these ligands seems to suggest that the substituent on the phosphorous atom has a dramatic impact on the yield of the reaction. Unfortunately, low enantioselectivity was observed for this class of ligands.
Table 2-2. Ferrocene-Derived Ligand Screen$^{a,b}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Reaction Scheme</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-L14</td>
<td>(R,S)-Josiphs Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L15</td>
<td>(R)-(-)-[(S)-2-(Dicyclohexylphosphino) ferrocenyl]ethyl(dicyclohexylphosphine) Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L16</td>
<td>(R)-(-)-1-[(S)-2-(Dicyclohexylphosphino) ferrocenyl]ethyl-di-tert-butylphosphine Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L17</td>
<td>(R)-(-)-1-[(S)-2-Diphenyl phosphinoferrocenyl]ethyl(3,5-dimethylphenylphosphine)</td>
<td>39%</td>
<td>0%</td>
</tr>
<tr>
<td>II-L18</td>
<td>(R)-(-)-1-[(S)-2-Diphenyl phosphinoferrocenyl]ethyl(3,5-dimethylphenylphosphine) Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L19</td>
<td>(S)-(+)-1-[(R)-2-(2-furylphosphino) ferrocenyl]ethyl(3,5-xylyl)phosphine</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>II-L20</td>
<td>(R)-(+)-1-[(R)-2-(2-Diphenylphosphinophenyl) ferrocenyl]ethyl(diphenyl)phosphine</td>
<td>69%</td>
<td>7%</td>
</tr>
<tr>
<td>II-L21</td>
<td>(S,S)-Et-Ferrotane Decomposition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtBu, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, toluene (0.15 M), 110 °C, 14 h. $^b$ Enantiomeric excess was determined by chiral HPLC analysis.
Several other monodentate ligands were screened as shown below in Table 2-3. BINOL-derived monodentate ligand (R)-MOP (II-L22) and chiral phosphite ligands (II-L25, II-L26 and II-L27) provided low yields, low enantioselectivities or both. Menthol-derived ligand (S)-NMDPP (II-L24) provided a promising lead with formation of II-31a in 76% yield and 18% ee. Ligands that are known to be effective for enantioselective Tsuji-Trost allylation (II-L28), copper-catalyzed carboamination reactions (II-L29), and oxidative cyclizations (II-L30) provided no desired product.
Table 2-3. Monodentate Phosphine, Phosphite and Nitrogen Ligand Screen$^{a,b}$

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-L22</td>
<td>(R)-MOP</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>II-L23</td>
<td>(R)-2-[2-(Diphenylphosphino)phenyl]-4-(1-methyl)phenyl-5-dihydroxazole</td>
<td>76%</td>
<td>18%</td>
</tr>
<tr>
<td>II-L24</td>
<td>(S)-NMDPP</td>
<td>57%</td>
<td>0%</td>
</tr>
<tr>
<td>II-L25</td>
<td>(S,S)-Reetz D-Diphosphonite</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>II-L26</td>
<td>18%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>II-L27</td>
<td>57%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>II-L28</td>
<td>(R,R)-DACH phenyl Trost Ligand</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>II-L29</td>
<td>(S,S)-PhBox</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>II-L30</td>
<td>(-)-Sparteine</td>
<td>Decomposition</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtfBu, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, toluene (0.15 M), 110 °C, 14 h. $^b$ Enantiomeric excess was determined by chiral HPLC analysis.
We then elected to investigate chiral phosphoramidite ligands, as several recent studies have demonstrated these ligands are highly effective in other Pd-catalyzed alkene addition reactions.\textsuperscript{12} As shown in Table 2-4, promising results were obtained with BINOL-derived phosphoramidites \((S,S,S)-\text{II-L41}\) and \((S,R,R)-\text{II-L42}\). Phosphoramidites composed of \((+)-\text{bis}[\text{R}-1\text{-phenethyl}]\text{amine derivatives were important for enantioselectivities, as decreased ee and lowered yields were observed for ligands containing achiral amine derivatives (II-L31−II-L36). Furthermore, the yield and enantioselectivity of the carboamination reaction was sensitive to minor changes to the structure of the ligand. For example, phosphoramidite ligand II-L38, which contained a \textit{trans}-2,5-disubstituted pyrrolidine, resulted in decomposition of the starting material, whereas dimethoxy-substituted ligand II-L40 provided pyrrolidine product II-31a in lower yield (14% yield), but similar ee as ligand \((S,R,R)-\text{II-L42}\) (65% ee).
Table 2-4. Phosphoramidite Ligand Screen\textsuperscript{a,b,c}

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Structure</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-L31</td>
<td><img src="image" alt="Structure II-L31" /></td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>(R)-MONOPHOS</td>
<td>(S)-Pipphos</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>15% yield, 5% ee</td>
<td>47% yield, 0% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L34</td>
<td><img src="image" alt="Structure II-L34" /></td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>(S)-Pipphos</td>
<td>(R)-MONOPHOS</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>2% yield, 0% ee</td>
<td>10% yield, 0% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L38</td>
<td><img src="image" alt="Structure II-L38" /></td>
<td>48%</td>
<td>-30%</td>
</tr>
<tr>
<td>(S)-Pipphos</td>
<td>(R)-MONOPHOS</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>48% yield, -30% ee</td>
<td>Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L39</td>
<td><img src="image" alt="Structure II-L39" /></td>
<td>36%</td>
<td>-20%</td>
</tr>
<tr>
<td>(S)-Pipphos</td>
<td>(R)-MONOPHOS</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>36% yield, -20% ee</td>
<td>10% yield, 20% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L40</td>
<td><img src="image" alt="Structure II-L40" /></td>
<td>14%</td>
<td>65%</td>
</tr>
<tr>
<td>(S)-Pipphos</td>
<td>(R)-MONOPHOS</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>14% yield, 65% ee</td>
<td>14% yield, 65% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S,S,S)-II-L41</td>
<td><img src="image" alt="Structure (S,S,S)-II-L41" /></td>
<td>57%</td>
<td>44%</td>
</tr>
<tr>
<td>(S)-Pipphos</td>
<td>(R)-MONOPHOS</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>(S,S,S)-II-L41</td>
<td>57% yield, 44% ee</td>
<td>57% yield, 44% ee</td>
<td></td>
</tr>
<tr>
<td>(S,R,R)-II-L42</td>
<td><img src="image" alt="Structure (S,R,R)-II-L42" /></td>
<td>63%</td>
<td>65%</td>
</tr>
<tr>
<td>(S)-Pipphos</td>
<td>(R)-MONOPHOS</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>(S,R,R)-II-L42</td>
<td>63% yield, 65% ee</td>
<td>63% yield, 65% ee</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtfBu, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, toluene (0.15 M), 110 °C, 14 h. \textsuperscript{b} Enantiomeric excess was determined by chiral HPLC analysis. \textsuperscript{c} Negative ee values indicate the opposite enantiomer is formed.
From the results shown in Table 2-4, phosphoramidites composed of (+)-bis[(R)-1-phenethyl]amine were important for enantioselectivity. We wanted to explore the effect of substitution on the binaphthol backbone of phosphoramidite ligand II-L42 and decided to synthesize a variety of binaphthol derivatives (Scheme 2-9). Starting from (S)-BINOL (II-L43), protection of the diol as a methoxy methyl ether proceeded in nearly quantitative yield to afford protected BINOL derivative II-L44. Treatment of II-L44 with 2 equivalents of n-BuLi followed by addition of MeI and then MOM-deprotection afforded methyl substituted BINOL derivative II-L45 in 70% yield over 2 steps. To install aryl substitution at the C3 and C3’ positions, II-L44 was first lithiated with n-BuLi and then quenched with 1,2-dibromotetrachloroethane to provide brominated analog II-L46. Coupling of II-46 and PhB(OH)2 in the presence of catalytic Pd(PPh3)4, Na2CO3 in DME at 90 °C and deprotection of the methoxymethyl ether afforded II-47 in 63% yield over 2 steps. To functionalize the C6 and C6’ positions of the BINOL backbone, II-L43 was exposed to neat bromine at -78 °C, which facilitated selective bromination. MOM-protection of diol II-L48 provided II-L49 in nearly quantitative yield. Coupling of II-L49 with PhB(OH)2 followed by deprotection of the methoxymethyl ether yielded II-L50 in 60% yield over 2 steps. With binaphthol derivatives II-L45, II-L47 and II-L50 in hand, we were ready to synthesize analogs of phosphoramidite ligand (S,R,R)-II-L42.
Scheme 2-9. Synthesis of BINOL Derivatives

Phosphoramidite ligands II-L51–II-L55 were synthesized in moderate yields according to a slightly modified procedure reported by Alexakis (Table 2-5). It was important to let the diol, PCl₃ and Et₃N stir for 30 minutes to ensure that the chlorophosphite had been formed. Then, addition of the chiral amine-HCl salt in CH₂Cl₂ afforded the phosphoramidite ligand in moderate yield. We found that CH₂Cl₂ was imperative for reactivity and solubility of the amine-HCl salt, since employing other procedures involving tetrahydrofuran or toluene failed. Higher yields of the phosphoramidite ligands could also be obtained when the free amine was used or by following a more rigorous procedure developed by Rajanbabu.
Table 2-5. Synthesis of Phosphoramidite Analogs

As shown in Table 2-6, the newly synthesized phosphoramidite ligands were examined. When ligands II-L51 and II-L52 were employed, low yields and enantioselectivities were observed, which suggests that steric components at C3 and C3’ negatively affect reactivity and selectivity. We then examined 6,6’-disubstituted ligand II-L53, but no increase in ee was observed. Changing the backbone from (S)-BINOL to 2,2’-biphenol (II-L54) decreased reaction yield and enantioselectivity (39% yield and 40% ee), which implies that the chirality of the BINOL backbone is important. (S)-H8-BINOL derived ligand II-L55 provided promising results with enantioselectivities up to 77% ee. Further exploration led to the discovery that spriobiindane-derived phosphoramidite (R)-Siphos-PE (II-L56) provided useful levels of enantioselectivities (81% ee).
Table 2-6. Other Phosphoramidite Ligand Screen$^{a,b}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-L51</td>
<td>Boc-Ph-N-Ph</td>
<td>2 mol % Pd(OAc)$_2$, 4 mol % Ligand, NaOtBu, Toluene, 110 °C</td>
<td>17%</td>
</tr>
<tr>
<td>II-L52</td>
<td>Decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-L53</td>
<td>Boc-N-Ph-Ph</td>
<td>40%</td>
<td>65% ee</td>
</tr>
<tr>
<td>II-L54</td>
<td>Boc-N-Ph-Ph</td>
<td>39%</td>
<td>40% ee</td>
</tr>
<tr>
<td>II-L55</td>
<td>Boc-N-Ph-Ph</td>
<td>40%</td>
<td>77% ee</td>
</tr>
<tr>
<td>II-L56</td>
<td>(R)-Siphos-PE</td>
<td>50%</td>
<td>81% ee</td>
</tr>
</tbody>
</table>

$^a$ Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtBu, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, toluene (0.15 M), 110 °C, 14 h. $^b$ Enantiomeric excess was determined by chiral HPLC analysis.

2.5.1 Optimization of Reaction Conditions

With a suitable ligand in hand, we sought to optimize the reaction conditions by first examining the effect of $N$-protecting groups on the carbaminoation reaction. The coupling of a variety of $N$-protected-pent-4-enylamine derivatives and 2-bromonaphthalene were surveyed in the presence of Pd(OAc)$_2$, (R)-Siphos-PE and NaOtBu (Table 2-7). $N$-aryl derivatives II-32a-e provided pyrrolidines II-33a-e in good yields, but no enantioselectivity was observed. Relative to the $N$-Boc protecting group, $N$-aryl protecting groups are less sterically demanding which could be responsible for the
reduction in ee. From these results, the N-Boc protecting group appears to be a key component for enantioselectivity in this reaction.

**Table 2-7. N-Protecting Group Study**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protecting Group</th>
<th>Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc (II-24a)</td>
<td>50% (II-31a)</td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td>Acyl (II-32a)</td>
<td>No Rxn (II-33a)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Benzoyl (II-32b)</td>
<td>No Rxn (II-33b)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>p-CNPh (II-32c)</td>
<td>63% (II-33c)</td>
<td>3%</td>
</tr>
<tr>
<td>5</td>
<td>PMP (II-32d)</td>
<td>61% (II-33d)</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>Cbz (II-32e)</td>
<td>No Rxn (II-33e)c,d</td>
<td>-</td>
</tr>
</tbody>
</table>

*a Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaO\text{tBu}, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, toluene (0.15 M), 110 °C, 14 h. b Enantiomeric excess was determined by chiral HPLC analysis. c 2 equiv of Cs$_2$CO$_3$ was used. d Use of dioxane as the solvent yielded similar results.

The effect of other reaction parameters such as base and solvent were explored. Efforts to employ weak bases such as Cs$_2$CO$_3$ and K$_3$PO$_4$ led to low conversion and in the latter case, diminished enantioselectivities. Stronger bases such as KOtBu increased decomposition of starting material (Table 2-8). Ethereal solvents such as tetrahydrofuran, dioxane, and diglyme were examined, but produced pyrrolidines in lowered yields.
Other palladium sources were surveyed but did not influence the enantioselectivity of the reaction. We elected to use Pd$_2$(dba)$_3$ as a general palladium source, since it was most effective across a broad range of coupling partners. It is important to note that the palladium source could be optimized for individual aryl halides for higher yields of pyrrolidine product if needed. Finally, a lower reaction temperature of 90 °C was optimal for reaction conversion. The reaction could also be conducted at lower temperatures (65 °C), but longer reaction times were needed. In general, the enantioselectivity remained constant across a range of temperatures (65−110 °C).

We found that the use of 2.5 mol % Pd$_2$(dba)$_3$ as a precatalyst, a ligand:metal ratio of 1.5:1, and a lowered reaction temperature of 90 °C produced II-31a in 78% yield and 82% ee. Before examining the scope of the reaction, we wanted to screen other
commercially available spirobiindane-derived ligands (Table 2-9). (S)-Siphos-PE (II-L57), the diastereomer of (R)-Siphos-PE (II-L56), provided pyrrolidine product II-31a in modest yield under the reaction conditions, but with opposite enantioregistration. From this result, it seems there is a matched pair for (R)-Siphos-PE and the spirobiindane diol is responsible for absolute configuration. Conversely, phosphite and phosphine ligands (R)-SHIP (II-L58) and (R)-SITCP (II-L59) produced lower yields and enantioselectivities. These results are consistent with previous ligand screens, which demonstrate the importance of the spirobiindane backbone and chiral amine on enantioselectivity.

**Table 2-9. Spirobiindane-Derived Ligand Screen**

<table>
<thead>
<tr>
<th></th>
<th>Boc</th>
<th>NH</th>
<th>2.5 mol % Pd₂(dba)₃</th>
<th>7.5 mol % Ligand</th>
<th>NaOₜBu, Toluene, 90 °C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>II-24a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>II-31a</td>
</tr>
<tr>
<td>II-L56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(R)-Siphos-PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78% yield, 82% ee</td>
</tr>
<tr>
<td>II-L57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(S)-Siphos-PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55% yield, -78% ee</td>
</tr>
<tr>
<td>II-L58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(R)-SHIP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47% yield, 25% ee</td>
</tr>
<tr>
<td>II-L59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(R)-SITCP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12% yield, 0% ee</td>
</tr>
</tbody>
</table>

*Conditions: Reactions were conducted on a 0.2 mmol scale with 1.0 equiv substrate, 2.0 equiv 2-bromonaphthalene, 1.0 equiv NaOₜBu, 2.5 mol % Pd₂(dba)₃, 7.5 mol % ligand, toluene (0.2 M), 90 °C, 12-15 h. *Enantiomeric excess was determined by chiral HPLC analysis. Negative ee values indicate opposite enantiomer is formed.*
2.6 Enantioselective Synthesis of 2-Substituted Pyrrolidines

The optimized conditions were effective for carboamination reactions between substrates II-24a-c and different aryl and alkenyl halide electrophiles. As shown in Table 2-10, these transformations for the coupling of aryl bromides proceeded in moderate to good yield and provided the desired products with ee’s ranging from 72 - 92%. Although most experiments were conducted on a small scale, the coupling II-24a with 2-bromonaphthalene gave nearly identical results on both small (0.2 mmol) and larger (1.0 mmol) scales (II-31a). Electron-donating groups on the aryl bromide were well tolerated as enantioselectivities up to 92% ee were observed (II-31j), although this method was less effective with electron-poor aryl bromides. For example, reactions of tert-butyl p-bromobenzoate (II-31g) and m-bromobenzotri fluoride (II-31k) proceeded in acceptable yields, but efforts to employ 2-(2-bromophenyl)-1,3-dioxalane, 3-bromobenzonitrile, and 4-bromobenzophenone were unsuccessful. Substrate II-24b bearing gem-dimethyl substitution at C2 was transformed in similar yields and selectivities as in the case of II-24a, although the use of a substrate bearing diethyl acetal at C2 (II-24c) gave pyrrolidine product with lower ee (II-31n). Use of aryl iodide electrophiles (II-31b, II-31d, II-31k) gave product yields and enantioselectivities similar to those obtained with aryl bromides, but significantly lower reaction times (1 h). Conversely, aryl chlorides were unreactive under these conditions, and low yields were obtained with aryl triflate coupling partners due to competing base-mediated cleavage of the sulfonate ester. Efforts to employ weak bases such as Cs₂CO₃ or K₃PO₄ led to low reactivity. Since oxidative addition is more challenging for aryl chlorides, attempts at heating the reaction to higher temperatures (136 °C) in xylenes to facilitate oxidative addition only led to substrate decomposition.
Table 2-10. Catalytic Asymmetric Synthesis of 2-(Arylmethyl)pyrrolidines\textsuperscript{a,b,c}

\begin{tabular}{|c|c|c|c|}
\hline
II-24a: & II-24b: & II-24c: & \textbf{2.5 mol} % Pd\textsubscript{2}(dba)\textsubscript{3} \\
R = H & R = Me & R = OEt & \textbf{7.5 mol} % (R)-Siphos-PE \\
\textbf{NaO}B\textsubscript{u}, Toluene, 90 °C & & & \\
\hline
\textbf{II-31a} & \textbf{II-31b} & \textbf{II-31c} & \\
78\% yield, 82\% ee & 75\% yield, 84\% ee & 73\% yield, 87\% ee & \\
(75\% yield, 82\% ee)\textsuperscript{d} & (74\% yield, 85\% ee)\textsuperscript{d} & & \\
\hline
\textbf{II-31d} & \textbf{II-31e} & \textbf{II-31f} & \\
72\% yield, 86\% ee & 64\% yield, 90\% ee & 68\% yield, 85\% ee & \\
(70\% yield, 86\% ee)\textsuperscript{f} & & & \\
\hline
\textbf{II-31g} & \textbf{II-31h} & \textbf{II-31i} & \\
61\% yield, 72\% ee & 66\% yield, 80\% ee & 80\% yield, 88\% ee & \\
\hline
\textbf{II-31j} & \textbf{II-31k} & \textbf{II-31l} & \\
70\% yield, 92\% ee & 70\% yield, 91\% ee & 80\% yield, 82\% ee & \\
(71\% yield, 91\% ee)\textsuperscript{g} & (71\% yield, 91\% ee)\textsuperscript{g} & & \\
\hline
\textbf{II-31m} & \textbf{II-31n} & & \\
69\% yield, 85\% ee & 64\% yield, 75\% ee & & \\
\hline
\end{tabular}

\textsuperscript{a} Conditions: Reactions were conducted on a 0.2 mmol scale with 1.0 equiv substrate, 2.0 equiv ArBr, 1.0 equiv NaO\textsubscript{B}u, 2.5 mol % Pd\textsubscript{2}(dba)\textsubscript{3}, 7.5 mol % ligand, toluene (0.2 M), 90 °C, 12-15 h. \textsuperscript{b} Enantiomeric excess was determined by chiral HPLC analysis. \textsuperscript{c} Isolated yield (average of two or more experiments). \textsuperscript{d} This reaction was conducted on a 1.0 mmol scale. \textsuperscript{e} 2.0 equiv of 2-iodotoluene was used. \textsuperscript{f} 2.0 equiv of 4-iodoanisole was used. \textsuperscript{g} 2.0 equiv of 3-iodobenzotrifluoride was used.
As shown below in Table 2-11, the best enantioselectivities were obtained with β-bromostyrene (up to 94% ee) as the electrophilic coupling partner (II-31o, II-31p). Alkenyl halides bearing aliphatic chains (II-31r, II-31s) were also effective coupling partners for the reaction. Two equivalents of the alkenyl coupling partner were required, since dimerization of the alkenyl bromide can be problematic. Low yields were obtained when low boiling alkenyl bromides such as 1-bromo-propene were employed in the reaction, even in excessive quantities.

Table 2-11. Catalytic Asymmetric Synthesis of 2-(Alkenylmethyl)pyrrolidines$^{a,b,c}$

<table>
<thead>
<tr>
<th></th>
<th>2.5 mol % Pd$_2$(dba)$_3$</th>
<th>7.5 mol % (R)-Siphos-PE</th>
<th>NaO$_t$Bu, Toluene, 90 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>R$^1$</td>
<td>R$^1$-X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-24a: R = H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-24b: R = Me</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-31o</td>
<td>R$^1$ = Ph</td>
<td>62% yield, 91% ee</td>
<td></td>
</tr>
<tr>
<td>II-31p</td>
<td>R$^1$ = Ph</td>
<td>61% yield, 94% ee</td>
<td></td>
</tr>
<tr>
<td>II-31q</td>
<td>R$^1$ = C$<em>8$H$</em>{17}$</td>
<td>70% yield, 93% ee</td>
<td></td>
</tr>
<tr>
<td>II-31r</td>
<td>R$^1$ = C$<em>8$H$</em>{17}$</td>
<td>62% yield, 91% ee</td>
<td></td>
</tr>
<tr>
<td>II-31s</td>
<td>R$^1$ = C$<em>8$H$</em>{17}$</td>
<td>61% yield, 82% ee</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Conditions: Reactions were conducted on a 0.2 mmol scale with 1.0 equiv substrate, 2.0 equiv alkenylBr, 1.0 equiv NaO$_t$Bu, 2.5 mol % Pd$_2$(dba)$_3$, 7.5 mol % ligand, toluene (0.2 M), 90 °C, 12-15 h.

$^b$ Enantiomeric excess was determined by chiral HPLC analysis. $^c$ Isolated yield (average of two or more experiments).

In general, side products were not observed in crude reaction mixtures, and it is likely that modest yields result from competing base-mediated substrate decomposition. Secondary tert-butyl carbamates have been shown to undergo elimination reactions to
afford reactive isocyanates when heated in the presence of NaO\textsubscript{t}Bu.\textsuperscript{17} When a solution of II-24\textsuperscript{a} and NaO\textsubscript{t}Bu in toluene-d\textsubscript{8} was heated to 90 °C for about 3 h, 35% decomposition of II-24\textsuperscript{a} to the isocyanate was observed.

1,1- and 1,2-disubstituted alkenes II-25 and II-26 were examined for the coupling of 2-bromonaphthalene (Scheme 2-10). Under the optimized reaction conditions, no pyrrolidine product formation was observed. Efforts to employ a combination of weaker bases (Cs\textsubscript{2}CO\textsubscript{3}, K\textsubscript{3}PO\textsubscript{4}), ethereal solvents (dioxane, diglyme) and higher temperatures often led to low conversion to pyrrolidine products (II-34 and II-35). Substitution on the alkene seems to shut down alkene insertion in the asymmetric carboamination reaction.

In our studies on intramolecular insertion of alkenes into Pd–N bonds, we have observed that dppf(Pd)(aryl)amido complexes that bear 1,1-disubstituted alkenes undergo slower syn-aminopalladation than the corresponding unsubstituted alkene dppf(Pd)(aryl)amido complexes.\textsuperscript{18}

Scheme 2-10. Asymmetric Carboamination of Substituted N-Boc-pent-4-enylamines

We were also interested in exploring the possibility of achieving catalyst control in substrates bearing stereocenters to provide disubstituted products that are hard to access with achiral catalysts. In previous studies on diastereoselective synthesis of pyrrolidines, the carboamination reaction proceeds in good selectivity for \textit{cis}-2,5-disubstituted pyrrolidines and \textit{trans}-2,3-disubstituted pyrrolidines.\textsuperscript{9} Our goal was to use our Pd/Siphos-PE system and override any inherent substrate control in the alkene
insertion step. This would potentially provide access to either pyrrolidine diastereomer via substrate-controlled achiral carboamination reaction (cis-2,5- and trans-2,3-disubstituted pyrrolidines) or catalyst-controlled asymmetric palladium reaction (trans-2,5 or cis-2,3-disubstituted pyrrolidines). We decided to test the feasibility of this idea with racemic substrates II-36 and II-37 (Scheme 2-11). If there was any catalyst control, a change in diastereoselectivity in favor of the trans-2,5-disubstituted and cis-2,3-disubstituted product would be observed respectively. Alternatively, a kinetic resolution of II-36 or II-37 could also occur. Unfortunately, subjecting racemic substrates II-36 and II-37 to the reaction conditions resulted in decomposition of the starting material and no product formation, which demonstrates the sensitivity of the Pd/Siphos-PE system to subtle changes to the substrate.

**Scheme 2-11. Catalyst Control vs. Substrate Control**

\[
\begin{align*}
\text{BocHN} & + \text{Br} \rightarrow \text{Decomposition of S.M.} \\
\text{II-36} & \quad 2.5 \text{ mol} \% \text{Pd}_2(\text{dba})_3 & 7.5 \text{ mol} \% (R)-\text{Siphos-PE} \\
\text{NaO} & , \text{Toluene, 90 °C} \\
\text{BocHN} & + \text{Br} \rightarrow \text{Decomposition of S.M.} \\
\text{II-37} & \quad 2.5 \text{ mol} \% \text{Pd}_2(\text{dba})_3 & 7.5 \text{ mol} \% (R)-\text{Siphos-PE} \\
\text{NaO} & , \text{Toluene, 90 °C}
\end{align*}
\]

2.7 **Total Synthesis of (−)-Tylophorine**

In order to illustrate the utility of the enantioselective carboamination reaction and establish the absolute configuration of the pyrrolidine products, a short total synthesis of (−)-tylophorine (II-1) was pursued (Scheme 2-12). (−)-Tylophorine is a phenanthroindolizidine alkaloid that exhibits potent antitumor and antiviral activities,\(^{19}\) and there has been considerable interest in the development of efficient synthetic routes
to tylophorine and other related phenanthroindolizidine alkaloids. Our enantioselective synthesis of (−)-tylophorine employs a route analogous to that developed by Herr for the construction of (±)-tylophorine. Aryl bromide II-38 was prepared in four steps and then coupled with II-24a using our Pd/Siphos-PE system. The coupling of II-24a and aryl bromide II-38 proceeded smoothly in 69% yield and 88% ee. Intermediate II-39 was converted to (−)-tylophorine (II-1) in two steps via deprotection of the Boc protecting group followed by treatment with refluxing formalin. The absolute stereochemistry of pyrrolidine products II-31a-s were assigned based on analogy to (−)-tylophorine (II-1).

Scheme 2-12. Synthesis of (−)-Tylophorine

2.8 Mechanistic Considerations

The mechanism of Pd/phosphine catalyzed alkene carboamination reactions is believed to involve intramolecular alkene insertion into the Pd N bond of an intermediate L_nPd(Ar)(NRR’) complex (e.g. II-40). Carbon carbon bond-forming reductive elimination from II-41 then leads to the formation of pyrrolidine products II-42.
that result from net suprafacial addition of the aryl and the nitrogen atom across the alkene (Scheme 2-13). Studies on the reactivity of (dppf)Pd(Ar)[N(Ar)(CH2)3CH=CH2 complexes have indicated that the rates of aminopalladation and reductive elimination are comparable and aminopalladation is not reversible under the stoichiometric conditions.  

**Scheme 2-13. Syn-Aminopalladation Mechanism**

It appears that the absolute stereochemistry of the product is determined during the C-N bond forming step (II-40 to II-41). However, the Pd/Siphos-PE system is different from the bidentate phosphine ligands (e.g., dpe-phos or dppb) used for the synthesis of racemic pyrrolidines. Thus, we sought to determine if the Pd/Siphos-PE system also occurred via syn-aminopalladation. As shown in Scheme 2-14, coupling of deuterated substrate II-24d and bromobenzene provided pyrrolidine product II-31t, which results from suprafacial addition of the alkene into the Pd N and suggests that both the asymmetric and nonasymmetric variants of the carboamination reaction proceed through similar pathways. The stereochemistry of II-31t was established by conversion to known compound II-43.

**Scheme 2-14. Deuterium-Labeling Study**
Although the precise structure of the transition state leading to the major enantiomer is not clear, our data provides some information about the enantiodetermining step. The enantioselectivities obtained in the conversion of II-24a to II-31a did not change when ligand:metal ratios were adjusted from 1:1 to 2:1, which suggests a monoligated palladium complex is involved in the enantiodetermining step. The poor asymmetric induction obtained with chiral bis-phosphines (Table 2-1) may be due to dissociation of one arm of the bis-phosphine ligand prior to aminopalladation, which would place much of the chiral steric bulk away from the reactive site. A related hypothesis has previously been invoked to account for the effect of reaction conditions on asymmetric induction in enantioselective intramolecular Heck reactions involving chiral bis-phosphine BINAP ligands.

The high selectivities obtained with these ligands in our carboamination reactions may likely arise from steric bulk and chiral elements on both the diol and amine groups. Toste and coworkers have reported X-ray structural data on AuCl-(R)-Siphos-PE complex II-44. As shown in Figure 2-3, these phosphoramidite ligands exhibit a high degree of steric bulk around the metal center, which appear to be projected around the metal center to a much greater degree than chiral-bis phosphines when bound to a single phosphorous atom.
2.9 Summary and Future Directions

In conclusion, we have developed enantioselective Pd-catalyzed alkene carboamination reactions that afford 2-(arylmethyl)- or 2-(alkenylmethyl)pyrrolidines) in good yields and enantioselectivities. This method provides access to an important class of nitrogen heterocycles and a new route to enantiomerically enriched phenanthroindolizidines. Further studies on the design of more efficient phosphoramidite ligand derivatives for these transformations are currently ongoing. We are also interested in synthesizing a variety of Pd/phosphoramidite complexes and performing modeling studies to gain insight on the structural features of the catalyst system that are responsible for asymmetric induction.
Experimental Section

General Considerations

All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Palladium acetate, tris(dibenzylideneacetone)dipalladium (0), allylpalladium chloride dimer, and dichlorobis(acetonitrile)palladium (II) were purchased from Strem Chemical Co. and used without further purification. (R)-Siphos-PE and all other ligands were either purchased from commercial sources (Strem Chemical Co. or Aldrich Chemical Co.) and used without further purification, or were synthesized according to published procedures.25 All aryl and alkenyl bromides, except for 9-bromo-2,3,6,7-tetramethoxyphenanthrene (II-38),21 (Z)-β-bromostyrene,26 (Z)-1-bromo-1-decene,27 and (E)-1-bromo-1-decene,27 were obtained from commercial sources and were used without further purification. Tert-butyl pent-4-en-1-ylcarbamate (II-24a),9f tert-butyl (2,2-dimethylpent-4-en-1-yl)carbamate (II-24b),11 (E)-tert-butyl-5-d-pent-4-en-1-ylcarbamate (II-24d),9f tert-butyl (1-phenylpent-4-en-1-yl)carbamate (II-25),9f and tert-butyl (3-methylpent-4-en-1-yl)carbamate (II-26)9f were prepared according to published procedures. Toluene was purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure by 1H NMR, GC and/or combustion analysis. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Table 2-10, Table 2-11, Scheme 2-12, and Scheme 2-14 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 2-10, Table 2-11, Scheme 2-12, and Scheme 2-14.

Experimental Procedures and Compound Characterization Data:

Synthesis of Substrate II-24c

2,2-Diethoxypent-4-enenitrile. A flame dried flask was cooled under a stream of nitrogen and charged with diisopropylamine (2.4 mL, 17.2 mmol) and THF (60 mL). The resulting solution was cooled to −78 °C, n-BuLi (6.8 mL, 17.2 mmol) was added dropwise, and the reaction mixture was stirred for 30 minutes at −78 °C.
Diethoxyacetanitrile (2 mL, 14.4 mmol) was added dropwise, the solution was stirred for 1 hr at –78 °C, then allyl bromide (1.5 mL, 17.2 mmol) was added dropwise and the mixture was warmed to rt and stirred for 12 h. The reaction mixture was then cooled to 0 °C and quenched with water (10 mL). The mixture was diluted with ether (50 mL), transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with ether (2 x 50 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography to afford 0.470 g (20%) of the title compound as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.88–5.75 (m, 1 H), 5.30–5.22 (m, 2H), 3.74–3.62 (m, 4 H), 2.67 (d, J = 6.8 Hz, 2 H), 1.25 (t, J = 6.8 Hz, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 129.7, 120.5, 116.0, 98.8, 59.9, 41.5, 14.8; IR (film) 1683, 1054 cm⁻¹; MS (ESI): 170.1172 (170.1176 calcd for C₉H₁₅NO₂, M + H⁺).

tert-Butyl (2,2-diethoxypent-4-en-1-yl)carbamate (II-24c). A flame dried flask was cooled under a stream of nitrogen and charged with a solution of LiAlH₄ in ether (4.2 mL, 4.2 mmol, 1 M). The solution was cooled to 0 °C and a solution of 2,2-diethoxypent-4-enenitrile (0.470 g, 2.8 mmol) in Et₂O (10 mL) was added dropwise. The resulting solution was stirred overnight at room temperature, then was diluted with 10 mL of ether, cooled to 0 °C. Water (0.16 mL) was added dropwise, followed by a solution of 10 M NaOH (0.16 mL) and additional water (0.48 mL). A white precipitate formed and adhered to the walls of the reaction vessel. The solution was decanted, and the precipitate was washed with ether (10 mL). The combined organic layers were filtered through celite, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in methylene chloride (15 mL) and solid Boc₂O (0.676 g, 3.1 mmol) was added. The resulting mixture was stirred at rt for 12 h, then the solution was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 500 mg (65%) of the title compound as a clear viscous oil. ¹H NMR (400 MHz, CDCl₃) δ 5.88–5.71 (m, 1 H), 5.14–5.06 (m, 2H), 4.58 (s, 1 H), 3.55–3.43 (m, 4 H), 3.28 (d, J = 6.0 Hz, 2 H), 2.40 (d, J = 7.2 Hz, 2 H), 1.44 (s, 9 H), 1.17 (t, J = 6.8 Hz, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 155.5, 132.6, 118.3, 101.1, 79.2, 55.9, 42.4, 38.1,
Synthesis and Characterization Data for Pyrrolidine Products


A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with Pd₂(dba)₃ (2.5 mol % complex, 5 mol % Pd), (R)-Siphos-PE (7.5 mol %) and NaOtBu (1.0-2.0 equiv). The tube was purged with nitrogen, then a solution of the amine substrate (0.2 mmol) and aryl halide (2.0 equiv) or alkenyl halide (2.0 equiv) in toluene (0.2 M) was added via syringe (aryl bromides that were solids at room temperature were added following the addition of NaOtBu). The mixture was heated to 90 °C with stirring until the starting material had been consumed as judged by GC or ¹H NMR analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH₄Cl (2 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo.

The crude product was purified by flash chromatography on silica gel.

(R)-(−)-tert-Butyl 2-(napthalen-2-ylmethyl)pyrrolidine-1-carboxylate (II-31a). The general procedure was employed for the coupling of 2-bromonaphthalene (83 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaOtBu (19 mg, 0.2 mmol). This procedure afforded 50 mg (80%) of the title compound as a pale yellow oil. Spectroscopic data were consistent with those previously reported in the literature.⁹e [α]₂₃⁰_D −3.9 (c 1.0, CH₂Cl₂). The enantiopurity was determined to be 82% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 15.7 and 17.0 min).
(R)-(−)-tert-Butyl 2-(-2-methylbenzyl)pyrrolidine-1-carboxylate (II-31b). The general procedure was employed for the coupling of 2-bromotoluene (69 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.20 mmol) and NaOEtBu (19 mg, 0.2 mmol). This procedure afforded 44 mg (80%) of the title compound as a pale yellow oil. Spectroscopic data were consistent with those previously reported in the literature.9e \([\alpha]_{D}^{23} = -22.0 \ (c\ 1.0, \ CH_2Cl_2)\). The enantiopurity was determined to be 84% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, \(\lambda = 254\) nm, RT = 9.7 and 10.8 min). When 2-iodotoluene (87 mg, 0.4 mmol) was employed as the coupling partner, this procedure afforded 40.5 mg (74%) of the title compound in 85% ee.

(Boc)

\[
\begin{align*}
\text{Boc} & \quad \text{CH}_3 \\
\text{N} & \quad \text{OMe}
\end{align*}
\]

(R)-(−)-tert-Butyl 2-(3-methoxybenzyl)pyrrolidine-1-carboxylate (II-31c). The general procedure was employed for the coupling of 3-bromoanisole (75 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaOEtBu (19 mg, 0.2 mmol). This procedure afforded 43.7 mg (75%) of the title compound as a pale yellow oil. \([\alpha]_{D}^{23} = -5.2 \ (c\ 1.0, \ CH_2Cl_2)\); \(^1\)H NMR (400 MHz, C\(_6\)D\(_5\)CD\(_3\), 100 °C) \(\delta\) 7.05–6.97 (m, 1 H), 6.77 (s, 1 H), 6.74 (d, \(J = 7.6\) Hz, 1 H), 6.63 (dd, \(J = 2.0, 8.4\) Hz, 1 H), 4.02–3.95 (m, 1 H), 3.45 (s, 3 H) 3.32–3.22 (m, 1 H), 3.20–3.04 (m, 2 H), 2.51 (dd, \(J = 9.2, 12.8\) Hz, 1 H), 1.53–1.30 (m, 13 H); \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_5\)CD\(_3\), 100 °C) \(\delta\) 160.6, 154.2, 141.3, 129.3, 122.2, 115.9, 112.2, 78.6, 59.0, 54.8, 46.8, 40.8, 29.9, 28.7, 23.4; IR (film) 1691, 1395 cm\(^{-1}\); MS (ESI) 314.1731 (314.1732 calcd for C\(_{17}\)H\(_{25}\)NO\(_3\), M + Na\(^+\)). The enantiopurity was determined to be 87% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, \(\lambda = 254\) nm, RT = 15.6 and 17.1 min).
(R)-(+)\-tert-Butyl-2-(4-methoxybenzyl)pyrrolidine-1-carboxylate (II-31d). The general procedure was employed for the coupling of 4-bromoanisole (75 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaO\textsubscript{t}Bu (19 mg, 0.2 mmol) using Pd\textsubscript{2}(dba\textsubscript{3}) (4.6 mg, 0.005 mmol) as the palladium source. This procedure afforded 39 mg (67%) of the title compound as a pale yellow oil. [\(\alpha\)]\textsubscript{23}\textsuperscript{D} +4.8 (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}). \textsuperscript{1}H NMR (400 MHz, C\textsubscript{6}D\textsubscript{5}CD\textsubscript{3}, 100 °C) \(\delta\) 7.03–6.97 (m, 2 H), 6.74–6.68 (m, 2 H), 4.00–3.92 (m, 1 H), 3.40–3.22 (m, 1 H), 3.03 (dd, \(J = 8.8, 13.2\) Hz, 1 H), 2.50 (dd, \(J = 8.8, 13.2\) Hz, 1 H), 1.54–1.32 (m, 13 H); \textsuperscript{13}C NMR (100 MHz, C\textsubscript{6}D\textsubscript{5}CD\textsubscript{3}, 100 °C) \(\delta\) 159.1, 154.2, 131.9, 129.0, 114.5, 78.5, 59.2, 54.9, 46.9, 39.8, 29.9, 28.7, 20.4; IR (film) 1691, 1392 cm\textsuperscript{-1}; MS (ESI) 314.1734 (314.1732 calcd for C\textsubscript{17}H\textsubscript{25}NO\textsubscript{3}, M + Na\textsuperscript{+}). The enantiopurity was determined to be 86% ee by chiral HPLC analysis (\(R,R\)-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, \(\lambda = 231\) nm, RT = 25.8 and 27.5 min). When 4-iodoanisole was employed as the coupling partner, this procedure afforded 40 mg (70%) of the title compound in 86% ee.

(R)-(+)\-tert-Butyl 2-{4-[(tert-butyldimethylsiloxy)benzyl]}pyrrolidine-1-carboxylate (II-31e). The general procedure was employed for the coupling of (4-bromophenoxy)-tert-butyltrimethylsilane (115 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaO\textsubscript{t}Bu (19 mg, 0.2 mmol). This procedure afforded 48 mg (61%) of the title compound as a pale yellow oil. [\(\alpha\)]\textsubscript{23}\textsuperscript{D} +8.9 (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}). \textsuperscript{1}H NMR (400 MHz, C\textsubscript{6}D\textsubscript{5}CD\textsubscript{3}, 100 °C) \(\delta\) 6.98 (d, \(J = 8.4\) Hz, 2 H), 6.73 (d, \(J = 8.4\) Hz, 2 H), 4.02–3.91 (m, 1 H), 3.35–3.23 (m, 1 H), 3.20–3.10 (m, 1 H), 3.01 (d, \(J = 13.2\) Hz, 1 H), 2.50 (dd, \(J = 8.8, 13.2\) Hz, 1 H), 1.47–1.31 (m, 13 H), 0.96 (s, 9 H), 0.12 (s, 6 H); \textsuperscript{13}C NMR (100 MHz, C\textsubscript{6}D\textsubscript{5}CD\textsubscript{3}, 100 °C) \(\delta\) 154.6, 132.6, 130.6, 129.0, 120.2, 78.5, 59.1, 36.8, 39.9, 29.9, 28.7, 23.9, 23.4, 18.4, -4.4; IR (film) 1691, 1653, 1394, 1256; MS (ESI)
414.2446 (414.2440 calcd for C\textsubscript{22}H\textsubscript{37}NO\textsubscript{3}Si, M + Na\textsuperscript{+}). The enantiopurity was determined to be 90% ee by chiral HPLC analysis (\textit{R},\textit{R}-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, \( \lambda = 254 \) nm, RT = 9.4 and 9.8 min).

\((\textit{R})-(+)-\text{tert-Butyl} \quad \text{2-[4-}\text{-}\text{tert-butyl} \text{dimethylsiloxy} \text{methylbenzyl} \text{pyrrolidine-1-carboxylate (II-31f).}\) The general procedure was employed for the coupling of 4-(\textit{tert}-butyl\textit{dimethylsilyl})-hydroxymethylbromobenzene (121 mg, 0.4 mmol) with \textit{tert}-butyl pent-4-en-1-ylcarbamate \textit{II-24a} (37 mg, 0.2 mmol) and NaOtBu (19 mg, 0.2 mmol). This procedure afforded 50 mg (62%) of the title compound as a pale yellow oil. \([\alpha]^{23}_D +0.8\) (\(c\ 1.0, \text{CH}_2\text{Cl}_2\)). \(^1\text{H} \text{NMR (}400 \text{ MHz, } C_6D_5CD_3, 100 \ ^\circ \text{C}) \delta 7.19\ (d, J = 7.2 \text{ Hz, } 2 \text{ H}), 7.10–7.05\ (m, 2 \text{ H}), 4.61\ (s, 2 \text{ H}), 4.01–3.94\ (m, 1 \text{ H}), 3.28\ (dd, J = 8.8, 17.6 \text{ Hz, } 1 \text{ H}), 3.18–3.05\ (m, 2 \text{ H}), 2.52\ (dd, J = 8.8, 12.4 \text{ Hz, } 1 \text{ H}), 1.48–1.30\ (m, 13 \text{ H}), 0.94\ (s, 9 \text{ H}), 0.04\ (s, 6 \text{ H}); \(^{13}\text{C} \text{NMR (}100 \text{ MHz, } C_6D_5CD_3, 100 \ ^\circ \text{C}) \delta 154.2, 139.7, 138.5, 129.6, 126.7, 78.6, 65.4, 59.1, 46.8, 40.4, 29.9, 28.7, 26.1, 23.4, 18.5, –5.2; \text{IR (film) } 1696, 1394 \ \text{cm}^{-1}; \text{MS (ESI) } 428.2602\ (428.2597 \text{ calcd for } C_{23}H_{39}NO_3Si, M + Na^+).\) The enantiopurity was determined to be 85% ee by chiral HPLC analysis (\textit{R},\textit{R}-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, \( \lambda = 254 \) nm, RT = 13.1 and 14.1 min).

\((\textit{R})-(+)-\text{tert-Butyl} \quad \text{2-[4-}\text{-}\text{tert-butyloxycarbonyl} \text{methylbenzyl} \text{pyrrolidine-1-carboxylate (II-31g).}\) The general procedure was employed for the coupling of \textit{tert}-butyl\text{-}4-bromobenzoate (103 mg, 0.4 mmol) with \textit{tert}-butyl pent-4-en-1-ylcarbamate \textit{II-24a} (37 mg, 0.2 mmol) and NaOtBu (19 mg, 0.2 mmol). This procedure afforded 46 mg (64%) of the title compound as a pale yellow oil. \([\alpha]^{23}_D +6.8\ (c\ 1.0, \text{CH}_2\text{Cl}_2).\) \(^1\text{H} \text{NMR (}400 \text{ MHz, } C_6D_5CD_3, 100 \ ^\circ \text{C}) \delta 7.96\ (d, J = 8.0 \text{ Hz, } 2 \text{ H}), 7.07\ (d, J = 8.0 \text{ Hz, } 2 \text{ H}), 3.98–3.89\ (m, 1 \text{ H}), 3.30–3.21\ (m, 1 \text{ H}), 3.14–3.04\ (m, 2 \text{ H}), 2.51\ (dd, J = 9.2, 12.4 \text{ Hz, } 1 \text{ H}), 1.48\ (s, 9
H), 1.46 (s, 9 H), 1.42–1.27 (m, 4 H); $^{13}$C NMR (100 MHz, C$_6$D$_5$CD$_3$, 100 °C) δ 165.5, 154.2, 144.4, 131.2, 129.9, 129.5, 80.2, 78.7, 58.8, 46.8, 40.6, 29.9, 28.7, 28.3, 23.4; IR (film) 1713, 1696, 1394 cm$^{-1}$; MS (ESI) 384.2153 (384.2151 calcd for C$_{21}$H$_{31}$NO$_4$, M + Na$^+$). The enantiopurity was determined to be 72% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 13.5 and 14.8 min).

(F)-(+)- tert-Butyl 2-(4-fluorobenzyl)pyrrolidine-1-carboxylate (II-31h). The general procedure was employed for the coupling of 1-bromo-4-fluorobenzene (70 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaO$t_Bu$ (19 mg, 0.2 mmol). This procedure afforded 37 mg (66%) of the title compound as a pale yellow oil. [$\alpha$]$^{23}_D$ +4.1 (c 1.0, CH$_2$Cl$_2$). $^1$H NMR (400 MHz, C$_6$D$_5$CD$_3$, 100 °C) δ 6.97–6.88 (m, 2 H), 6.79–6.72 (m, 2 H), 3.92–3.84 (m, 1 H), 3.30–3.21 (m, 1 H), 3.14–3.06 (m, 1 H), 2.97 (dd, J = 2.6, 13.2 Hz, 1 H), 2.48–2.40 (dd, J = 8.4, 12.8 Hz, 1 H), 1.45 (s, 9 H), 1.40–1.30 (m, 4 H); $^{13}$C NMR (100 MHz, C$_6$D$_5$CD$_3$, 100 °C) δ 162.2 (d, J = 243 Hz), 154.2, 135.4, 131.0 (d, J = 7.4 Hz), 115.2 (d, J = 20 Hz), 78.7, 58.9, 46.8, 39.8, 29.9, 28.7, 23.4; IR (film) 1692, 1394 cm$^{-1}$; MS (ESI) 302.1534 (302.1532 calcd for C$_{16}$H$_{22}$FNO$_2$, M + Na$^+$). The enantiopurity was determined to be 80% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 9.7 and 10.3 min).

(S)-(+) tert-Butyl 4,4-dimethyl-2-(naphthalen-2-ylmethyl)pyrrolidine-1-carboxylate (II-3i). The general procedure was employed for the coupling of 2-bromonaphthalene (83 mg, 0.4 mmol) with tert-butyl (2,2-dimethylpent-4-en-1-yl)carbamate II-24b (43 mg, 0.2 mmol) and NaO$t_Bu$ (19 mg, 0.2 mmol). This procedure afforded 55 mg (81%) of the title
compound as a pale yellow oil. \([\alpha]^{23}_D +31.7 \ (c \ 1.0, \ \text{CH}_2\text{Cl}_2)\). \(^1\text{H}\) NMR (400 MHz, 
C\(_6\)D\(_3\)CD\(_3\), 100 °C) \(\delta 7.62–6.53 \ (m, \ 4 \ H), 7.28 \ (d, \ J = 8.8 \ Hz, \ 1 \ H), 7.25–7.16 \ (m, \ 2 \ H), 4.16 \ (dq, \ J = 4.8, 8.0 \ Hz, \ 1 \ H), 3.50 \ (dd, \ J = 2.4, 12.8 \ Hz, \ 1 \ H), 3.38 \ (d, \ J = 10.4 \ Hz, \ 1 \ H), 2.83–2.75 \ (m, \ 2 \ H), 1.54–1.33 \ (m, \ 11 \ H), 0.79 \ (s, \ 3 \ H), 0.76 \ (s, \ 3H); \(^{13}\text{C}\) NMR (100 MHz, 
C\(_6\)D\(_3\)CD\(_3\), 100 °C) \(\delta 154.9, 137.1, 134.4, 132.9, 128.4, 128.2, 128.1, 127.9, 127.8, 125.9, 125.3, 78.7, 60.1, 59.0, 45.8, 41.6, 37.1, 28.7, 26.4, 26.1; IR (film) 1689, 1164 cm\(^{-1}\); MS (ESI) 362.2093 (362.2096 calcd for C\(_{22}\)H\(_{29}\)NO\(_2\), M + Na\(^+\)). The enantiopurity was determined to be 88% ee by chiral HPLC analysis (\(R,R\)-Whelk-O 1, 25 cm x 4.6 mm, 1% \(i\)PrOH/hexanes, 1 mL/min, \(\lambda = 254 \text{ nm}, \text{RT} = 11.2 \text{ and } 12.6 \text{ min}).

\[\text{(S)-(+)\text{-}\text{tert-Butyl} \ 2-[4-(dimethylamino)benzyl]-4,4-dimethylpyrroldine-1-carboxylate (II-31j)}\]. The general procedure was employed for the coupling of 4-bromo-N,N-dimethylaniline (80 mg, 0.4 mmol) with \text{tert-butyl} (2,2-dimethylpent-4-en-1-yl)carbamate II-24b (43 mg, 0.2 mmol) and NaO\(_{tBu}\) (19 mg, 0.2 mmol). This procedure afforded 44.6 mg (67%) of the title compound as a pale yellow oil. \([\alpha]^{23}_D +49.1 \ (c \ 1.0, \ \text{CH}_2\text{Cl}_2); \(^1\text{H}\) NMR (400 MHz, 
C\(_6\)D\(_3\)CD\(_3\), 100 °C) \(\delta 7.05–7.02 \ (m, \ 1 \ H), 6.96–6.94 \ (m, \ 1 \ H), 6.57–6.52 \ (m, \ 2 \ H), 4.09–4.00 \ (m, \ 1 \ H), 3.37 \ (d, \ J = 10.4 \ Hz, \ 1 \ H), 3.26 \ (dd, \ J = 2.4, 13.2 \ Hz, \ 1 \ H), 2.77 \ (d, \ J = 10.8 \ Hz, \ 1 \ H), 2.66–2.56 \ (m, \ 7 \ H), 1.49–1.33 \ (m, \ 11 \ H), 0.80 \ (s, \ 3 \ H), 0.76 \ (s, \ 3 \ H); \(^{13}\text{C}\) NMR (100 MHz, 
C\(_6\)D\(_3\)CD\(_3\), 100 °C) \(\delta 154.9, 149.9, 130.5, 113.5, 78.5, 60.1, 59.3, 45.8, 40.4, 37.0, 30.6, 28.8, 26.6, 26.2 \ (1 \ peak \ is \ missing \ due \ to \ incidental \ equivalence); \ IR (film) 1691, 1163 cm\(^{-1}\); MS (ESI) 333.2546 (333.2542 calcd for C\(_{20}\)H\(_{32}\)N\(_2\)O\(_2\), M + Na\(^+\)). The enantiopurity was determined to be 92% ee by chiral HPLC analysis (\(R,R\)-Whelk-O 1, 25 cm x 4.6 mm, 1% \(i\)PrOH/hexanes, 1 mL/min, \(\lambda = 254 \text{ nm}, \text{RT} = 19.4 \text{ and } 22.0 \text{ min}).
(S)-(+-)tert-Butyl 4,4-dimethyl-2-[3-(trifluoromethyl)benzyl]pyrrolidine-1-carboxylate (II-31k). The general procedure was employed for the coupling of 3-bromobenzotrifluoride (90 mg, 0.4 mmol) with tert-buty1 (2,2-dimethylpent-4-ene-1-yl)carbamate II-24b (43 mg, 0.2 mmol) and NaOtBu (19 mg, 0.2 mmol). This procedure afforded 50.2 mg (70%) of the title compound as a pale yellow oil [α]23D +25.2 (c 1.0, CH2Cl2); 1H NMR (400 MHz, C6D5CD3, 100 °C) δ 7.45 (s, 1 H), 7.27 (d, J = 7.6 Hz, 1 H), 7.15 (d, J = 7.6 Hz, 1 H), 7.04–6.97 (m, 1 H), 3.98 (m, 1 H), 3.31 (d, J = 10.4 Hz, 1 H), 3.18 (dd, J = 2.8, 12.8 Hz, 1 H), 2.70–2.62 (m, 2 H), 1.46 (s, 9 H), 1.42–1.32 (m, 1 H), 1.21–1.14 (m, 1 H), 0.75 (s, 3 H), 0.72 (s, 3 H); 13C NMR (100 MHz, C6D5CD3, 100 °C) δ 154.8, 140.7, 133.1, 131.2 (q, J = 31.7 Hz), 126.6, 126.3, 125.0 (q, J = 270 Hz), 123.2, 78.9, 60.0, 58.6, 45.4, 40.8, 37.1, 28.6, 26.3, 25.9 (one peak is missing due to incidental equivalence); IR (film) 1695, 1163 cm–1; MS (ESI) 380.1827 (380.1813 calcd for C19H26F3NO2, M + Na+). The enantiopurity was determined to be 91% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 0.5 mL/min, λ = 254 nm, RT = 14.6 and 15.9 min). When 3-iodobenzotrifluoride was employed as the coupling partner, this procedure affords the title compound in 72% yield and 91% ee.

(S)-(+-)tert-Butyl 2-[4-(tert-buty1)benzyl]-4,4-dimethylpyrrolidine-1-carboxylate (II-31l). The general procedure was employed for the coupling of 1-bromo-4-tert-butylbenzene (85 mg, 0.4 mmol) with tert-buty1 (2,2-dimethylpent-4-ene-1-yl)carbamate II-24b (43 mg, 0.2 mmol) using NaOtBu (19 mg, 0.2 mmol). This procedure afforded 48 mg (70%) of the title compound. [α]23D +25.7 (c 1.0, CH2Cl2). 1H NMR (400 MHz, C6D5CD3, 100 °C) δ 7.22 (d, J = 8.0 Hz, 2 H), 7.10 (d, J = 8.4 Hz, 2 H), 4.12–4.02 (m, 1 H), 3.42–3.30 (m, 2 H), 2.79 (d, J = 10.8 Hz, 1 H), 2.62 (dd, J = 8.8, 12.8 Hz, 1 H), 1.51–1.40 (m, 10 H), 1.36–1.21 (m, 10 H), 0.80 (s, 3 H), 0.75 (s, 3 H); 13C NMR (100 MHz,
C₆D₅CD₃, 100 °C) δ 154.9, 149.1, 136.5, 129.6, 125.3, 78.6, 60.1, 59.1, 45.9, 41.0, 37.1, 34.4, 31.5, 28.7, 26.5, 26.2; IR (film) 1694, 1394 cm⁻¹; MS (ESI) 368.2557 (368.2560 calc. for C₂₂H₃₅NO₂, M + Na⁺). The enantiopurity was determined to be 82% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 7.2 and 8.9 min).

(S)-(+)−tert-Butyl 2-(4-methoxybenzyl)-4,4-dimethylpyrrolidine-1-carboxylate (II-31m). The general procedure was employed for the coupling of 4-bromoanisole (75 mg, 0.4 mmol) with tert-butyl (2,2-dimethylpent-4-en-1-yl)carbamate II-24b (43 mg, 0.2 mmol) using NaOtBu (19 mg, 0.2 mmol). This procedure afforded 45 mg (70%) of the title compound as a pale yellow oil. [α]²³ D +39.1 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₅CD₃, 100 °C) δ 7.05–6.97 (m, 2 H), 6.72 (d, J = 8.8 Hz, 2 H), 4.08–3.99 (m, 1 H), 3.45–3.35 (m, 4 H), 3.26 (dd, J = 2.8, 13.2 Hz, 1 H) 2.76 (d, J = 10.8 Hz, 1 H), 2.63 (dd, J = 9.2, 13.2 Hz, 1 H), 1.53–1.42 (m, 10 H), 1.36–1.29 (s, 1 H), 0.81 (s, 3 H), 0.77 (s, 3 H); ¹³C NMR (100 MHz, C₆D₅CD₃, 100 °C) δ 159.1, 154.9, 131.6, 130.7, 114.4, 78.6, 60.1, 59.2, 54.9, 45.7, 40.4, 37.0, 28.7, 26.5, 26.4; IR (film) 1691, 1164 cm⁻¹; MS (ESI) 342.2038 (342.2045 calc. for C₁₉H₂₉NO₃, M + Na⁺). The enantiopurity was determined to be 85% ee by HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 11.7 and 13.5 min).
(S)-(+)–tert-Butyl 2-[(1,1′-biphenyl)-4-ylmethyl]-4,4-diethoxypyrrolidine-1-carboxylate (II-31n). The general procedure was employed for the coupling of 4-bromobiphenyl (70 mg, 0.4 mmol) with tert-butyl (2,2-diethoxypent-4-en-1-yl)carbamate II-24c (55 mg, 0.2 mmol) and NaOtBu (19 mg, 0.2 mmol). This procedure afforded 55 mg (65%) of the title compound as a pale yellow oil. \([\alpha]_D^{23} +6.0\) (c 1.0, CH2Cl2). 1H NMR (400 MHz, CDCl3, 25 °C) δ 7.44–7.36 (m, 4 H), 7.23–7.16 (m, 4 H), 7.11–7.08 (m, 1 H), 4.23–4.15 (m, 1 H), 3.81 (d, J = 11.6 Hz, 1 H), 3.40–3.23 (m, 6 H), 2.80 (dd, J = 9.6, 12.8 Hz, 1 H), 1.97–1.90 (m, 1 H), 1.86–1.79 (m, 1 H), 1.47 (s, 9 H), 1.03 (td, J = 7.2, 16.4 Hz, 6 H); 13C NMR (100 MHz, C6D5CD3, 100 °C) δ 154.6, 141.7, 139.8, 138.7, 130.1, 128.8, 127.4, 127.2, 127.1, 107.0, 79.0, 58.5, 57.9, 57.5, 53.6, 40.5, 30.9, 28.7, 15.4, 15.3; IR (film) 1696, 1394 cm⁻¹; MS (ESI) 448.2462 (448.2464 calcd for C26H35NO4, M + Na⁺). The enantiopurity was determined to be 75% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 17.7 and 20.7 min).

(R,E)-(+)–tert-Butyl 2-cinamylpyrrolidine-1-carboxylate (II-31o). The general procedure was employed using for the coupling of (E)-β-bromostyrene (73 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaOtBu (39 mg, 0.4 mmol) using Pd2(dba)3 (4.6 mg, 0.0015 mmol) as the palladium source. This procedure afforded 46.8 mg (81%) of the title compound as a pale yellow oil. Spectroscopic data were consistent with those previously reported in the literature.\[^9e\] \([\alpha]_D^{23} +38.2\) (c 1.0, CH2Cl2). The enantiopurity was determined to be 93% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 13.0 and 14.8 min).
(R,Z)-(+)–tert-Butyl 2-(3-phenylallyl)pyrrolidine-1-carboxylate (II-31p). The general procedure was employed for the coupling of (Z)-β-bromostyrene (73 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaOrBu (39 mg, 0.4 mmol) using Pd₂dba₃ (4.6 mg, 0.005 mmol) as the palladium source. This procedure afforded 36 mg (63%) of the title compound as a pale yellow oil. [α]²³D +55.3 (c 1.0, CH₂Cl₂). ¹H NMR (400 MHz, C₆D₅CD₃, 100 °C) δ 7.21 (d, J = 8.0 Hz, 2 H), 7.13 (t, J = 7.6 Hz, 2 H), 7.01 (d, J = 7.2 Hz, 1 H), 6.42 (d, J = 12.0 Hz, 1 H), 5.55 (td, J = 7.6, 11.6 Hz, 1 H), 3.84–3.79 (m, 1 H), 3.34–3.24 (m, 1 H), 3.18–3.09 (m, 1 H), 2.86–2.76 (m, 1 H), 2.38 (td, J = 7.6, 14.8 Hz, 1 H), 1.62–1.32 (m, 13 H); 13C NMR (125 MHz, C₆D₅CD₃, 100 °C) δ 154.3, 138.2, 131.2, 129.1, 128.3, 128.2, 126.7, 78.5, 57.6, 46.8, 33.7, 30.5, 28.6, 23.6; IR (film) 1692, 1392, 1170 cm⁻¹; MS (ESI) 310.1784 (310.1783 calcd for C₁₈H₂₅NO₂, M + Na⁺). The enantiopurity was determined to be 94% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 7.0 and 8.9 min).

(S,E)-(+)–tert-Butyl 2-cinanyl-4,4-dimethylpyrrolidine-1-carboxylate (II-31q). The general procedure was employed for the coupling of (E)-β-bromostyrene (73 mg, 0.4 mmol) with tert-butyl (2,2-dimethylpent-4-en-1-yl)carbamate II-24b (43 mg, 0.2 mmol) and NaOrBu (39 mg, 0.4 mmol). This procedure afforded 45 mg (72%) of the title compound as a pale yellow oil. [α]²³D +63.5 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₅CD₃, 100 °C) δ 7.20 (d, J = 7.6 Hz, 2 H), 7.01 (d, J = 7.2 Hz, 1 H), 6.42 (d, J = 12.0 Hz, 1 H), 5.55 (td, J = 7.6, 11.6 Hz, 1 H), 3.84–3.79 (m, 1 H), 3.34–3.24 (m, 1 H), 3.18–3.09 (m, 1 H), 2.86–2.76 (m, 1 H), 2.38 (td, J = 7.6, 14.8 Hz, 1 H), 1.62–1.32 (m, 13 H); 13C NMR (100 MHz, C₆D₅CD₃, 100 °C) δ 154.8, 138.5, 133.0, 128.6, 127.1, 127.0, 126.5, 78.6, 60.2, 57.5, 45.9, 38.8, 37.2,
28.7, 26.5, 26.1; IR (film) 1692, 1167 cm⁻¹; MS (ESI) 338.2086 (338.2091 calcd for C₂₀H₂₉NO₂, M + Na⁺). The enantiopurity was determined to be 93% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 9.3 and 11.2 min).

(R,Z)-(+)–tert-Butyl 2-(undec-2-en-1-yl)pyrrolidine-1-carboxylate (II-31r). The general procedure was employed for the coupling of (Z)-1-bromo-1-decene (88 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaOtBu (39 mg, 0.4 mmol). This procedure afforded 40 mg (62%) of the title compound as a pale yellow oil. [α]²³ D +32.3 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₅CD₃, 100 ºC) δ 5.50–5.41 (m, 1 H), 5.40–5.31 (m, 1 H), 3.85–3.77 (m, 1 H), 3.38–3.29 (m, 1 H), 3.26–3.18 (m, 1 H), 2.63–2.53 (m, 1 H), 2.20–2.04 (m, 2 H), 1.75–1.23 (m, 26 H), 0.83 (t, J = 6.8 Hz, 3 H); ¹³C NMR (125 MHz, C₆D₅CD₃, 100 ºC) 154.2, 132.3, 126.2, 78.4, 57.7, 46.9, 32.5, 32.2, 30.3, 30.1, 29.9, 29.7, 29.6, 28.7, 27.8, 23.7, 22.9, 13.9; IR (film) 1697, 1393; MS (ESI) 346.2726 (346.2722 calcd for C₂₀H₃₇NO₂, M + Na⁺). The enantiopurity was determined to be 91% ee by conversion to N-tosyl derivative S₁ followed by chiral HPLC analysis.

(R,Z)-(+)–1-Tosyl-2-(undec-2-en-1-yl)pyrrolidine (S₁). The conversion of (R,Z)-(+)–tert-butyl 2-(undec-2-en-1-yl)pyrrolidine-1-carboxylate (37 mg, 0.11 mmol) to the title compound was accomplished using a procedure analogous to that described above for the preparation of S₁. This procedure afforded 24.8 mg (60%) of the title compound as a pale yellow oil. [α]²³ D +78.2 (c 1.0, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.53–5.44 (m, 1 H), 5.39–5.29 (m, 1 H), 3.65–3.57 (m, 1 H), 3.45–3.37 (m, 1 H), 3.20–3.12 (m, 1 H), 2.64–2.56 (m, 1 H), 2.42 (s, 3 H), 2.31–2.21 (m, 1 H), 2.05 (q, J = 6.8 Hz, 2 H), 1.84–1.74 (m, 1 H), 1.63–1.44 (m, 3 H),
1.38–1.23 (m, 12 H), 0.88 (t, J = 6.4 Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.1, 134.9, 132.9, 129.5, 127.5, 124.9, 60.3, 49.1, 34.1, 31.9, 30.2, 29.6, 29.5, 29.3, 29.2, 27.5, 23.9, 22.6, 21.5, 14.1; IR (film) 1652, 1348, 1160 cm$^{-1}$; MS (ESI) 400.2290 (400.2286 calcd for C$_{22}$H$_{35}$NO$_2$S, M + Na$^+$). The enantiopurity was determined to be 91% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 1% iPrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 10.3 and 11.5 min).

(R,E)-(+)–tert-Butyl 2-(undec-2-en-1-yl)pyrrolidine-1-carboxylate (II-31s). The general procedure was employed for the coupling of (E)-1-bromo-1-decene (88 mg, 0.4 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (37 mg, 0.2 mmol) and NaOtBu (39 mg, 0.4 mmol). This procedure afforded 39 mg (60%) of the title compound as a pale oil. $[\alpha]^{23}_D$ +22.1 (c 1.0, CH$_2$Cl$_2$). $^1$H NMR (400 MHz, C$_6$D$_5$CD$_3$, 100 °C) δ 5.47–5.30 (m, 2 H), 3.82–3.73 (m, 1 H), 3.36–3.27 (m, 1 H), 3.22–3.14 (m, 1 H), 2.49–2.41 (m, 1 H), 1.96 (q, J = 6.8 Hz, 2 H), 1.65–1.21 (m, 26 H), 0.86, (t, J = 6.8 Hz, 3 H); $^{13}$C NMR (100 MHz, C$_6$D$_5$CD$_3$, 100 °C) δ 154.2, 133.2, 127.1, 78.3, 57.6, 46.8, 37.9, 33.0, 32.2, 30.2, 29.9, 29.8, 29.6, 29.5, 28.7, 23.6, 22.9, 13.9; IR (film) 1695, 1394 cm$^{-1}$; MS (ESI) 346.2717 (346.2722 calcd for C$_{20}$H$_{37}$NO$_2$, M + Na$^+$). The enantiopurity was determined to be 82% ee by conversion to N-tosyl derivative S2 followed by chiral HPLC analysis.

(R,E)-(+)–1-Tosyl-2-(undec-2-en-1-yl)pyrrolidine (S2). A flame dried flask was charged with (R,E)-(+)–tert-butyl 2-(undec-2-en-1-yl)pyrrolidine-1-carboxylate (34 mg, 0.11 mmol) and methylene chloride (1 mL). Trifluoroacetic acid (0.1 mL, 1.3 mmol) was added dropwise and the reaction was monitored by TLC analysis. Upon consumption of starting material, the solution was concentrated in vacuo. Benzene (5 mL) was added, and the resulting was concentrated to facilitate removal of trifluoroacetic acid. This procedure was repeated two additional times with 5 mL portions of benzene. The resulting crude
product was dissolved in ether (1 mL), and tosyl chloride (32 mg, 0.17 mmol) and triethylamine (77 μL, 0.55 mmol) were added. The resulting mixture was stirred at rt for ca 12 h, then additional ether (5 mL) was added and the mixture was washed with NaHCO₃ and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography to afford 23 mg (55%) of the title compound as a pale oil. [α]²³D +72.6. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 5.51–5.42 (m, 1 H), 5.38–5.30 (m, 1 H), 3.63–3.56 (m, 1 H), 3.40–3.33 (m, 1 H), 3.18–3.10 (m, 1 H), 2.54–2.47 (m, 1 H), 2.41 (s, 3 H), 2.26–2.16 (m, 1 H), 1.97 (q, J = 6.8 Hz, 2 H), 1.80–1.69 (m, 1 H), 1.66–1.42 (m, 3 H), 1.38–1.20 (m, 12 H), 0.86 (t, J = 6.8 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 143.1, 134.8, 133.9, 129.5, 127.4, 125.6, 60.1, 49.1, 39.5, 32.6, 31.8, 29.8, 29.4, 29.3, 29.2, 29.1, 23.9, 22.6, 21.4, 14.0; IR (film) 1348, 1160 cm⁻¹; MS (ESI) 400.2283 (400.2286 calcd for C₂₂H₃₅NO₂S). The enantiopurity was determined to be 82% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 1% iPrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 15.7 and 17.4 min).

(R)-(–)-tert-Butyl-2-[(2,3,6,7-tetramethoxyphenanthrene-9-yl)methyl]pyrrolidine-1-carboxylate (II-39). The general procedure was employed for the coupling of 9-bromo-2,3,6,7-tetramethoxyphenanthrene II-38 (38 mg, 0.1 mmol) with tert-butyl pent-4-en-1-ylcarbamate II-24a (24 mg, 0.13 mmol). This procedure afforded 30 mg (62%) of the title compound as an off-white solid. mp: 92–95 °C; [α]²³D –74.0 (c 0.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃, 25 °C) δ 8.30 (s, 1 H), 7.81 (s, 1 H), 7.78 (s, 1 H), 7.36 (s, 1 H), 7.17 (s, 1 H), 4.30–4.19 (m, 4 H), 4.12 (s, 3 H), 4.11 (s, 3 H), 4.02 (s, 3 H), 3.92 (d, J = 5.4 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.36–3.29 (m, 1 H), 2.59 (t, J = 11.9 Hz, 1 H), 2.05–1.98 (m, 1 H), 1.88–1.78 (m, 2 H), 1.75–1.63 (m, 1 H), 1.51 (s, 9 H). The enantiopurity
was determined to be 88% ee by transforming the title compound to (R)-(−)-tylophorine and assaying by chiral HPLC.

(R)-(−)-Tylophorine (II-I). The title compound was synthesized following the procedure reported by Herr. A mixture of (R)-(−)-tert-butyl-2-[(2,3,6,7-tetramethoxyphenanthrene-9-yl)methyl]pyrrolidine-1-carboxylate II-39 (33 mg, 0.07 mmol) in a solution of HCl in methanol (2.0 mL, 1.25 M, 2.5 mmol) was stirred at room temperature under nitrogen for 4 h. A 37% solution of formalin (2.0 mL, 24.6 mmol) was added and the mixture was refluxed overnight. The reaction mixture was cooled to room temperature and diluted with water (5 mL) and aqueous 2 M NaOH (10 mL). The resulting mixture was extracted with methylene chloride (3 x 10 mL), then the organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to provide (R)-(−)-tylophorine as a light yellow solid (27 mg, 99 % yield), mp: 272–274 °C (lit. mp: 273 – 275 °C). [α]$_{D}^{23}$ = −62.0 (c 0.10, CHCl$_3$) (lit. [α]$_{D}^{30}$ = −76.0 (c 0.10, CHCl$_3$).$^{28}$ $^1$H NMR (400 MHz, CDCl$_3$) δ 7.83 (d, $J$ = 2 Hz, 2 H), 7.32 (s, 1 H), 7.17 (s, 1 H), 4.63 (d, $J$ = 14.4 Hz, 1 H), 4.11 (s, 6 H), 4.05 (s, 6 H), 3.67 (d, $J$ = 14.8 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.41–3.34 (m, 1 H), 2.96–2.87 (m, 1 H), 2.55–2.42 (m, 2 H), 2.30–2.20 (m, 1 H), 2.11–1.99 (m, 1 H), 1.97–1.90 (m, 1 H), 1.84–1.73 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.7, 148.5, 148.4, 126.3, 125.8, 124.3, 123.6, 123.4, 103.9, 103.4, 103.2, 103.1, 60.2, 56.0, 55.9, 55.2, 54.0, 33.8, 31.3, 21.6 (4 peaks are missing due to incidental equivalence). Spectroscopic properties were consistent with those reported in the literature.$^{28}$ The enantiopurity was determined to be 88% ee by chiral HPLC analysis (chiralcel AD-H, 0.46 cm x 25 cm, 25% iPrOH/hexanes 0.1% Et$_3$N, 1.0 mL/min, $\lambda$ = 254 nm, RT = 10.0 and 12.7 min).
Deuterium Labeling Studies

(1R,2S)-(−)-tert-Butyl [2d-(2-benzylpyrrolidine)]-1-carboxylate (II-31t). The general procedure was employed for the coupling of bromobenzene (126 mg, 0.8 mmol) with (E)-tert-butyl-5-d-pent-4-en-1-ylcarbamate II-24d (75 mg, 0.4 mmol, 80% d-incorporation). This procedure afforded 66 mg (63%) of the title compound as a pale yellow oil with 80% d-incorporation. No loss or migration of the isotope was observed. 

\[ \alpha \] _D$^\text{23}$ = −1.0 (c 1.0, CH$_2$Cl$_2$). $^1$H NMR (400 MHz, C$_6$D$_5$CD$_3$, 100 °C) $\delta$ 7.13–6.98 (m, 5 H), 4.00–3.94 (m, 1 H), 3.32–3.23 (m, 1 H), 3.17–3.04 (m, 2 H), 1.50–1.30 (m, 13 H); $^{13}$C NMR (125 MHz, C$_6$D$_5$CD$_3$, 100 °C) $\delta$ 154.2, 139.8, 129.7, 128.5, 126.3, 78.6, 58.9, 46.8, 40.4 (m), 29.9, 28.7, 23.3; IR (film) 1686, 1394 cm$^{-1}$; MS (ESI) 285.1685 (285.1689 calcd for C$_{16}$H$_{22}$DNO$_2$, M + Na$^+$). The enantiopurity was determined to be 86% ee by chiral HPLC analysis (R,R-Whelk-O 1, 25 cm x 4.6 mm, 1% iPrOH/hexanes, 1 mL/min, $\lambda$ = 254 nm, RT = 10.4 and 11.2 min). The relative stereochemistry of II-31t was assigned by conversion to II-43 as shown below.

(10S,10aR)-(−)-10-d-2,3,10a-Tetrahydropyrrolo[1,2-b]isoquinolin-5(1H)-one (II-43). A flame dried flask was cooled under a stream of nitrogen and charged with (1R,2S)-(−)-tert-butyl [2d-(2-benzylpyrrolidine)]-1-carboxylate II-31t (60 mg, 0.23 mmol) and 4-dimethylaminopyridine (85 mg, 0.69 mmol). The flask was purged with nitrogen, CH$_2$Cl$_2$ (6 mL) was added, and the resulting solution was cooled to 0 °C. A solution of triflic anhydride (0.2 mL, 1.15 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise, and the resulting cloudy mixture was allowed to warm to rt and stir overnight. A solution of Na$_2$CO$_3$ (10 mL, 1 M) was added, the resulting mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 5 mL) and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in
The crude product was purified by flash chromatography on silica gel to afford 22 mg (51%) of the title compound as a colorless solid with ~80% deuterium incorporation as judged by $^1$H NMR analysis. The relative stereochemistry was assigned by comparison of $^1$H NMR data to those previously obtained for this known compound.$^9$ $[^{\alpha}]^{23}_D$ $-$140.0 (c 1.0, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 8.51–8.47 (m, 1 H), 7.11–7.06 (m, 2 H), 6.81–6.77 (m, 1 H), 3.62–3.56 (m, 1 H), 3.46–3.38 (m, 1 H), 3.12–3.05 (m, 1 H), 2.15 (d, $J$ = 13.5 Hz, 1 H), 1.47–1.41 (m, 1 H), 1.37–1.30 (m, 1 H), 1.17–1.07 (m, 1 H), 0.98–0.90 (m, 1 H).
References:


10 Qifei Yang, unpublished results.


24 No X-ray structural data for palladium complexes of (R)-Siphos-PE (II-L56) has been reported in the literature. However, this is evident in X-ray data reported for an


Chapter 3

Preliminary Studies on Enantioselective Pd-Catalyzed Desymmetrization Reactions for the Synthesis of cis-2,5-Disubstituted Pyrrolidines

3.1 Introduction

The enantioselective desymmetrization of prochiral or achiral compounds is one of the most common and powerful methods for the synthesis of enantioenriched molecules. Desymmetrization of symmetrical substrates can be achieved with a chiral, nonracemic reagent or catalyst, where the differentiation of rate between two enantiotopic groups allow, in principle, for selective formation of one enantioenriched product. In addition, desymmetrization reactions can provide enantioenriched products that contain quaternary centers that are challenging to synthesize. Desymmetrization reactions have also been used in a variety of transformations for the synthesis of enantioenriched alcohols, amines, bicyclic heterocycles and natural products. This chapter will focus on our ongoing efforts toward the development of an enantioselective Pd-catalyzed desymmetrization carboamination reaction. Preliminary studies with readily available chiral ligands have identified promising ligand scaffolds.

3.2 Enantioselective Pd-Catalyzed Desymmetrization Reactions

In order to provide context for our work in this area, a brief summary of Pd-catalyzed desymmetrization reactions that involve alkene insertion is presented in this
section. The Heck reaction is an important method for carbon-carbon bond formation, and the first examples of asymmetric Heck reactions were independently reported by Shibasaki and Overman in 1989. Shibasaki’s report described the first enantioselective desymmetrization reaction of racemic alkenyl iodide III-1, which afforded cis-decalin derivative III-2. A catalyst composed of Pd(OAc)\(_2\), and \((R)\)-BINAP was able to effect the formation of III-2 in 74% yield and 46% ee (Scheme 3-1). Further studies led to the use of alkenyl triflate substrates III-3 and III-4, which respectively led to III-5 and III-6 with drastic improvements in enantioselectivity (up to 91% ee). It is hypothesized that Heck reactions employing aryl and alkenyl triflates coupling partners proceed via a cationic pathway, where stable bidentate phosphine palladium interactions are potentially responsible for high enantioselectivities. One of the benefits of employing triflate coupling partners is that costly silver salts can be replaced with inexpensive bases such as K\(_2\)CO\(_3\), and hydrocarbon solvents could be used in place of NMP.

Scheme 3-1. First Enantioselective Heck Desymmetrization Reaction

More recently, phosphoramidites and amino acid derivatives have been identified as efficient ligands for asymmetric Heck desymmetrization reactions. As shown in Scheme 3-2, Feringa and coworkers developed an intramolecular asymmetric Heck reaction of cyclohexadienones III-7 to generate tricyclic III-8, which is catalyzed by Pd(OAc)\(_2\) and phosphoramidite ligand III-L1 (Scheme 3-2). It is important to note that the stereocenter generated is not created at the site of C-C bond formation, but rather
through a desymmetrization of the substrate itself. The use of an aryl triflate derivative of III-7 resulted in lower reaction conversions, and the addition of silver salts did not lead to improvement.

**Scheme 3-2.** Pd/Phosphoramidite Catalyzed Desymmetrization Reaction

Yu and coworkers have described a unique enantioselective CH olefination reaction catalyzed by α-amino acids. The reaction couples diphenylacetic acid derivatives III-9 with styrene derivatives using Pd(OAc)$_2$ and Boc-Ile-OH$\cdot$H$_2$O (III-L2) as a catalyst, to provide products such as III-10 in good yields and high selectivity. The authors propose that upon CH activation, the reaction proceeds through a boat-like intermediate (III-11), which the authors propose is responsible for high asymmetric induction for the formation of III-10 (Scheme 3-3).

**Scheme 3-3.** Enantioselective Pd-Catalyzed CH Olefination
Pd-catalyzed asymmetric allylic substitution reactions have also emerged as an efficient method for the construction of carbon-carbon and carbon-heteratom bonds. A wide range of nucleophiles can be employed and a variety of functional groups can be tolerated. Trost reported an enantioselective desymmetrization reaction of Boc-activated cyclopenten-1,4-diol **III-12** for the synthesis of **III-15** via successive Pd-catalyzed asymmetric amination reactions in one pot (Scheme 3-4). Treatment of **III-12** and *N*-methoxyamide **III-13** with catalytic Pd$_2$(dba)$_3$, **III-L3** and HOAc in CH$_2$Cl$_2$ facilitated desymmetrization of **III-12** to form intermediate **III-14**. After 3.5 h, another portion of the Pd$_2$(dba)$_3$ and **III-L3** was added to catalyze a subsequent intramolecular allylic amination reaction. Piperazone **III-15** was prepared in 82% yield and 97.5% ee, and subsequently served as an intermediate in the synthesis of (−)-agelastatin A.

**Scheme 3-4. Asymmetric Pd-Catalyzed Allylic Amination Reactions**

As discussed in Chapter 2, we have recently developed Pd-catalyzed asymmetric carboamination reactions for the synthesis of 2-(arylmethyl)- and 2-
(alkenymethyl)pyrrolidines.\textsuperscript{8} However, asymmetric carboamination reactions of substituted \textit{N}-Boc-pent-4-enylamines were unsuccessful. We wanted to explore and develop an enantioselective Pd-catalyzed carboamination reaction for the desymmetrization of III-16 for the synthesis of enantiomerically enriched \textit{cis}-2,5-disubstituted pyrrolidines III-17, which generates 2 stereocenters and provides opportunities for further functionalization (Scheme 3-5).

\textbf{Scheme 3-5. Synthetic Strategy for \textit{cis}-2,5-Disubstituted Pyrrolidines}

3.3 \textbf{Previous Studies and Substrate Synthesis}

Initial studies were conducted by Dr. Qifei Yang, a former post-doctoral researcher in the group, for the coupling of III-16a and 2-bromonaphthalene with Pd\textsubscript{2}(dba)\textsubscript{3} and chiral ligands. As shown below in Scheme 3-6, monodentate phosphine ligand (S)-NMDPP provided III-17a in 80% yield and 48% ee. Bis-phosphine ligands and monodentate phosphoramidite ligands such as (R)-BINAP and (R)-MONOPHOS provided low yields and enantioselectivities of pyrrolidine product III-17a.

\textbf{Scheme 3-6. Preliminary Studies}
From our prior studies on asymmetric carboamination reaction of γ-aminoalkenes, the N-protecting group (Boc) on the substrate and the use of phosphoramidite ligands were important for high enantioselectivity. Thus, we prepared N-Boc aminodialkene \textbf{III-16b} from alcohol \textbf{III-19}, which was generated by Grignard addition of homoallyl magnesium bromide to ethyl formate (\textbf{III-18}). Nucleophilic displacement of the alcohol on \textbf{III-19}, followed by hydrazine monohydrate cleavage to the amine and Boc protection provided \textbf{III-16b} (Scheme 3-7).

\textbf{Scheme 3-7. Substrate Synthesis}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textbf{III-18}};\node (B) at (2,0) {\textbf{III-19}};\node (C) at (4,0) {\textbf{III-16b}};
\draw[->] (A) -- (B) node[midway, above] {2.5 equiv.\text{ THF, }0\text{°C to rt}} node[midway, below] {86\% yield};\draw[->] (B) -- (C) node[midway, left] {1) \text{ PPh}_3\text{, DIAD phthalimide}} node[midway, below] {38\% yield over 3 steps} node[midway, above] {2) \text{ NH}_2\text{NH}_2\text{H}_2\text{O} \quad 3) \text{ Boc}_2\text{O}};
\end{tikzpicture}
\end{center}

3.4 Ligand Screen

In our initial experiments, we examined the coupling of N-Boc aminodialkene \textbf{III-16b} and 2-bromonaphthalene using commercially available bis-phosphines, monodentate phosphines and phosphite ligands (Table 3-1). The coupling of \textbf{III-16b} and 2-bromonaphthalene provided \textbf{III-17b} in good diastereoselectivity for the \textit{cis}-2,5-disubstituted pyrrolidines (20:1 dr), however, low yields and enantioselectivities were observed. The preference for the \textit{cis}-2,5-disubstituted pyrrolidine can be explained through minimization of A\textsuperscript{(1,3)}-strain in the transition state leading to the favored product.\textsuperscript{9} Bis-phosphine ligands such as (S)-BINAP (\textbf{III-L4}) were ineffective for enantioenrichment. Reexamination of monodentate ligand (S)-NMDPP (\textbf{III-L12}) resulted in base-mediated decomposition of \textbf{III-16b}, which is in sharp contrast to the good yield.

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and promising enantioselectivities obtained for N-Ph aminodialkene derivative III-16a (Table 3-1). It seems that smaller monodentate ligands are more effective for desymmetrization reactions of N-aryl aminodialkene derivatives than N-Boc aminodialkenes. The poor reactivity and selectivity observed with III-16b is consistent with our prior results on reactions employing N-Boc-pent-4-enylamines substrates, in which bidentate bis-phosphines, monodentate phosphines, and phosphites were ineffective for enantioselective carboamination reactions.8
### Table 3-1. Initial Ligand Screen

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Enantiomeric Excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-L4 (S)-BINAP</td>
<td>46%</td>
<td>7%</td>
</tr>
<tr>
<td>III-L5 (S)-tol-BINAP</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>III-L6 (S)-SEGPHOS</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>III-L7 (S)-PHANEPHOS</td>
<td>38%</td>
<td>22%</td>
</tr>
<tr>
<td>III-L8 (R,R)-NORPHOS</td>
<td>47%</td>
<td>-7%</td>
</tr>
<tr>
<td>III-L9 catAsium D(R)</td>
<td>36%</td>
<td>5%</td>
</tr>
<tr>
<td>III-L10 (S,S)-CHIRAPHOS</td>
<td>64%</td>
<td>4%</td>
</tr>
<tr>
<td>III-L11 (R)-MOP</td>
<td>65%</td>
<td>-4%</td>
</tr>
<tr>
<td>III-L12 (S)-NMDPP</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>III-L13 (R,S)-Ph-Bn-Siphox</td>
<td>15%</td>
<td>-20%</td>
</tr>
<tr>
<td>III-L14 (S,S)-Reetz D-Diphosphonite</td>
<td>Decomposition</td>
<td></td>
</tr>
</tbody>
</table>

---

*a* Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtBu, 1 mol % Pd$_2$(dba)$_3$, 4 mol % ligand, toluene (0.15 M), 90-110 °C, 12-15 h.  
*b* Enantiomeric excess was determined by chiral HPLC analysis.  
*c* Negative ee values indicate the major enantiomer was the opposite configuration of other examples in the table.
Our recent success with phosphoramidite ligands for the enantioselective synthesis of 2-substituted pyrrolidines prompted us to explore these ligands for enantioselective desymmetrization reactions. As shown in Table 3-2, promising results were obtained with BINOL-derived ligands (S,S,S)-III-L19 and (S,R,R)-III-L20 for the coupling of III-16b and 2-bromonaphthalene. In contrast to previous studies on asymmetric carboamination reactions, better results in the desymmetrization reactions are obtained with a BINOL backbone, rather than a spirobiindane backbone. (R)-Siphos-PE (III-L24) provided comparable enantioselectivities (53% ee) to ligand (S,R,R)-III-L19, but III-17b was produced in lower yield (11% yield).

In general, side products were not observed in these reactions, and it is likely that the modest yields result from base-mediated substrate decomposition (Boc decomposition and alkene isomerization). Weak bases such as K₂CO₃ and Cs₂CO₃ led to low conversions. Increased yields could be obtained by employing higher catalyst loading similar to previously reported asymmetric carboamination reactions.⁸
Table 3-2. Phosphoramidite Ligand Screen$^{a,b,c}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-L16 (R)-MONOPHOS</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>III-L17 (S)-Pipphos</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td>III-L18</td>
<td>27%</td>
<td>16%</td>
</tr>
<tr>
<td>(S,S,S)-III-L19</td>
<td>29%</td>
<td>71%</td>
</tr>
<tr>
<td>(S,R,R)-III-L20</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>III-L21</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>III-L22</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>III-L23</td>
<td>20%</td>
<td>62%</td>
</tr>
<tr>
<td>III-L24 (R)-Siphos-PE</td>
<td>11%</td>
<td>53%</td>
</tr>
<tr>
<td>III-L25 (S)-Siphos-PE</td>
<td>20%</td>
<td>-39%</td>
</tr>
</tbody>
</table>

$^a$ Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtBu, 1 mol % Pd$_2$(dba)$_3$, 4 mol % ligand, toluene (0.15 M), 90 °C, 12-15 h. $^b$ Enantiomeric excess was determined by chiral HPLC analysis. $^c$ Negative ee values indicate the major enantiomer was the opposite configuration of other examples in the table.
3.5 Summary and Future Directions

Our preliminary studies on enantioselective Pd-catalyzed desymmetrization reactions have yielded promising results with chiral BINOL-derived phosphoramidite ligands, which provide enantioselectivities up to 71% ee. In these desymmetrization reactions, the BINOL backbone is important for reactivity and selectivity, which is in contrast to previously reported asymmetric carboamination reactions that employ spirobiindane-derived phosphoramidite (R)-Siphos-PE for the synthesis of enantioenriched 2-substituted pyrrolidines. Future directions include synthesis of other BINOL-derived phosphoramidite ligand analogs (Figure 3-1), establishing the absolute stereochemistry of cis-2,5-disubstituted pyrrolidine products and examining other N-aryl aminodialkene substrates with monodentate ligands similar to (S)-NMDPP.

**Figure 3-1.** BINOL-derived Phosphoramidite Analogs

\[
\begin{align*}
\text{R} &= \text{Me, Ph, SiMe}_3, \text{OMe} \\
\end{align*}
\]
Experimental Section

General Considerations

All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Tris(dibenzylideneacetone)dipalladium (0) were purchased from Strem Chemical Co. and used without further purification. All ligands were either purchased from commercial sources (Strem Chemical Co. or Aldrich Chemical Co.) or used without further purification, or were synthesized according to published procedures. 2-bromonaphthalene was obtained via commercial sources and nona-1,8-dien-5-ol (III-19) was synthesized according to literature procedure. All solvents were purified with a GlassContour solvent purification system. The yields reported in the supporting information describe the result of a single experiment.

Experimental Procedures and Compound Characterization Data:

Synthesis of Substrate III-16b

2-(Nona-1,8-dien-5-yl)isoindoline-1,3-dione (S1). A flame dried flask round bottom flask was charged with nona-1,8-dien-5-ol (2.38 g, 17 mmol), PPh₃ (4.9 g, 18.7 mmol), phthalimide (2.75 g, 18.7 mmol), THF (85 mL) and cooled to 0 °C. DIAD (4.0 mL, 20.4 mmol) was added dropwise over the course of 30 minutes and slowly warmed up to rt and stirred overnight. The mixture was concentrated and diluted with a 2:1 mixture of hexanes/ether (50 mL). The solution was filtered through a pad of celite and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford 3.61 g (79%) of 2-(nona-1,8-dien-5-yl)isoindoline-1,3-dione as a pale yellow oil.

$^1$H NMR (500 MHz, CDCl₃) $\delta$ 7.80 (dd, $J$ = 3.0, 5.5 Hz, 2 H), 7.69 (dd, $J$ = 3.0, 5.5 Hz, 2 H); 5.78 5.69 (m, 2 H), 4.95 (q, $J$ = 1.5 Hz, 1 H), 4.92 (q, $J$ = 1.5 Hz, 1 H), 4.87 (dd, $J$ = 1.5 Hz, 10.0 Hz, 2 H), 4.23 (quint, $J$ = 5.0 Hz, 1 H), 2.50 2.16 (m, 2 H), 2.06 1.94 (m, 4 H), 1.82 1.74 (m, 2 H); $^{13}$C NMR (125 MHz, CDCl₃) 168.6, 137.4, 133.8, 131.8, 123.0, 115.1, 51.1, 31.5, 30.8; IR (film) 1707, 1372 cm⁻¹; MS (ESI) 270.1488 (270.1489 calcd for C₁₇H₁₉NO₂, M + H⁺).
**tert-Butyl nona-1,8-dien-5-ylcarbamate (III-16b).** A flame dried round bottom flask was charged with 2-(nona-1,8-dien-5-yl)isoindoline-1,3-dione S1 (3.61 g, 13.4 mmol) and 95% EtOH (70 mL). Hydrazine monohydrate (65%, 2 mL, 26.8 mmol) was added and the mixture was heated at 80 °C until starting material had been consumed as judged by TLC (ca. 6 h). Boc₂O (6.1 g, 28.1 mmol) was added portion wise and the solution was stirred overnight. The mixture was concentrated and diluted with water (50 mL). The solution was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel to afford 1.55 g (48%) of the title compound as a white solid. mp 38-40 °C; ¹H NMR (500 MHz, CDCl₃) δ 5.86 5.76 (m, 2 H), 5.20 4.92 (m, 4 H), 4.30 4.24 (m, 1 H), 3.64 3.56 (m, 1 H), 2.16 2.02 (m, 5 H), 1.66 1.50 (m, 2 H), 1.43 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) 155.6, 138.2, 114.8, 78.9, 49.9, 34.8, 30.2, 28.4; IR (film) 3389, 1705, 1364 cm⁻¹; MS (ESI) 240.1957 (240.1958 calcd for C₁₄H₂₅NO₂, M + H⁺).

**General Procedure for the Enantioselective Pd-Catalyzed Desymmetrization:**

(±)-(2R⁺,5R⁺)-tert-butyl 2-(but-3-en-1-yl)-5-(naphthalen-2-ylmethyl)pyrrolidine-1-carboxylate (III-17b). A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with charged with Pd₂(dba)₃ (1.4 mg, 1 mol % complex, 2 mol % Pd), chiral ligand (4 mol %) and NaOtBu (17 mg, 0.18 mmol). The tube was purged with nitrogen, then a solution of the amine substrate III-16b (36 mg, 0.15 mmol) and 2-bromonaphthalene (37 mg, 0.18 mmol) in toluene (1 mL, 0.15 M) was added via syringe. The mixture was heated to 90 °C or 110 °C with stirring until the starting material had been consumed as judged by GC or ¹H NMR analysis (ca. 12-15 h). The reaction mixture
was cooled to room temperature, quenched with saturated aqueous NH₄Cl (2 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound as a pale yellow oil as a 1:1 mixture of rotomers. The data are for the mixture. ¹H NMR (500 MHz, CDCl₃) δ 7.86 7.75 (m, 3 H), 7.64 (s, 1 H), 7.48 7.32 (m, 3 H), 5.86 5.74 (m, 1 H), 5.06 4.92 (m, 2 H), 4.31 4.02 (m, 2 H), 3.90 3.56 (m, 1 H), 2.80 2.66 (m, 1 H), 2.18 1.84 (m, 4 H), 1.78 1.70 (m, 2 H), 1.68 1.62 (m, 1 H), 1.58 1.40 (m, 9 H), 1.36 1.24 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 154.9, 138.3, 138.1, 136.6, 133.5, 132.1, 127.7, 127.5, 127.4, 125.8, 125.2, 114.7, 114.4, 79.1, 78.8, 59.9, 58.3, 49.9, 42.1, 40.9, 34.8, 34.7, 30.7, 30.1, 29.2, 28.7, 28.6, 28.5, 28.4; IR (film) 1708, 1393, 1366, 905, 727 cm⁻¹; MS (ESI) 366.2424 (366.2428 calcd for C₂₄H₃₁NO₂, M + H⁺). The enantiomeric excess for compounds III-17b in Table 3-1 and Table 3-2 were determined by chiral HPLC analysis (chiralcel AD-H, 0.46 cm x 25 cm, 1% iPrOH/hexanes, 1.0 mL/min, λ = 254 nm, RT = 5.3(minor) and 6.4(major) min). The absolute configuration of the pyrrolidine products have yet to be determined.

The diastereoselectivity was determined by TFA-mediated deprotection of crude product of III-17b to provide III-20 as shown below, and was found to be 20:1 dr as judged by ¹H NMR analysis. The stereochemistry of the major diastereomer of compound III-17b was determined by ¹H NMR nOe analysis of the corresponding derivative III-20.

(±)-(2R,5R)-2-(but-3-en-1-yl)-5-(naphthalen-2-ylmethyl)pyrrolidine (III-20). A flame-dried flask was charged with III-17b (55 mg, 0.15 mmol) and CH₂Cl₂ (1 mL). The solution was cooled to 0 °C, trifluoroacetic acid (0.1 mL, 1.5 mmol) was then added slowly and the resulting mixture was stirred at rt for 1 h. The crude mixture was concentrated in vacuo. The crude product was redissolved in CH₂Cl₂ (5 mL), and 2 M
NaOH (5 mL) was added. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to afford 38 mg (95%) of the title compound as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.82 7.77 (m, 3 H), 7.67 (s, 1 H), 7.44 (dquint, J = 1.5, 7.0 Hz, 2 H), 7.37 (dd, J = 1.5, 8.5 Hz, 1 H), 5.00 (dd, J = 1.5, 17.0 Hz, 1 H), 4.94 (d, J = 10.5 Hz, 1 H), 3.34 (quint, J = 7.0 Hz, 1 H), 3.01 2.94 (m, 2 H), 2.93 2.87 (m, 1 H), 2.14 2.00 (m, 2 H), 1.90 1.74 (m, 3 H), 1.65 1.46 (m, 3 H), 1.41 1.33 (m, 1 H), 1.27 (s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 137.7, 133.5, 132.0, 127.8, 127.6, 127.5, 127.4, 127.1, 125.8, 125.2, 114.3, 60.4, 58.5, 42.9, 35.9, 31.6, 30.8, 30.7; IR (film) 3337 cm⁻¹; MS (ESI) 266.1905 (266.1903 calcd for C₁₉H₂₃N, M + H⁺)
References:


Chapter 4

Enantioconvergent Synthesis of (+)-Aphanorphone via Asymmetric Pd-Catalyzed Carboamination

4.1 Introduction

The tricyclic alkaloid aphanorphone (IV-1) is a benzomorphan derived natural product isolated from the blue-green algae Aphanizomenon flos-aquae in 1988 by Shimizu and Clardy.\(^1\) Although to date no biological activity of aphanorphone has been reported, aphanorphone shares common structural features with other bioactive (analgesic) benzomorphan alkaloids, such as eptazocine (IV-2), pentazocine (IV-3), and morphine (IV-4) (Figure 4-1).

**Figure 4-1.** 3-Benzomorphan Alkaloids

4.2 Previous Enantioselective Syntheses of Aphanorphone

Aphanorphone has been the target of numerous synthetic efforts over the past twenty-three years.\(^2\)\(^-\)\(^4\) Previous enantioselective syntheses of aphanorphone have involved two main strategies: 1) C-N bond formation of Ring C via intermediate IV-5 which contains the benzylic quaternary carbon center (Figure 4-2, path a),\(^2\) or 2) C-C bond
formation of Ring B and the benzylic quaternary carbon center through Friedel-Crafts alkylation of IV-6 or radical cyclization of IV-7 respectively (Figure 4-2, path b). 3, 4

**Figure 4-2.** 2-4 Strategies for the Enantioselective Synthesis of Aphanorphine

![Chemical structures of Aphanorphine (IV-1), IV-5, IV-6, IV-7, and IV-9, showing C-N bond formation and aziridination/reductive cleavage pathways.]

4.21 **Enantioselective Synthesis of (−)-Aphanorphine via C-N Bond Formation (path a)**

**Aziridination/Reductive Cleavage Strategy**

Two years after the isolation of aphanorphine by Shimizu and Clardy, Takano reported the first enantioselective total synthesis of (−)-aphanorphine. 2a As shown below in Scheme 4-1, Takano’s strategy for C-N bond formation was aziridination and reductive cleavage of IV-5 to form (−)-aphanorphine. Amine IV-5 could be accessed via reduction of ester IV-8 followed by S_N2 displacement with an amine nucleophile. The ester IV-8 could come from intermediate IV-9 via a Pummerer reaction followed by Friedel-Crafts ring closure. Conjugate addition and Wharton rearrangement of readily available enone IV-11 could provide isomeric enone IV-10, which upon hydrogenation of the alkene, alkylation, and saponification yields IV-9.
As shown in Scheme 4-2, readily available (+)-dienone IV-11 was converted to IV-12 via 1,4-conjugate addition of 3-methoxyphenylmagneisum bromide in the presence of copper(I) bromide followed by retro-Diels Alder to afford enone IV-12 in 87% yield. Wharton rearrangement facilitated by H$_2$O$_2$ and hydrazine monohydrochloride converted IV-12 into an allylic alcohol, which was then oxidized to provide isomeric enone IV-13 in 62% yield. Enone IV-13 was then hydrogenated and subsequent alkylation with trimethylene dithiosylate and KO$_2$Bu furnished IV-14 in 53% yield. Upon saponification with KOH and immediate exposure to diazomethane, cyclic ketone IV-14 was converted to ring-opened ester IV-15 in 79% yield. Treatment of IV-15 with m-CPBA generated monosulphoxide IV-16 as a mixture of diastereomers, which were converted to a single regioisomer IV-19 upon exposure to TFAA in refluxing toluene. It is believed that TFAA-catalyzed Pummerer reaction occurs via transient intermediates IV-17 and IV-18, which facilitates cyclization and loss of 1,2-dithiolane and
trifluoacetate ion. Intermediate IV-19 has also been targeted by many other groups for the formal synthesis of ( )-aphanorphine.\textsuperscript{2b-2f}

**Scheme 4-2. Synthesis of Key Intermediate IV-19**

Ester IV-19 was reduced to the corresponding alcohol, which was converted to amine IV-20. A Nagata reaction with Pb(OAc)\textsubscript{4} and K\textsubscript{2}CO\textsubscript{3} effected efficient intramolecular aziridination across the alkene of IV-20 to yield an unstable aziridine, which was immediately exposed to methyl fluorosulphonate to provide stable quaternary ammonium salt IV-21. Meyers’ has also reported a synthesis of ( )-apanorphine via amino mercuration of common \textit{N}-methylated intermediate IV-20.\textsuperscript{2c} The ammonium salt IV-21 was converted to IV-22 via reduction with lithium aluminium hydride, which
selectively cleaved the benzylic bond. Amine IV-22 was obtained in 24% yield over 3 steps from IV-20. Finally, BBr$_3$-mediated deprotection of IV-22 provided ( )-aphanorphine in 65% yield (Scheme 4-3).

**Scheme 4-3.**$^{2a}$ Completion of the Synthesis of ( )-Aphanorphine

The first enantioselective synthesis of ( )-aphanorphine was accomplished in 18 steps and 1.3% overall yield.$^{2a}$ Takano’s synthesis utilizes an interesting Pummerer reaction of monosulphoxide IV-16 and a Nagata aziridination for C-N bond formation of ring C.

4.22 Enantioselective Synthesis of ( )-Aphanorphine via C-C Bond Formation (path b)

**Friedel-Crafts Alkylation Cyclization Strategy**

An efficient and facile formal synthesis of ( )-aphanorphine was reported by Zhai and coworkers.$^{3a}$ In Zhai’s strategy, ring B of the tricycle could be constructed via Friedel-Crafts alkylation of pyrrolidinol IV-23 with stereospecific formation of the benzylic carbon stereocenter. Rings A and C could be generated from 4-methoxyphenylacetaldehyde IV-26, where a Roush methallylation of IV-26 generates
chiral homoallylic alcohol **IV-25**, which could be converted to epoxy amine **IV-24** and then to tertiary alcohol **IV-23** (Scheme 4-4). 3a

**Scheme 4-4.** Zhai’s Retrosynthetic Analysis

4-methoxyphenylacetaldehyde **IV-26** was obtained via oxidation of commercially available 4-methoxynaphenethyl alcohol. 5 As shown in Scheme 4-5, the Roush methallylation of 4-methoxyphenylacetaldehyde **IV-26** with methallylmagneisum chloride and (+)-DIP-chloride provided (**R**) homoallylic alcohol **IV-25** in 85% yield and 95% ee. Stereoselective epoxidation of **IV-25** with 2 mol % VO(acac)2 and tert-butyl hydrogen peroxide yielded epoxide **IV-27a-b** in 96% yield as a 2:1 mixture of inseparable diastereomers. Treatment of **IV-27a-b** with HN3, PPh3 and DEAD in benzene provided azides **IV-28a-b** in good yield. Other nucleophiles such as (Boc)NHTs and (Cbz)NHTs resulted in low yields or elimination products. Selective hydrogenation of azides **IV-28a-b** was achieved with Lindlar’s catalyst and exposure to TsCl and triethylamine in ether at room temperature produced sulfonamides **IV-29a** (65%) and **IV-29b** (33%) in 98% overall yield. At this point, the diastereomers were separated by column chromatography. An intramolecular epoxy displacement with refluxing NaH in benzene converted **IV-29a** to pyrrolidinol **IV-30** in 88% yield. It is important to note that
under the same reaction conditions, diastereomer IV-29b did not undergo cyclization. Lewis-acid catalyzed intramolecular Friedel-Crafts cyclization of IV-30 with AlCl₃ formed the benzylic quarternary carbon center and provided tricyclic product IV-31 in 88% yield and 99% ee. Finally, reductive desulfurization with Red-Al in refluxing xylene provides IV-32 in 96% yield and N-methylation of the amine with formaldehyde and NaBH₃CN in MeOH at room temperature affords IV-33 in 98% yield.

**Scheme 4-5.** Enantioselective Synthesis of (−)-Aphanorphine

The formal synthesis of (−)-aphanorphine was accomplished in 10 steps and in 22% overall yield (including a presumed yield of 61-88% for the final step). The key features of this reaction are a base-promoted intramolecular endo epoxy displacement.
for the formation of pyrrolidinol IV-30 and Lewis-acid promoted Friedel-Crafts cyclization to generate the benzylic quaternary carbon center and construct the tricyclic core of (−)-aphanorphine. Although the vanadium-catalyzed epoxidation produced a mixture of inseparable diastereomers, the diastereomers were functionalized and later separated. Several other syntheses of aphantorphine have employed similar Friedel-Crafts alkylation strategies for the formation of the quaternary carbon stereocenter.3

Aryl Radical Cyclization Strategy

A Bu3SnH-mediated aryl radical cyclization was employed by Ishibashi for the construction of the benzylic quaternary center of (−)-aphanorphine (IV-1).4a The key transformation of Ishibashi’s strategy was a 6-exo aryl radical cyclization of highly functionalized pyrrolidine IV-36 to generate the tricyclic core IV-34 via radical intermediate IV-35. IV-36 can be prepared in four steps from pyrrolidine IV-37, which can be generated from trans-4-hydroxy-L-proline (IV-38) (Scheme 4-6).

Scheme 4-6. Ishibashi’s Retrosynthetic Analysis

Ishibashi’s total synthesis of (−)-aphanorphine is described below in Scheme 4-7.4a Pyrrolidine IV-39 was prepared from trans-4-hydroxy-L-proline (IV-38) via
esterification and protection of the amino and hydroxyl groups according to a procedure developed by Joullié and coworkers. Treatment of IV-39 with LiHMDS generated the lithium enolate and alkylation with 2-bromo-4-methoxybenzyl bromide provided a 4:1 mixture of IV-40 and its inseparable diastereomer. Desilylation of IV-40 with TBAF and recrystallization from n-hexane Et₂O produced alcohol IV-41 as one diastereomer in 68% yield. Oxidation of alcohol IV-41 and a Horner-Wittig reaction with the lithium salt of PhSCH₂P(O)Ph₂ in the presence of CeCl₃ followed by treatment with NaH provided radical precursor IV-42 in 78% yield. Treatment of IV-42 with Bu₃SnH and AIBN facilitated 6-exo radical cyclization to provide tricyclic IV-43 in 76% yield. In the absence of the sulfur substituent on IV-42, radical cyclization proceeded in low yields, clearing demonstrating the importance of the phenylthio group for radical-stabilization and cyclization. Refluxing IV-43 in 5 N NaOH provided carboxylic acid IV-44, which was condensed with 2-mercaptopyridine. Barton decarboxylation of the thiohydroxamate ester with Bu₃SnH and AIBN produced IV-45 in 52% yield. Desulfurization, deprotection of the benzyloxycarbonyl group and reductive methylation of IV-46 was accomplished in one pot with Raney Ni in MeOH. The synthesis of ( )-aphanorphine was finished via BBr₃-mediated demethylation of IV-46. However, no yield was reported for this last step.
Scheme 4-7. Ishibashi’s Total Synthesis of (−)-Aphanorphine

Ishibashi’s synthesis of (−)-aphanorphine was completed in 13 steps starting from commercially available trans-4-hydroxy-L-proline IV-38 (IV-46 was obtained in 11% overall yield). This synthesis utilized a Bu₃SnH-mediated aryl radical cyclization for the construction of the tricycle of IV-1 with concomitant formation of the benzylic quaternary center, which represents a unique and efficient method for the synthesis of 3-benzomorphane alkaloids.
4.23 **Summary**

Methods for the enantioselective synthesis of (−)-aphanorphine have either used C≡N bond formation (Figure 4-2, path a) or C–C bond formation (Figure 4-2, path b) for the synthesis of the tricyclic core of (−)-aphanorphine. Many of these syntheses of aphanorphine have employed chiral-pool starting materials or use stoichiometric amounts of a chiral reagent or auxiliary to set the absolute stereochemistry of the natural product. In contrast, asymmetric catalysis has occasionally been used to control the absolute configuration in aphanorphine synthesis. In these instances, the stereocenter was generated via reduction or desymmetrization of a prochiral starting material. One strategy that would enable facile access to aphanorphine and other 3-benzomorphan alkaloids would be a catalytic *enantioconvergent* synthesis, in which *both enantiomers* of a racemic starting material are converted to a single enantiomerically enriched product.

4.3 **Enantioconvergent Strategies in the Literature**

Enantioconvergent transformations or strategies have potential for significant potential synthetic utility, as they effect the conversion of *both enantiomers* of a racemic starting material to a single enantiomerically enriched product. Enantioconvergent strategies have been employed in the construction of natural products, where kinetic resolution methods are used to facilitate separation of two enantiomers. The enantiomer with the “correct” configuration is directly carried on towards the desired target, whereas the stereochemical configuration of the other enantiomer is inverted through one or more transformations. In most instances the stereochemical correction is achieved through functional-group interconversions, such as Mitsunobu reactions, oxidation/reduction sequences, and similar processes.
In 2005, Stoltz and coworkers described the first example of a catalytic enantioconvergent method for the synthesis of quaternary stereocenters starting from racemates that contain quaternary stereocenters. The method utilizes a catalytic asymmetric decarboxylative allylation to convert racemic α-substituted 2-carboxyallylcyclohexanones into highly enantioenriched cycloalkanones (Scheme 4-8).\textsuperscript{7b}

For example, treatment of (±)-IV-47 with a catalyst derived from Pd\textsubscript{2}(dba)\textsubscript{3} and (S)-t-BuPhox in Et\textsubscript{2}O produced allyl ketone (S)-IV-49 in 97% yield and 92% ee. The mechanism presumably proceeds through loss of CO\textsubscript{2} to form achiral Pd-enolate IV-48, which subsequently undergoes enantioselective allylation to produce (S)-IV-49 in high enantiopurity. This enantioconvergent methodology has also been applied toward the enantioselective total synthesis of (+)-Cassiol and (+)-Hamigeran B.\textsuperscript{7c,7d}

**Scheme 4-8. Pd-Catalyzed Decarboxylative Allylation of Racemic β-Ketoesters**

There is one total synthesis of ( )-aphanorphine that employed an enantioconvergent strategy, where at the outset of the synthesis, racemic ene-diol IV-50 was resolved to enantiopure intermediates (+)-IV-51 and ( )-IV-52 via lipase-catalyzed transesterification.\textsuperscript{2g} Both products were converted to the corresponding enantiomeric enones (+)-IV-53 and ( )-IV-54 through deprotection and oxidation sequences (Scheme 4-9).
Scheme 4-9. Chiral Resolution for the Synthesis of Enones (+)-IV-53 and (−)-IV-54

As shown below in Scheme 4-10, enones (+)-IV-53 and (−)-IV-54 were treated with 3-methoxyphenylmagnesium bromide in the presence of catalytic CuBr•SMe₂, and subsequent retro-Diels Alder in refluxing diphenyl ether provided (+)-IV-55 and (−)-IV-56 in good yields. To make this synthesis enantioconvergent, enone (−)-IV-56 was converted to (+)-IV-55 via Wharton rearrangement in 53% yield over 3 steps without loss of enantiomeric purity. Optically active enone (+)-IV-55 was then used to synthesize (−)-aphanorphine in 12 steps. This enantioconvergent synthesis of (−)-aphanorphine afforded the natural product in 23 steps (longest linear sequence reported) from commercially available materials.
In the rest of this chapter, we report an alternative, catalytic enantioconvergent approach to the construction of aphanorphine, in which a racemic intermediate is transformed into two enantiomERICALLY enriched diastereomers through asymmetric catalysis. The two diastereomers are then directly transformed to one enantioenriched product in an enantioconvergent C–C bond-forming step that generates an all-carbon quaternary stereocenter. Our approach enables us to access either enantiomer of aphanorphine from one common intermediate.

### 4.4 Catalytic Enantioconvergent Strategy for the Synthesis of (+)-Aphanorphine

As an alternative to existing strategies for the asymmetric synthesis of aphanorphine, we sought to develop an enantioconvergent route whereby a simple racemic starting material could be transformed to the enantiomERICALLY enriched alkaloid (Scheme 4-11). It seemed that two key transformations could be used to accomplish this
goal: an enantioselective Pd-catalyzed carboamination reaction that was recently developed in our laboratory, and an intramolecular Friedel-Crafts ring closure similar to that used in prior aphanorphine syntheses described in Section 4.2. As shown in Scheme 4-11, we envisioned that a catalyst-controlled asymmetric Pd-catalyzed carboamination reaction of racemic substrate IV-60 could be used to set the C2 stereocenter of pyrrolidines IV-59a-b, thereby providing a mixture of enantioenriched diastereomers. This mixture of diastereomers would then be converted to one product IV-57 in a Friedel-Crafts alkylation reaction, which would proceed via carbocation intermediate IV-58. A two-step reduction and demethylation would be used to transform IV-57 to (+)-aphanorphine. Racemic substrate IV-60 could be generated from commercially available N-Boc-1-amino-2-propanol IV-61 in three steps.

**Scheme 4-11. Asymmetric Carboamination/Friedel-Crafts Alkylation Strategy**

This enantioconvergent strategy has several attractive features: a) the substrate required for the asymmetric carboamination reaction could be prepared in a concise, straightforward manner; b) analogs of the natural product could potentially be generated
through use of different aryl halides in the carboamination step; c) either enantiomer of the natural product should be accessible, as the absolute stereochemistry in the carboamination reaction would be controlled by the ligand; and d) this general strategy could potentially be adapted to provide access to a broad array of fused- or bridged bicyclic alkaloids that contain a benzylic all-carbon quaternary stereocenter.

4.5 Enantioselective Synthesis of (+)-Aphanorphine

To test the feasibility of this strategy, we elected to pursue a synthesis of the non-natural (+)-enantiomer of aphanorphine, as only a few prior studies have targeted (+)-aphanorphine, and the ligand needed to generate the isomer of the natural product, (R)-Siphos-PE, is commercially available. In order to obtain IV-57 in high enantioselectivity, it would be necessary to generate a 1:1 mixture of diastereomers in the asymmetric carboamination reaction of IV-60, as any degree of substrate control in the reaction of IV-60 could lead to erosion of enantiomeric purity in the final product (Scheme 4-11). However, prior studies in our group have illustrated that diastereoselectivities are low for substrates bearing homoallylic substituents. For example, treatment of IV-62 with catalytic Pd$_2$(dba)$_3$ and dpe-phos produced pyrrolidines IV-63 in low diastereoselectivity, presumably due to lack of A$^{(1,3)}$ strain and 1,3-diaxial interactions in the transition state (Scheme 4-12). To test this hypothesis, we elected to synthesize a substrates bearing different substituents at the homoallylic position (Me vs. OR) to study their effect on diastereoselectivity.
Scheme 4-12. Synthesis of 2,4-Disubstituted Pyrrolidines

![Scheme 4-12 diagram]

Commercially available N-Boc-1-amino-2-propanol IV-61 was oxidized to ketone IV-64, followed by addition of allylmagnesium bromide to afford racemic tertiary alcohol IV-65 in good yield. Protection of the tertiary alcohol with TMS-imidazole or TBS-triflate proceeded smoothly to provide aminoalkenes IV-66 and IV-67 respectively (Scheme 4-13). Efforts to protect sterically hindered tertiary alcohol IV-65 with other functional groups such as TIPS, TBDPS, Me, and Bn were unsuccessful.

Scheme 4-13. Substrate Synthesis

![Scheme 4-13 diagram]

Treatment of γ-amino alkenes IV-66 and IV-67 with Pd(OAc)₂ and dpe-phos provided 2,4-disubstituted pyrrolidines in moderate yields and low diastereoselectivity (Scheme 4-14). Not surprisingly, the similarity in size of the homoallylic group in IV-68 (methyl vs. OTMS), suggested there would be little substrate bias toward either diastereomer (1:1 dr). Subjecting TBS-protected γ-amino alkene IV-67 under the reaction conditions provided pyrrolidine IV-69 with a slight preference for one diastereomer (1.4:1 dr). Therefore, we elected to use TMS-protected γ-amino alkene IV-66, since the substrate should have little effect on asymmetric induction in Pd-catalyzed carboamination reaction step.
Scheme 4-14. Diastereoselectivity Study

The coupling reaction between IV-66 and 4-bromoanisole was examined using our previously reported conditions for enantioselective alkene carboamination reactions (Scheme 4-15). After slight optimization of reaction conditions, the transformation afforded a 1:1 mixture of diastereomers IV-68a and IV-68b in 75% yield. In our prior studies, we found that optimal results were achieved with substrate concentrations of 0.2 M. However, increased yields were obtained in reactions using 0.33 M concentration or higher. The higher concentration presumably increased the rate of carboamination versus substrate decomposition. We initially sought to separate the diastereomers and assay each individually to determine enantiomeric purity. Unfortunately, separation of the isomers was not possible. In addition, routes to prepare racemic samples of each diastereomer appeared to be cumbersome. As such, we elected to transform the mixture of isomers IV-68a-b to known compound IV-71, which we could then assay for enantiomeric purity.3a

To this end, treatment of IV-68a-b with TFA led to cleavage of both the N-Boc and O-TMS groups, and tosylation of the resulting pyrrolidine derivative provided IV-70a-b in 83% yield (1:1 dr) over two steps. The enantioconvergent intramolecular Friedel-Crafts alkylation of the mixture of diastereomers IV-70a-b provided IV-71 in 63% yield, and analysis by chiral HPLC indicated the molecule had been formed with 81% ee.
With a concise route to enantiomerically enriched diastereomers IV-68a-b in hand, we sought to complete the synthesis of (+)-aphanorphine. We envisioned that an enantioconvergent Friedel-Crafts alkylation of IV-68a-b should provide IV-57, which could be transformed to the target in two steps (reduction and demethylation). Unfortunately, the Friedel-Crafts alkylation proved to be problematic (Scheme 4-16). A variety of conditions were surveyed for reactions of IV-68a-b and desilylated analogs IV-72a-b, but all of the conditions examined provided low yields of the desired product IV-57. Competing cleavage of the N-Boc group was frequently observed, along with formation of unidentifiable side products.

Although the conversion of IV-68a-b to IV-57 was not successful, N-tosylated derivative IV-71 has previously served as an intermediate in Zhai’s syntheses of aphanorphine. Thus, after some modification of literature procedures, IV-71 was
transformed to **IV-73** in 64% yield via cleavage of the \( N \)-tosyl group with Red-Al followed by \( N \)-methylation under Eschweiler-Clarke conditions (Scheme 4-17). After quenching of the excess Red-Al, it was imperative to filter the crude mixture through a pad of celite before proceeding onto the \( N \)-methylation step. Any aluminium byproducts decreased yields in the subsequent \( N \)-methylation step. Although \( \text{BBr}_3 \)-mediated aryl ether cleavage of **IV-73** has previously been a key feature of prior syntheses,\(^2 \text{-}^4\) this step proved to be quite challenging. Many of the described approaches to aphanorphine are formal syntheses, which stop prior to the challenging and selective \( O \)-demethylation step.

**Scheme 4-17.** Deprotection/\( N \)-Methylation

![Scheme 4-17 Deprotection/N-Methylation](image)

Initial attempts to \( O \)-demethylate **IV-73** with 2 equivalents of \( \text{BBr}_3 \) resulted in demethylation of both the aryl methyl ether and \( N \)-methyl substituent to afford **IV-74** (Scheme 4-18).\(^2 \text{a}\) Rather perplexed, we sought to run a variety of optimization studies. When the reaction was conducted at lowered temperatures (-78 °C and -30 °C), only starting material was observed. Reducing the amount of \( \text{BBr}_3 \) (1 equivalent) used in the reaction led to recovered starting material. From our results, it seemed that this challenging demethylation step was temperature sensitive.

**Scheme 4-18.** Initial Attempts at \( \text{BBr}_3 \)-Mediated Demethylation

![Scheme 4-18 Initial Attempts at BBr3-Mediated Demethylation](image)
However, after some experimentation and correspondence with Professor Raymond Funk, we found that the conditions reported by Funk provided satisfactory results.\textsuperscript{14} With careful control of the reaction temperature, and gradual warming from –30 °C to 0 °C in 10 °C increments over the course of 2 h, we were able to effect the conversion of $\text{IV-73}$ to (+)-aphanorphine in 63% yield (Scheme 4-19).

\textbf{Scheme 4-19.} Completion of the Synthesis

\begin{center}
\begin{tikzpicture}
\node (in) at (0,0) {$\text{MeO}$};
\node (in1) at (0.5,0) {$\text{Me}$};
\node (in2) at (1,0) {$\text{N-Me}$};
\node (in3) at (1.5,0) {$\text{H}$};
\node (out) at (3,0) {$\text{HO}$};
\node (out1) at (3.5,0) {$\text{Me}$};
\node (out2) at (4,0) {$\text{N-Me}$};
\node (out3) at (4.5,0) {$\text{H}$};
\node (reaction) at (2.5,1) {$\text{BBr}_3, \text{CH}_2\text{Cl}_2$};
\node (temp) at (2.2,0.5) {$(-30 \rightarrow 0 \,^\circ\text{C})$};
\node (yield) at (2.8,0) {$63\% \text{ yield}$};
\draw[->] (in) -- (in1) -- (in2) -- (in3) -- (reaction) -- (temp) -- (yield) -- (out) -- (out1) -- (out2) -- (out3);
\end{tikzpicture}
\end{center}

4.6 \textbf{Summary and Future Directions}

We have developed a concise synthesis of (+)-aphanorphine that affords the target molecule in 10 steps and 13% overall yield from commercially available starting materials. Importantly, this synthesis demonstrates the viability of a new, enantioconvergent strategy for the construction of benzomorphan-type alkaloids. Our synthesis of (+)-aphanorphine facilitates the formation of two C–C bonds, one C–N bond, and two rings and converts a readily available racemic substrate to an enantiomerically enriched product. A benzylic quaternary stereocenter is generated during the enantioconvergent C–C bond-forming step, and the product is formed with a synthetically useful level of stereocontrol. Further studies include expansion of the asymmetric carboamination/Friedel-Crafts alkylation sequence toward the synthesis of other benzomorphan-type alkaloids.
Experimental Section

General Considerations:

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium and (R)-Siphos-PE were purchased from Strem Chemical Co. and used without further purification. All reagents were obtained from commercial sources and were used as obtained. Toluene, THF, methylene chloride and diethyl ether were purified using a GlassContour solvent purification system. The yields reported in the Supporting Information describe the result of a single experiment, whereas the yields reported in Scheme 4-13, Scheme 4-15, Scheme 4-17 and Scheme 4-19 are average yields of two or more experiments. Thus, the yields reported in the Supporting Information may differ from those shown in Scheme 4-13, Scheme 4-15, Scheme 4-17 and Scheme 4-19.

Experimental Procedures and Compound Characterization Data.

**tert-Butyl (2-oxopropyl)carbamate (IV-64).**

A flame-dried flask was cooled under a stream of nitrogen and charged with pyridinium chlorochromate (12.3 g, 57 mmol) and CH₂Cl₂ (50 mL). The flask was cooled in an ice-water bath and (±)-tert-butyl (2-hydroxypropyl)carbamate (5.0 g in 10 mL CH₂Cl₂, 28.5 mmol) was added to the solution. The resulting mixture was stirred overnight at rt, then Et₂O (100 mL) was added. The resulting black tar was filtered through a plug of silica gel and concentrated. The crude product was purified by flash chromatography on silica gel to afford 4.7 g (96%) of the title compound as a yellow oil. Spectroscopic properties were consistent with those reported in the literature.¹⁵ ¹H NMR (400 MHz, CDCl₃) δ 5.21 (s, br, 1 H), 4.03 (d, J = 4.5 Hz, 2 H), 2.18 (s, 3 H), 1.44 (s, 9 H).

**(±)-tert-Butyl (2-hydroxy-2-methylpent-4-en-1-yl)carbamate (IV-65).** A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of
allylmagnesium bromide (92 mL, 1 M in Et₂O) and additional Et₂O (25 mL). The resulting solution was cooled in an ice-water bath and a solution of tert-butyl (2-oxopropyl)carbamate (8.0 g, 46 mmol) in Et₂O (25 mL) was added slowly via syringe. The resulting mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca. 1.5 h). The mixture was then cooled in an ice-water bath and the reaction was quenched by the slow addition of water (100 mL). The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et₂O (2 x 100 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 9.3 g (94%) of the title compound as a brown oil that was used without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.95–5.81 (m, 1 H), 5.21–5.07 (m, 2 H), 4.90 (s, br, 1 H), 3.13 (d, J = 6.2 Hz, 2 H), 2.40 (s, 1 H), 2.23 (d, J = 7.4 Hz, 2 H), 1.45 (s, 9 H), 1.16 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 156.7, 133.4, 118.3, 79.1, 72.2, 49.6, 44.2, 28.1, 24.1; IR (film) 3369, 1694 cm⁻¹; MS (ESI): 238.1417 (238.1419 calc for C₁₁H₂₁NO₃, M + Na⁺).

(±)-tert-Butyl {2-methyl-2-[{(trimethylsilyl)oxy}pent-4-en-1-yl]carbamate (IV-66). A flame-dried flask equipped with a stirbar was cooled under a stream of nitrogen and charged with (±)-tert-butyl (2-hydroxy-2-methylpent-4-en-1-yl)carbamate (5.0 g, 23 mmol). Neat 1-(trimethylsilyl)-1H-imidazole (6.8 mL, 46 mmol) was added and the resulting mixture was stirred at rt until the starting material had been consumed as judged by TLC analysis (ca. 4 h). Water (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (4 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 6.0 g (90%) of the title compound as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.87–5.73 (m, 1 H), 5.09–5.01 (m, 2 H), 4.74 (s, br, 1 H), 3.16–2.99 (m, 2 H), 2.23 (d, J = 7.2 Hz, 2 H), 1.45 (s, 9 H), 1.19 (s, 3 H), 0.13 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃) δ 156.1, 133.9, 117.9, 79.0, 75.7, 50.0, 45.2, 28.3, 24.9, 2.5; IR (film) 3368, 1720 cm⁻¹; MS (ESI): 310.1815 (311.1833 calcd for C₁₄H₂₉NO₃Si, M + Na⁺).
(±)-*tert*-Butyl {2-[*tert*-butyldimethylsilyl]oxy}-2-methylpent-4-en-1-yl]carbamate (IV-67). A flame-dried flask was charged with (±)-*tert*-butyl (2-hydroxy-2-methylpent-4-en-1-yl)carbamate (0.3 g, 1.4 mmol) and CH₂Cl₂ (1.5 mL). The solution was cooled to 0 °C and 2,6-lutidine (0.5 mL, 2.2 mmol) was added dropwise followed by dropwise addition of neat TBSOTf (0.5 mL, 7 mmol). The resulting mixture was stirred at 0 °C for 30 min, then quenched with water. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 0.35 g (76%) of the title compound as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 5.86–5.74 (m, 1 H), 5.08–5.00 (m, 2 H), 4.70 (s, 1 H), 3.16–3.00 (m, 2 H), 2.23 (d, J = 9.5 Hz, 2 H), 1.44 (s, 9 H), 1.18 (s, 3 H), 0.87 (s, 9 H), 0.1 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) 156.1, 134.0, 117.9, 79.0, 75.4, 50.0, 43.3, 28.4, 25.8, 25.0, 18.1, –2.1; IR (film) 3463, 3352 cm⁻¹; MS (ESI): 352.2282 (352.2278 calcd for C₁₇H₃₅NO₃Si, M + Na⁺).

(±)-(2⁵S,4⁵RS)-*tert*-Butyl 2-(4-methoxybenzyl)-4-methyl-4-[(trimethylsilyl)oxy]pyrrolidine-1-carboxylate (IV-68a-b). A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with Pd₂(dba)₃ (191 mg, 0.2 mmol), (R)-Siphos-PE (303 mg, 0.06 mmol) and NaOctBu (960 mg, 0.5 mmol). The tube was evacuated and backfilled with nitrogen three times, then a solution of (±)-*tert*-butyl {2-methyl-2-[(trimethylsilyl)oxy]pent-4-en-1-yl]carbamate IV-66 (3.0 g, 10 mmol) and 4-bromoanisole (3.74 g, 20 mmol) in toluene (30 mL) was added via syringe. The resulting mixture was stirred at rt for 1 min then was immersed in 90 °C oil bath and stirred overnight (ca. 14 h). The mixture was then cooled to room temperature and saturated
aqueous ammonium chloride (10 mL) was added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 3.1 g (75%) of the title compound as a pale yellow oil. The product was judged to be a 1:1 mixture of rotamers and a 1:1 mixture of diastereomers by ¹H NMR analysis. Data are for the mixture. [α]²³D +18.4 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.17–7.03 (m, 2 H), 6.86–6.78 (m, 2 H), 4.19–3.82 (m, 1 H), 3.79 (s, 3 H), 3.76–3.10 (m, 2 H), 2.93–2.54 (m, 2 H), 1.94–1.79 (m, 1 H), 1.77–1.66 (m, 1 H), 1.55–1.47 (m, 9 H), 1.33–1.26 (m, 3 H), 0.14 (s, 4.5 H), 0.07 (s, 4.5 H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 157.7, 154.9, 154.7, 154.3, 153.0, 150.8, 130.5, 130.3, 130.2, 130.0, 126.5, 113.6, 113.5, 113.4, 113.3, 79.0, 78.9, 78.8, 78.6, 78.0, 77.8, 77.6, 59.9, 59.7, 59.1, 59.0, 58.8, 58.2, 57.9, 54.7, 46.6, 45.5, 44.5, 43.4, 39.6, 39.4, 38.3, 38.2, 28.3, 28.1, 28.0, 26.6, 26.5, 24.8, 24.7, 2.2, 1.9, 1.8, 1.7; IR (film) 2972, 1699, 1684 cm⁻¹; MS (ESI): 416.2228 (416.2233 calcd for C₂₁H₃₅NO₄Si, M + Na⁺).

(±)-tert-Butyl 4-[(tert-butyldimethylsilyl)oxy]-2-(4-methoxybenzyl)-4-methylpyrrolidine-1-carboxylate (IV-69). The title compound was prepared from (±)-tert-butyl 2-[(tert-butyldimethylsilyl)oxy]-2-methylpent-4-en-1-yl]carbamate IV-67 (1.5 g, 4.6 mmol) using a procedure analogous to that described for the synthesis of IV-68a-b except that Pd(OAc)₂ (20.7 mg, 0.09 mmol) was employed as the palladium source, and Dpe-phos (99 mg, 0.184 mmol) was used as ligand. This procedure afforded 1.24 g (62 %) of the title compound as a pale yellow oil. The product was judged to be a ~1:1 mixture of rotamers and a ~1.4:1 mixture of diastereomers mixture of diastereomers by ¹H NMR analysis. Data are for the mixture. ¹H NMR (400 MHz, CDCl₃) δ 7.15–7.01 (m, 2 H), 6.85–6.76 (m, 2 H), 4.18–3.80 (m, 1 H), 3.76 (s, 3 H), 3.54–3.40 (m, 0.5 H), 3.34–3.06 (m, 2 H), 2.87–2.75 (m, 1 H), 2.74–2.57 (m, 0.5 H), 1.88–1.68 (m, 2 H), 1.58–1.42 (m, 9 H), 1.30–1.22 (m, 3 H), 0.96 0.78 (m, 9 H), 0.08–0.01 (m, 6 H); ¹³C NMR
(+)-(5S,3RS)-5-(4-Methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (IV-70a-b). A round-bottom flask equipped with a stirbar was charged with (+)-(2S,4RS)-tert-Butyl 2-(4-methoxybenzyl)-4-methyl-4-[(trimethylsilyl)oxy]pyrrolidine-1-carboxylate and CH₂Cl₂ (7.6 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (5.7 mL, 76.2 mmol) was added, and the solution was warmed to rt and stirred until the starting material had been consumed as judged by TLC analysis (ca. 10 min). The reaction mixture was diluted with water, basified with NH₄OH, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was dissolved in THF (5 mL) and the resulting solution was added to a stirring solution of triethylamine (3.2 mL, 22.9 mmol), tosyl chloride (2.18 mg, 11.4 mmol) and THF (10 mL). The reaction mixture was stirred overnight at rt, then saturated NaHCO₃ (10 mL) was added. The mixture was transferred to a separatory funnel and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 2.3 g (80%) of the title compound as a colorless oil. The product was judged to be a 1:1 mixture of diastereomers by ¹H NMR analysis. Data are for the mixture. [α]²³_D +65.7 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.82–7.73 (m, 2 H), 7.36–7.30 (m, 2 H), 7.20 (d, J = 8.0 Hz, 1.2 H), 7.14 (d, J = 8.4 Hz, 0.8 H), 6.88–6.80 (m, 2 H), 4.02–3.94 (m, 0.5 H), 3.83–3.75 (m, 3.5 H), 3.42–3.37 (m, 1 H), 3.30–3.21 (m, 1 H), 3.18–3.07 (m, 1 H), 3.03 (d, J = 10.4 Hz, 0.6 H), 2.83 (dd, J = 9.2, 13.6 Hz, 0.4 H), 2.44–2.41 (m, 3 H), 1.84–1.74 (m, 1 H), 1.64–1.54 (m, 2
(±)-(1S,4S)-8-Methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-1,4-methano-
benzo[d]azepine (IV-71).  

A flame-dried round-bottom flask was charged with aluminum trichloride (8.0 g, 60 mmol) and CH2Cl2 (100 mL). The flask was cooled to 0 °C and a solution of (+)-(5S,3RS)-5-(4-methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (2.15 g, 5.7 mmol) in CH2Cl2 (20 mL) was added via syringe. The resulting mixture was allowed to slowly warm to rt and was stirred overnight. The reaction mixture was then poured into a solution of saturated aqueous NaHCO3 (50 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH2Cl2 (2 x 50 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 1.2 g (60%) of the title compound as a pale yellow solid. The enantiomeric excess was determined to be 81% ee by chiral HPLC analysis (Chiralpak AD-H 0.46 cm x 25 cm, 1 % iPrOH/hexanes, 1 mL/min, λ = 254 nm, RT = 8.0 and 9.8 min). Spectroscopic properties were consistent with those previously reported in the literature. [α]23 D +16.0 (c 1.0, CH2Cl2) [for ent-IV-71 lit. 3a [α]27 D −16.9 (c 0.89, CHCl3)]; mp: 137–140 °C (lit. 3a mp 136–138 °C); 1H NMR (400 MHz, CDCl3) δ 7.70 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 6.97 (d, J = 8.4 Hz, 1 H), 6.78 (d, J = 2.5 Hz, 1 H), 6.72 (dd, J = 2.6, 8.3 Hz, 1 H), 4.41–4.35 (m, 1 H), 3.78 (s, 3 H), 3.40 (dd, J = 1.2, 8.7 Hz, 1 H), 3.11 (d, J = 16.6 Hz, 1 H), 3.02 (d, J = 8.6 Hz, 1 H), 2.93 (dd, J = 2.8, 16.5 Hz, 1 H), 2.42 (s, 3 H), 1.79 (d, J = 11.5 Hz, 1 H), 1.50–1.38 (m, 4 H).
(+)-(2S,4RS)-tert-Butyl 4-hydroxy-2-(4-methoxybenzyl)-4-methylpyrrolidine-1-carboxylate (IV-72a-b). A round-bottom flask was charged with (+)-(2S,4RS)-tert-butyl 2-(4-methoxybenzyl)-4-methyl-4-([(trimethylsilyl)oxy]pyrrolidine-1-carboxylate (100 mg, 0.254 mmol) and tetrabutylammonium fluoride (0.51 mL, 0.51 mmol) 1 M solution in THF) and the resulting solution was stirred until the starting material had been consumed as judged by TLC analysis (ca. 1 h). The reaction mixture was diluted with water (5 mL) and CH2Cl2 (5 mL) then was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH2Cl2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na2SO4 and concentrated. The crude product was purified by flash chromatography on silica gel to afford 73 mg (90%) of the title compound as a colorless viscous oil. The product was judged to be a 1:1 mixture of rotamers and a 1:1 mixture of diastereomers by 1H NMR analysis. Data are for the mixture. [α]23D +23.0 (c 1.0, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 7.18–7.02 (m, 2 H), 6.84–6.78 (m, 2 H), 4.24–3.88 (m, 1 H), 3.79 (s, 3 H), 3.70–3.08 (m, 2.5 H), 3.00–2.60 (m, 1.5 H), 1.96–1.70 (m, 2 H), 1.51 (s, 9 H), 1.38–1.24 (m, 3 H); 13C NMR (100 MHz, CDCl3) δ 157.9, 155.1, 154.6, 131.1, 130.4, 130.1, 113.7, 79.4, 77.2, 76.1, 75.7, 75.2, 59.9, 59.5, 59.3, 58.2, 57.7, 55.0, 45.1, 44.5, 43.0, 42.5, 39.7, 39.5, 38.5, 38.1, 28.5, 26.7, 24.7; IR (film) 3420, 1682 cm–1; MS (ESI): 344.1833 (344.1838 calcd for C18H27NO4, M + Na+).

(+)-(1S,4S)-8-Methoxy-1-methyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[d]azepine (S1). A flame-dried round-bottom flask was charged with (+)-(1S,4S)-8-methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[d]azepine (1.1 g, 3.1 mmol) and xylene (15 mL). A solution of Red-Al was added (3.5 M in toluene, 3.3 mL, 11.4 mmol) and the mixture was heated to reflux for 1 h. The solution was cooled to 0 °C, diluted

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with ether and quenched with a few drops of water. The solution was filtered through a pad of celite and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 450 mg (71%) of the title compound as a yellow oil. \([\alpha]^{23}_D +38.2 \text{ (c 1.0, CH}_2\text{Cl}_2); \)\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.02 (d, \(J = 8.5\) Hz, 1 H), 6.82 (d, \(J = 2.5\) Hz, 1 H), 6.71 (dd, \(J = 3.0, 8.5\) Hz, 1 H), 3.85–3.79 (m, 4 H), 3.11–3.02 (m, 2 H), 2.92 (d, \(J = 10\) Hz, 1 H), 2.78 (m, 2 H), 1.96–1.92 (m, 1 H), 1.86 (d, \(J = 11\) Hz, 1 H), 1.49 (s, 3 H).

\((-\rangle-8\text{-O}-methylphanorphine (IV-73).\) A flame-dried round-bottom flask was charged with \((+-)(1S,4S)-8\text{-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzod]azepine (300 mg, 1.5 mmol), a solution of 37\% aqueous formalin (1.8 mL) and formic acid (2.8 mL). The reaction mixture was heated to 100 °C for 1.5 h, then cooled to rt, diluted with water (10 mL), and basified with 10\% NaOH solution. The mixture was transferred to a separatory funnel and extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 294 mg (90\%) of the title compound as a pale yellow oil. Spectroscopic properties are consistent with those previously reported in the literature. \([\alpha]^{23}_D –5.8 \text{ (c 1.0, CHCl}_3), [\text{lit.}^{12a} [\alpha]^{27}_D –7.4 \text{ (c 0.35, CHCl}_3]); \)\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.02 (d, \(J = 8.4\) Hz, 1 H), 6.78 (d, \(J = 2.8\) Hz, 1 H), 6.68 (dd, \(J = 2.8, 8.4\) Hz, 1 H), 3.78 (s, 3 H), 3.42 (m, 1 H), 3.02 (d, \(J = 16.4\) Hz, 1 H), 2.88–2.84 (m, 2 H), 2.82 (d, \(J = 1.2\) Hz, 1 H), 2.76 (d, \(J = 9.2\) Hz, 1 H), 2.48 (s, 3 H), 2.02 (ddd, \(J = 1.2, 5.6, 10.8\) Hz, 1 H), 1.48 (s, 3 H).
(1S,4S)-1-methyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzod[azepin-8-ol (IV-74).

Attempts to demethylate (–)-8-O-methylaphanorphine IV-73 according to a reported procedure by Takano resulted in formation of undesired product IV-74.12a 1H NMR (500 MHz, CD3OD) δ 7.00 (d, J = 8.0 Hz, 1 H), 6.80 (s, 1 H), 6.72 6.68 (m, 1 H), 4.09 4.03 (m, 1 H), 3.32 3.17 (m, 7 H), 2.18 (d, J = 12.0 Hz, 1 H), 1.53 (s, 3 H); 13C NMR (125 MHz, CD3OD) δ 158.4, 146.1, 130.2, 124.2, 116.3, 112.5, 75.6, 70.2, 48.5, 23.7, 35.9, 21.0.

(+)-aphanorphine (IV-1). Demethylation of (–)-8-O-methylaphanorphine was carried according to reported procedure.14 A flame-dried round-bottom flask was charged with IV-73 (40 mg, 0.18 mmol) and CH2Cl2 (1 mL) and cooled to –30 °C. BBr3 (1.0 M in CH2Cl2, 0.36 mL) was added slowly dropwise. The reaction mixture was stirred for 30 min at –30 °C, 30 min at –20 °C, 30 min at –10 °C and then 30 min at 0 °C. The reaction was quenched at 0 °C with aqueous NaHCO3 and extracted with CH2Cl2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The resulting residue was taken up in 2 mL of 3 M NaOH and heated at 100 °C for 5 min. The solution was acidified with 1 M HCl and basified with saturated aqueous NaHCO3. The aqueous layer was extracted with CH2Cl2 (3 x 10 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The crude solid was triturated with acetone to afford 23 mg (63%) of the title compound as a white solid. Spectroscopic properties are consistent with the present literature. [α]23D +28.0 (c 0.1, MeOH) [lit.12a [α]27D +37.5 (c 0.16, MeOH)]; mp 202–208 °C (lit.12a mp 215–222). 1H NMR (400 MHz, CD3OD) δ 6.89 (d, J = 8 Hz, 1 H), δ 6.67 (d, J = 2.4 Hz, 1 H), δ 6.56 (dd, J = 2.4, 8.4 Hz, 1 H), 3.38 (m, 1 H), 2.97 (d, J = 16.8 Hz, 1 H), 2.85 (m, 2 H), 2.63 (d, J = 9.6 Hz, 1 H), 2.40 (s, 3 H), 2.01 (q, J = 5.6 Hz, 1 H), 1.83 (d, J = 11.2 Hz, 1 H), 1.44 (s, 3 H); 13C
NMR (100 MHz, CD$_3$OD) $\delta$ 156.6, 148.6, 131.2, 125.2, 114.5, 110.9, 72.7, 63.4, 44.3, 42.8, 42.1, 36.7, 21.7.
References:


Chapter 5

Preliminary Studies on Asymmetric Pd-Catalyzed Reactions for the Synthesis of Other 5-Membered Heterocycles

5.1 Introduction

5-membered heterocycles such as imidazolidin-2-ones, isoxazolidines, pyrazolidines, and tetrahydrofurans are important motifs found in a wide array of molecules that possess interesting biological activities.¹ This chapter describes our preliminary studies on asymmetric Pd-catalyzed alkene functionalization reactions for the synthesis of imidazolidin-2-ones, isoxazolidines, pyrazolidines, and tetrahydrofurans, which builds on the study of enantioselective pyrrolidine synthesis described in Chapter 2. We have identified some promising ligand scaffolds for these transformations and promising leads will be followed up by future group members.

5.2 Enantioselective Synthesis of Imidazolidin-2-ones

5.21 Biological Importance

The imidazolidin-2-one core is an important scaffold in pharmaceutical and medicinal chemistry. Cyclic ureas have been demonstrated to act as potent HIV protease inhibitors,² 5-HT₃ receptor antagonists,³ NK₁ antagonists,⁴ and chiral auxiliaries.⁵ For example, imidazolidin-2-one V-1 has been implicated as a potential HIV protease
inhibitor and imidazolidin-2-one \textbf{V-2} has been demonstrated to act as a potent Neurokinin antagonist (Figure 5-1).²⁴

\textbf{Figure 5-1. Biologically Important Imidazolidin-2-ones}

![Figure 5-1. Biologically Important Imidazolidin-2-ones](image)

5.22 \textit{Asymmetric Methods for the Synthesis of Imidazolidin-2-ones}

Imidazolidin-2-ones are generally prepared by carbonylation of chiral 1,2-diamines with phosgene or phosgene derivatives.⁶ As shown in Scheme 5-1, BOC-alanine \textit{N}-hydroxysuccinimide ester \textbf{V-3} is condensed with benzylamine to provide amide \textbf{V-4}. TFA deprotection, amide reduction and subsequent cyclization with triphosgene provide cyclic urea \textbf{V-5} in 60% over 3 steps. However, the preparation of chiral 1,2-diamines often requires several steps.⁷

\textbf{Scheme 5-1. Cyclization of 1,2-Diamines with Triphosgene}

![Scheme 5-1. Cyclization of 1,2-Diamines with Triphosgene](image)

An alternative method for the synthesis of chiral imidazolidin-2-ones involves intramolecular S_{N}2 reactions of substrates based on \textit{N}-(2-hydroxyethyl)urea \textbf{V-7} (Scheme 5-2). Treatment of enantioenriched 1,2-amino alcohol \textbf{V-6} with phenylisocyanate generates acyclic urea \textbf{V-7}, which upon exposure to TsCl and \textit{t}-BuOK, facilitates cyclization to yield imidazolidin-2-one \textbf{V-8}. However, this method requires the synthesis of chiral 1,2-amino alcohol substrates.
As previously discussed in Chapter 1, an asymmetric catalytic approach toward the synthesis of imidazolidin-2-ones was developed by Shi,\(^8\) where treatment of conjugated dienes (V-9) and di-tert-butylaziridinone (V-10) with Pd\(_2\)(dba)\(_3\) and tetramethylpiperidine-derived phosphoramidite V-L* afforded cyclic ureas V-11 in good yield and high enantioselectivity (Scheme 5-3). The reaction is believed to proceed through oxidative addition of Pd(0) to V-10, followed by syn-aminopalladation and reductive elimination to yield V-11.\(^8c\)

**Scheme 5-3. Asymmetric Pd-Catalyzed Diamination Reaction**

**5.23 Project Goals and Previous Work**

We sought to develop a method where readily accessible achiral starting material such as V-12 could be coupled with aryl or alkenyl halide to provide chiral imidazolidin-2-one V-13 via asymmetric Pd-catalyzed carboamination reactions (Scheme 5-4). This method would be amenable toward analog synthesis of V-13, which may be cleaved to provide functionalized chiral 1,2-diamines V-14.
Dr. Jonathan Fritz, a former graduate student in our group, developed a method which enabled the construction of racemic imidazolidin-2-ones $V-13$ via Pd-catalyzed carboamination reactions between $N$-allylureas $V-12$ and aryl bromides. As shown in Scheme 5-5, Dr. Fritz also examined an asymmetric variant of this reaction for the coupling of $V-12a$ and 2-bromotoluene. After a brief ligand screen, he discovered that a catalyst system of Pd$_2$(dba)$_3$ and (S)-Phanephos provided cyclic urea $V-13a$ in 86% yield and 32% ee.\(^9\)

Scheme 5-5. Asymmetric Pd-Catalyzed Carboamination Reaction of $N$-allylurea $V-12a$

5.24 Ligand Screen

We decided to examine the coupling of $V-12a$ and 2-bromonaphthalene with catalytic Pd$_2$(dba)$_3$ and other chiral phosphine ligands (Table 5-1). 2-bromonaphthalene was used in place of 2-bromotoluene to minimize the influence of aryl halide steric properties on the aminopalladation step. Bis-phosphine ligand $V$-$L2$ was found to be a promising lead, yielding $V-13b$ in 60% yield and 45% ee. However, most bidentate and monodentate phosphine ligands effected the formation of $V-13b$ in relatively low ee.
As shown below, chiral phosphite ligands were screened for the coupling of \textbf{V-12a} and 2-bromonaphthalene (Table 5-2).\textsuperscript{11} A phosphite ligand derived from cinchonidine (\textbf{V-L13}) provided promising enantioselectivities (65% ee). Other ligands derived from chiral alcohols such as menthol (\textbf{V-L9}), and 2-phenylethanol (\textbf{V-L10}) provided low yields and ee. In comparison to the other phosphite ligands screened, it seems that the cinchonidine alkaloid is important for selectivity and may provide a greater degree of enantioselective bias in the aminopalladation step.
Table 5-2. Phosphite Ligand Screen$^{a,b,c}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-L8</td>
<td>18%</td>
<td>0%</td>
</tr>
<tr>
<td>V-L9</td>
<td>58%</td>
<td>-10%</td>
</tr>
<tr>
<td>V-L10</td>
<td>44%</td>
<td>-6%</td>
</tr>
<tr>
<td>V-L11</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>V-L12</td>
<td>50%</td>
<td>-43%</td>
</tr>
<tr>
<td>V-L13</td>
<td>52%</td>
<td>65%</td>
</tr>
</tbody>
</table>

$^{a}$ Conditions: Reactions were conducted on a 0.20 mmol scale with 1.0 equiv substrate, 2.0 equiv 2-bromonaphthalene, 2.0 equiv NaOtfBu, 2 mol % $\text{Pd}_2(\text{dba})_3$, 6 mol % ligand, toluene (0.2 M), 90 °C, 12-15 h. $^b$ Enantiomeric excess was determined by chiral HPLC analysis. $^c$ Negative ee values indicate the major enantiomer was the opposite configuration of other examples in the table.

Several phosphoramidites were examined to determine their effect on enantioselectivity. As shown in Table 5-3, phosphoramidite ligands V-L18, V-L20, and V-L21 provided good yields and promising enantioselectivities (up to 58% ee) of V-13b. Phosphoramidite ligands that contained (+)-bis[(R)-1-phenethyl]amine were important for enantioselectivity, as phosphoramidite ligand V-L14 and V-L19 failed to provide any selectivity (0% ee). In addition, substitution at the 3 and 3’ positions of the BINOL
backbone decreased enantioselectivity (V-L17). It seems that there is matched pair for chiral ligand (S)-Siphos-PE (V-L21), which provided V-13b in higher ee in comparison to (R)-Siphos-PE. Also, a partially hydrogenated diol backbone (V-L18, V-L21) seems to be important for higher enantioselectivities.
Table 5-3. Phosphoramidite Ligand Screen$^{a,b,c}$

We also decided to examine the coupling of different acyclic urea substrates ($V$-$12b$, $V$-$12c$) and 2-bromonaphthalene in the presence of Pd$_2$(dba)$_3$ and (R)-Siphos-PE (Scheme 5-6). The coupling proved ineffective, as these substrates provided no desired...
product under the reaction conditions. Previous control experiments have demonstrated that base-mediated substrate decomposition to the corresponding N-allyl amine may occur and be responsible for low reaction conversions.\textsuperscript{9b}

**Scheme 5-6. Effect of Substrate on Enantioselectivity**

\[ \text{V-12b} + \text{Br-Ph} \rightarrow \text{V-13c} \]

\[ \text{V-12c} + \text{Br-Ph} \rightarrow \text{V-13d} \]

5.25 **Summary and Future Directions**

In summary, we have identified bidentate phosphine (V-L2), monodentate phosphite (V-L13), and phosphoramidite (V-L21) ligands as potential scaffolds for the enantioselective synthesis of 4-substituted imidazolidin-2-ones. It is unique that three different types of ligands provide promising enantioselectivities for these reactions. We have also discovered that N-aryl substituted substrates are necessary for reactivity and selectivity. Further studies will include the synthesis of closely related ligands to examine factors that dictate selectivity (Figure 5-2).
5.3 Enantioselective Synthesis of Isoxazolidines

5.3.1 Biological Importance

Isoxazolidines are important synthetic intermediates for various natural products,\textsuperscript{12} and are core structures in biologically active compounds such as Pyrinodemin A (V-15),\textsuperscript{13a} PR968-234FB (V-16),\textsuperscript{13b} and V-17 (Figure 5-3).\textsuperscript{13c} These compounds exhibit cytotoxicity, anti-fungal activity, and can serve as transcriptional activators respectively.\textsuperscript{13} In addition, the NO bond can be cleaved to afford synthetically useful chiral 1,3-amino alcohols.\textsuperscript{14}

5.3.2 Asymmetric Methods for the Synthesis of Isoxazolidines

One of the most common methods employed for the asymmetric synthesis of isoxazolidines are 1,3-dipolar cycloaddition reactions between nitrones and alkenes.\textsuperscript{15}
These 1,3-dipolar cycloaddition reactions can be catalyzed by transition metal or organocatalysts. For example, Maruoka describes an asymmetric 1,3-dipolar cycloaddition reaction catalyzed by chiral bis-Ti(IV) oxide (S,S)-V-L22, which provides isoxazolidines in excellent diastereo- and enantiocontrol (Scheme 5-7). However, substrate scope is often limited to specific olefin substrates, which predominately afford the stereoisomer resulting from endo addition to the alkene.

**Scheme 5-7. Chiral Lewis Acid Catalyzed 1,3-Dipolar Cycloaddition**

5.33 **Project Goals and Previous Work**

In our group, we have previously developed a stereoselective synthesis of isoxazolidines through Pd-catalyzed carboetherification and carboamination reactions of N-butynylhydroxylamines. As shown below, our goal is to develop an asymmetric variant for the coupling of N-(but-3-enyl)hydroxyl amine derivatives V-20 (Scheme 5-8). The N-O bond of isoxazolidines V-21 may be cleaved to generate chiral 1,3-amino alcohol V-22.

**Scheme 5-8. Synthetic Strategy**
5.34  *Ligand Screen*

In our initial screen, we examined the coupling of **V-20a** with 2-bromonaphthalene using Pd$_2$(dba)$_3$ and commercially available ligands (Table 5-4). Moderate yields were obtained with bis-phosphine (R)-SDP (**V-L1**) and phosphite ligand **V-L10**, but low enantioselectivity was observed. Phosphoramidite ligand (R)-Siphos-PE (**V-L20**), which provided high selectivities for the formation of enantioenriched 2-substituted pyrrolidines,$^{18}$ did not effect formation of **V-21a**. Efforts to use other palladium sources such as Pd(OAc)$_2$ and weak bases such as Cs$_2$CO$_3$ led to low reactivity.
Table 5-4. Chiral Ligand Screen\textsuperscript{a,b} 

\begin{align*}
\text{V-20a} & \quad \text{Boc} \quad \text{NH} \quad \text{O} \\
& + \quad \text{Br} \quad \text{C} \quad \text{H} \\
& \quad \text{1 mol % Pd}_2(\text{dba})_3 \\
& \quad \text{4 mol % Ligand} \\
& \quad \text{NaOtBu, Toluene, 90 °C} \\
& \quad \text{V-21a}
\end{align*}

\begin{align*}
\text{V-L1} & \quad \text{PPh}_2 \\
& \quad \text{(R)-SDP} \\
& \quad 48\% \text{ yield, 0} \% \text{ ee} \\
\text{V-L2} & \quad \text{Decomposition} \\
\text{V-L23} & \quad \text{PPh}_2 \\
& \quad \text{(S)-BINAP} \\
& \quad 16\% \text{ yield, 7} \% \text{ ee} \\
\text{V-L24} & \quad \text{P(tol)_2} \\
& \quad \text{(S)-Tol-BINAP} \\
& \quad 10\% \text{ yield, 5} \% \text{ ee} \\
\text{V-L25} & \quad \text{(S)-SEGPHOS} \\
& \quad \text{Decomposition} \\
\text{V-L26} & \quad \text{PPh}_2 \\
& \quad \text{(S,S)-BDPP} \\
& \quad 25\% \text{ yield, 21} \% \text{ ee} \\
\text{V-L27} & \quad \text{PPh}_2 \\
& \quad \text{(S)-Quinap} \\
& \quad \text{Decomposition} \\
\text{V-L3} & \quad \text{PPh}_2 \\
& \quad \text{(R,S)-Ph-Bn-Siphox} \\
& \quad 10\% \text{ yield, 14} \% \text{ ee} \\
\text{V-L8} & \quad \text{P-OPh} \\
& \quad \text{(R)-SHIP} \\
& \quad \text{Decomposition} \\
\text{V-L10} & \quad \text{P-OPh} \\
& \quad \text{45\% yield, 8} \% \text{ ee} \\
\text{V-L20} & \quad \text{P-N} \\
& \quad \text{(R)-Siphos-PE} \\
& \quad \text{Decomposition}
\end{align*}

\textsuperscript{a} Conditions: Reactions were conducted on a 0.20 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.0 equiv \text{NaOtBu}, 1 mol % \text{Pd}_2(\text{dba})_3, 4 mol % ligand, toluene (0.2 M), 90 °C, 14 h. \textsuperscript{b} Enantiomeric excess was determined by chiral HPLC analysis.

5.35 \textit{Summary and Future Directions}

To this date, no chiral ligand has been identified as a primary lead for the asymmetric synthesis of isoxazolidines. Base-mediated substrate decomposition was observed in many of these reactions. Future studies will involve screening of other chiral
ligands and employing substrates such as **V-20b** or **V-23** for the enantioselective synthesis of isoxazolidines (Scheme 5-9). Recent work in the Wolfe lab has shown that the cyclizing atom (N or O) can have a drastic effect on diastereoselectivity for the synthesis of substituted isoxazolidines.\(^{17}\)

**Scheme 5-9.** Future Ligand Screen/Other Substrates

![Scheme 5-9](image)

5.4 **Enantioselective Synthesis of Pyrazolidines**

5.41 **Biological Importance**

Pyrazolidines are core structures in biologically relevant molecules such as anti-diabetic **V-25**,\(^{19}\) and potent neuroprotective agent FKBP12 antagonist **V-26** (Figure 5-4).\(^{20}\) Additionally, pyrazolidines may be oxidized to provide biologically active pyrazolines,\(^{21}\) or cleaved for the synthesis of enantioenriched 1,3-diamines, which have served as HIV-1 protease inhibitors.\(^{22}\)

**Figure 5-4.** Biologically Important Pyrazolidines
5.42 Asymmetric Methods for the Synthesis of Pyrazolidines

A recent method for the enantioselective synthesis of pyrazolidines was described by Kobayashi,\textsuperscript{23} which involved chiral zirconium catalyst derived from (\textit{R})-\textit{V-L28} for the [3+2] cycloaddition reaction of hydrazones such as \textit{V-27} and ketene dimethyl acetal (Scheme 5-10). Although these reactions provided pyrazolidine products (\textit{V-28}) in good yield and enantioselectivity, other olefins substrates such as ethyl vinyl ether led to a mixture of diastereomers. Leighton and coworkers were able to address this limitation by using a chiral silicon Lewis acid (\textit{S,\textit{S}-V-L29}), which facilitated cycloaddition of hydrazone \textit{V-27} and ethyl vinyl ether for the synthesis of pyrazolidine \textit{V-29} in good yield, enantioselectivity, and diastereoselectivity (Scheme 5-10).\textsuperscript{24}

**Scheme 5-10. [3+2]-Cycloaddition Reactions**

Asymmetric gold-catalyzed hydroamination reactions have emerged as an efficient method for the synthesis of enantioenriched 2-vinyl pyrazolidines such as \textit{V-31}.\textsuperscript{25} Treatment of allene \textit{V-30} with chiral Au complex \textit{V-L30} provided \textit{V-31} in 98% yield and 99% ee. This method is high yielding and selective for the synthesis of
pyrazolidines, but the substrate scope is limited to homoallenic substrates shown in Scheme 5-11.

**Scheme 5-11.** Enantioselective Au-Catalyzed Hydroamination

![Scheme 5-11](image)

5.43 Project Goals and Previous Work

Our aim is to develop an asymmetric carboamination reaction that couples \( V-32a \) and an aryl or alkenyl halide for the formation of pyrazolidine \( V-33 \) (Scheme 5-12). The \( \text{N-N} \) bond may be cleaved to provide synthetically useful chiral 1,3-diamines \( V-34 \).

**Scheme 5-12.** Synthetic Strategy

![Scheme 5-12](image)

Preliminary work on asymmetric carboamination reactions for the synthesis of pyrazolidines were initially conducted by Dr. Natalie Giampietro, a former graduate student in the group. Of the chiral ligands screened, Dr. Giampietro typically observed decomposition of the starting material. One exception was the coupling of \( V-35 \) and 2-bromonaphthlene in the presence of \( \text{Pd}_2(\text{dba})_3 \) and bis-phosphine ligand \((R)\)-BINAP, which provided pyrazolidine product \( V-36 \) in 48% yield, but as a racemic mixture (Scheme 5-13).\(^{26}\)
5.44 **Ligand Screen**

A brief ligand screen was examined for the coupling of V-32a and 2-bromonaphthalene with Pd\(_2\)(dba)\(_3\) as the palladium source (Table 5-5). Bis-phosphines, monodentate phosphines, and phosphite ligands provided V-32a in low yield and ee. However, the use of Pd/(R)-Siphos-PE catalyst system afforded V-33a in moderate yield and ee. Base-mediated substrate decomposition was often observed in these reactions, which may be responsible for low yields. The non-cyclizing nitrogen may also coordinate to the palladium catalyst, which would lead to decreased reactivity.
Table 5-5. Chiral Ligand Screen\textsuperscript{a,b,c}

\[
\begin{array}{c}
\begin{array}{c}
\text{Boc} \\
\text{NH}
\end{array} \\
\begin{array}{c}
\text{NH} \\
\text{V-32a}
\end{array}
\end{array} + \begin{array}{c}
\begin{array}{c}
\text{Br} \\
\text{Br}
\end{array} \\
\begin{array}{c}
\text{V-33a}
\end{array}
\end{array} \\
\text{2 mol % Pd}_2(\text{dba})_3 \\
\text{6 mol % Ligand} \\
\text{NaOtBu, Toluene, 90 °C}
\]

\begin{itemize}
\item \textbf{V-L20} \textit{(R)-Siphos-PE} \\
37% yield, 43% ee
\item \textbf{V-L12} \textit{(S)-BINAP} \\
37% yield, 0% ee
\item \textbf{V-L8} \textit{(R)-SHIP} \\
15% yield, 15% ee
\item \textbf{V-L31} \textit{(R)-MOP} \\
16% yield, 45% ee
\item \textbf{V-L13} \\
15% yield, 15% ee
\end{itemize}

\textsuperscript{a} Conditions: Reactions were conducted on a 0.20 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 2.0 equiv NaOtBu, 2 mol % Pd\textsubscript{2}(\text{dba})\textsubscript{3}, 6 mol % ligand, toluene (0.20 M), 90 °C, 12-15 h. \textsuperscript{b} Enantiomeric excess was determined by chiral HPLC analysis. \textsuperscript{c} Negative ee values indicate the major enantiomer was the opposite configuration of other examples in the table.

5.45 Summary and Future Directions

Preliminary studies have identified \textit{(R)-Siphos-PE} as a potential ligand scaffold for the asymmetric synthesis of pyrazolidines. The non-cyclizing nitrogen atom on \textbf{V-32a} may be coordinating to the catalyst system, which may prevent alkene insertion and lead to substrate decomposition. Other phosphoramidite ligands and substrates bearing different \textit{N}-protecting groups should be examined.
5.5 Enantioselective Synthesis of Tetrahydrofurans

5.5.1 Biological Importance

The tetrahydrofuran core can be found in a variety of biologically active natural products that possess anti-tumor, anti-viral, and anti-microbial activity.\textsuperscript{27} For example, simplakidine A (V-37) and annonaceous acetogenin asimicin (V-38) are natural products that exhibit anti-cancer activity (Figure 5-5).\textsuperscript{27c,28}

**Figure 5-5.** Biologically Active Tetrahydrofuran Natural Products

5.5.2 Asymmetric Methods for the Synthesis of Tetrahydrofurans

There have been many methods developed for the stereoselective synthesis of tetrahydrofurans, which involve nucleophilic substitution processes or alkene functionalization reactions.\textsuperscript{29} However, asymmetric variants that provide enantioenriched tetrahydrofurans are less common. A classical method for the asymmetric synthesis of tetrahydrofurans is a stereoselective nucleophilic substitution reaction of functionalized chiral alcohols. As shown in Scheme 5-14, Britton and coworkers have demonstrated that microwave heating of chlorotriols such as V-39 facilitates regioselective cyclization for the formation of tetrasubstituted tetrahydrofuran (+)-Goniothalesdiol (V-40).\textsuperscript{30} The reaction is high yielding, regioselective and does not require protecting group manipulations, but the synthesis of the chlorotriol substrates can be lengthy.
Kang and coworkers reported a catalytic enantioselective iodocyclization of γ-hydroxy-cis-alkenes for the synthesis of enantioenriched 2-substituted tetrahydrofurans up to 90% ee (Scheme 5-15). Treatment of $\text{V-41}$ to a solution of $(R,R)$-Salen-Co(II) ligand $\text{V-L32}$, NCS, and iodine promoted enantioselective iodocyclization to generate tetrahydrofurans $\text{V-42}$. NCS was required for high enantioselectivities, which the authors speculate enhances the acidity of $\text{V-L32}$. The authors also state that this reaction is sensitive to the relative amounts of the involved reagents and requires a multi-step procedure to properly generate the active catalyst. Furthermore, the synthesis of analogs requires the use of different γ-hydroxy-cis-alkenes.

5.53 Project Goals and Previous Work

We were interested in developing an asymmetric Pd-catalyzed carboetherification reaction that would convert 4-penten-1-ol derivatives $\text{V-43}$ to tetrahydrofuran $\text{V-44}$ (Scheme 5-16). $^{31}$ This method would allow for the synthesis of a variety of
enantioenriched 2-(arylmethyl)- and 2-(alkenylmethyl)tetrahydrofurans from a common achiral intermediate.

**Scheme 5-16. Synthetic Strategy**

\[
\begin{align*}
\text{V-43} & \quad \text{Pd, L}^* \\
R = \text{H, Me, Ph} \\
\text{R}^1 = \text{aryl, alkenyl} \\
\text{Base, Solvent, Temp} & \quad \text{V-44}
\end{align*}
\]

Initial studies were conducted by Dr. Qifei Yang, who discovered that monodentate ligand (S)-NMDPP provided tetrahydrofuran V-44b in 45% ee (Scheme 5-17). However, no chiral ligand gave promising results when unsubstituted 4-penten-1-ol (V-43a) was employed as the substrate. My task was to examine other chiral ligands for asymmetric carboetherification reactions.

**Scheme 5-17. Preliminary Studies**

**5.54 Ligand Screen**

Chiral phosphine ligands were initially examined for the coupling of 4-penten-1-ol (V-43a) and 2-bromonaphthalene. As shown in Table 5-6, bidentate and monodentate phosphine ligands did not provide any promising leads for the enantioselective synthesis of V-44a.
<table>
<thead>
<tr>
<th>Ligand</th>
<th>Formula</th>
<th>Yield (%)</th>
<th>Enantiomeric Excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-L1</td>
<td>(R)-SDP</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>V-L23</td>
<td>(S)-BINAP</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>V-L27</td>
<td>(S)-Quinap</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>V-L31</td>
<td>(R)-MOP</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>V-L3</td>
<td>(R,Si)-Ph-Bn-Siphox</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>V-L33</td>
<td>(S)-NMDPP</td>
<td>Decomposition</td>
<td>Enantiomeric excess was determined by chiral HPLC analysis.</td>
</tr>
</tbody>
</table>

a Conditions: Reactions were conducted on a 0.50 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtfBu, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, THF (0.25 M), 65 °C, 12 h. b Enantiomeric excess was determined by chiral HPLC analysis.

In general, optically active phosphoramidite and phosphite ligands were ineffective at providing selectivity for the coupling of V-43a and 2-bromonaphthalene (Table 5-7). Phosphoramidite ligands such as (S,R,R)-V-L16 and (R)-Siphos-PE (V-L20) provided moderate yields of V-44a, but no enantioselectivity was observed. Substrate decomposition through oxidation of the alcohol V-43a to the corresponding aldehyde may contribute to the low yields in these reactions.33
Table 5-7. Phosphoramidite and Phosphite Ligand Screen$^{ab}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Structure</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-L14</td>
<td><img src="image" alt="V-L14" /></td>
<td>$2\ \text{mol}\ %\ Pd(OAc)_2$ $4\ \text{mol}\ %\ \text{Ligand}$ NaOtfBu, THF, 65 °C</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>V-L20</td>
<td><img src="image" alt="V-L20" /></td>
<td></td>
<td>(R)-Siphos-PE</td>
<td>21% yield, 0% ee</td>
</tr>
<tr>
<td>V-L34</td>
<td><img src="image" alt="V-L34" /></td>
<td></td>
<td></td>
<td>31% yield, 0% ee</td>
</tr>
<tr>
<td>V-L35</td>
<td><img src="image" alt="V-L35" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Conditions: Reactions were conducted on a 0.50 mmol scale with 1.0 equiv substrate, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaOtfBu, 2 mol % Pd(OAc)$_2$, 4 mol % ligand, THF (0.25 M), 65 °C, 12 h. Enantiomeric excess was determined by chiral HPLC analysis.

We examined V-43b as a substrate for asymmetric carboetherification reactions. Bis-phosphine ligands effectively catalyzed the coupling of V-43b and 2-bromonaphthalene in good yields, but low enantioselectivities. For example, a catalyst system of Pd$_2$(dba)$_3$ and (S)-H$_8$-BINAP (V-L36) provided tetrahydrofuran V-44b in 92% yield and 0% ee. The H$_8$-BINAP backbone seems to be important for high reactivity in these reactions (Table 5-8).
Table 5-8. Bidentate Phosphine Ligand Screen$^{a,b,c}$

As shown below in Table 5-9, a majority of the phosphoramidite and phosphite ligands screened provided tetrahydrofuran $\ce{V-44b}$ in low yields and enantioselectivities. However, 2-phenylcyclohexanol derived phosphite ligand $\ce{V-L10}$ generated $\ce{V-44b}$ in promising enantioselectivity (53% ee). In cases where no reaction was observed (e.g., $(S,S,S)$-$\ce{V-L15}$), conducting the reaction at higher temperatures (110 °C) in toluene did not facilitate reaction.

---

$^a$ Conditions: Reactions were conducted on a 0.25 mmol scale with 1.0 equiv substrate, 2.0 equiv 2-bromonaphthalene, 2.0 equiv NaOtBu, 1 mol % Pd$_2$(dba)$_3$, 4 mol % ligand, THF (0.25 M), 65 °C, 12 h. $^b$ Enantiomeric excess was determined by chiral HPLC analysis. $^c$ Negative ee values indicate the major enantiomer was the opposite configuration of other examples in the table.
Table 5-9. Phosphoramidite and Phosphite Ligand Screen

A screen of optically active monodentate phosphine ligands yielded promising results (Table 5-10). Treatment of V-43b and 2-bromonaphthalene with Pd$_2$(dba)$_3$ and (S)-Quinap (V-L27) provided 2-(arylmethyl)tetrahydrofuran V-44b in 83% yield and

---

Table 5-10. Phosphoramidite and Phosphite Ligand Screen

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Reaction</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,S,S)-V-L15</td>
<td>No Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S,R,R)-V-L16</td>
<td>No Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-L20</td>
<td>(R)-Siphos-PE</td>
<td>17%</td>
<td>12% ee</td>
</tr>
<tr>
<td>V-L37</td>
<td>38%</td>
<td>0% ee</td>
<td></td>
</tr>
<tr>
<td>V-L38</td>
<td>55%</td>
<td>0% ee</td>
<td></td>
</tr>
<tr>
<td>V-L8</td>
<td>(R)-SHIP</td>
<td>No Reaction</td>
<td></td>
</tr>
<tr>
<td>V-L10</td>
<td>17%</td>
<td>-53% ee</td>
<td></td>
</tr>
<tr>
<td>V-L13</td>
<td>No Reaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

a Conditions: Reactions were conducted on a 0.25 mmol scale with 1.0 equiv substrate, 2.0 equiv 2-bromonaphthalene, 2.0 equiv NaOrBu, 1 mol % Pd$_2$(dba)$_3$, 4 mol % ligand, THF (0.25 M), 65 °C, 12 h. b Enantiomeric excess was determined by chiral HPLC analysis. c Negative ee values indicate the major enantiomer was the opposite configuration of other examples in the table.
66% ee. We then decided to examine commercially available Quinap ligand derivatives V-L40 and V-L41, but they were not as effective as (S)-Quinap. It is interesting to note that the Pd/(S)-Quinap catalyst system was unproductive for 4-penten-1-ol (V-43a), which suggests that disubstitution at the C1 position of V-43b is important for enantioselectivity. Efforts to improve the ee by conducting the reaction at lower temperatures (25 °C) resulted in low conversion.

**Table 5-10. Monodentate Ligand Screen**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Enantiomeric Excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-L3</td>
<td>37%</td>
<td>-30% ee</td>
</tr>
<tr>
<td>V-L4</td>
<td>No Reaction</td>
<td>(R)-SITCP</td>
</tr>
<tr>
<td>V-L33</td>
<td>80%</td>
<td>40% ee</td>
</tr>
<tr>
<td>V-L39</td>
<td>No Reaction</td>
<td>(R)-dihydrooxazole</td>
</tr>
<tr>
<td>V-L40</td>
<td>3%</td>
<td>0% ee</td>
</tr>
<tr>
<td>V-L41</td>
<td>53%</td>
<td>44% ee</td>
</tr>
</tbody>
</table>

**Diagram:**

- **V-43b** + **Br** → **V-44b**

**Conditions:** Reactions were conducted on a 0.25 mmol scale with 1.0 equiv substrate, 2.0 equiv 2-bromonaphthalene, 2.0 equiv NaOtfBu, 1 mol % Pd2(dba)3, 4 mol % ligand, THF (0.25 M), 65 °C, 12 h. Enantiomeric excess was determined by chiral HPLC analysis. Negative ee values indicate the major enantiomer was the opposite configuration of other examples in the table.
5.55 Summary and Future Directions

In conclusion, we have examined different chiral ligands for the asymmetric carboetherification reaction of 4-penten-1-ol (V-43a) or 2-methylhex-5-en-2-ol (V-43b), and 2-bromonaphthalene. No chiral ligands were effective for enantioselective carboetherification of 4-penten-1-ol (V-43a), as decomposition of the substrate was often observed. Conversely, (S)-Quinap ligand provided promising results for enantioselective carboetherification of V-43b, generating 2-(naphthyl)tetrahydrofuran (V-44b) in high yield (83%) and promising enantioselectivity (66% ee). As shown below in Figure 5-6, future studies will involve the synthesis and examination of other closely related ligands such as (S)-Quinap derivatives (V-L42),34 (S)-H-MOP (V-L43),35 and (S)-Kenphos (V-L44),36 which have been effective for asymmetric hydroborations, hydrogenations and Suzuki-Miyaura processes respectively.

Figure 5-6. Other Monodentate Phosphine Ligands

\[ R = \text{Me, Cy, t-Bu (V-L42)} \quad (S)-\text{H-MOP (V-L43)} \quad (S)-\text{Kenphos (V-L44)} \]
Experimental Section

General Considerations

All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Palladium acetate and tris(dibenzylideneacetone)dipalladium (0) were purchased from Strem Chemical Co. and used without further purification. All ligands were either purchased from commercial sources (Strem Chemical Co. or Aldrich Chemical Co.) or used without further purification, or were synthesized according to published procedures.\(^{37}\) 4-penten-1-ol (V-43a) was purchased from Aldrich Chemical Co. and used without further purification. 1- Allyl-3-ethyl-1-phenylurea (V-12a),\(^9\) 1-allyl-3-ethyl-1-phenylurea (V-12b),\(^9\) 1-allyl-1-benzyl-3-tert-buty lurea (V-12c),\(^9\) tert-butyl but-3- enyloxycarbamate (V-20a),\(^{17b}\) tert-butyl 2-(2-methylpent-4-en-2-yl)hydrazinecarboxylate (V-32a),\(^{26}\) and 2-methylhex-5-en-2-ol (V-43b),\(^{31a}\) were prepared according to published procedures. Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be \(\geq95\%\) pure by \(^1\)H NMR, GC and/or combustion analysis.
Experimental Procedures and Compound Characterization Data

General Procedure for Enantioselective Pd-Catalyzed Carboamination:

1-Benzyl-3-(4-methoxyphenyl)-4-(naphthalen-2-ylmethyl)imidazolidin-2-one (V-13b). A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with Pd$_2$(dba)$_3$ (3.7 mg, 2 mol % complex, 4 mol % Pd), chiral ligand (6 mol %), 1-allyl-3-ethyl-1-phenylurea V-12a (50 mg, 0.2 mmol), 2-bromonaphthalene (83 mg, 0.4 mmol) and NaO$_{tBu}$ (38 mg, 0.4 mmol). The tube was purged with nitrogen and toluene (1 mL, 0.2 M) was added via syringe. The mixture was heated to 90 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis (ca. 12-15 h).

The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH$_4$Cl (2 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound as a pale yellow solid.

M$\text{p}$ 138–140 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81 7.79 (m, 1 H), 7.76 7.70 (m, 2 H), 7.52 7.44 (m, 5 H), 7.40 7.20 (m, 3 H), 7.18 7.12 (m, 3 H), 6.98 (d, $J = 15.0$ Hz, 2 H), 4.50 4.44 (m, 1 H), 4.38 (q, $J = 15.0$ Hz, 2 H), 3.84 (s, 3 H), 3.24 (t, $J = 9.0$ Hz, 1 H), 3.17 (dd, $J = 3.0$, 13.5 Hz, 1 H), 3.11 (dd, $J = 5.5$, 9.0 Hz, 1 H), 2.84 (dd, $J = 9.0$, 14.0 Hz, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.3, 156.4, 136.9, 133.8, 133.4, 132.3, 131.7, 128.5, 128.2, 128.0, 127.9, 127.6, 127.4, 127.3, 127.2, 126.1, 125.6, 123.6, 114.4, 55.5, 55.1, 47.9, 46.3, 38.2; IR (film) 1697, 1512, 1246 cm$^{-1}$; MS (ESI) 423.2061 (423.2067 calcd for C$_{28}$H$_{26}$N$_2$O$_2$, M + H$^+$). The enantiomeric excess for compounds V-13b in Tables 5-1, 5-2, and 5-3 were determined by chiral HPLC analysis (chiralcel OD-H, 0.46 cm x 15 cm, 20% iPrOH/hexanes, 2.0 mL/min, $\lambda = 254$ nm, RT = 6.0$^{(\text{major})}$ and 17.0$^{(\text{minor})}$ min).
**tert-Butyl 3-(naphthalen-2-ylmethyl)isoxazolidine-2-carboxylate (V-21a).** A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with Pd$_2$(dba)$_3$ (1.8 mg, 1 mol % complex, 2 mol % Pd), chiral ligand (4 mol %), 2-bromonaphthalene (50 mg, 0.24 mmol) and NaOtBu (19 mg, 0.20 mmol). The tube was purged with nitrogen, then a solution of tert-butyl but-3-enyloxycarbamate V-20a (37 mg, 0.2 mmol) and toluene (1 mL, 0.2 M) was added via syringe. The mixture was heated to 90 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis (ca. 12-15 h). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH$_4$Cl (2 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound as a pale yellow oil. Spectroscopic data were consistent with those previously reported in the literature.$^{17b}$ The enantiomeric excess for compounds V-21a in Table 5-4 was determined by chiral HPLC analysis (chiralcel OJ-H, 0.46 cm x 25 cm, 5% iPrOH/hexanes, 2.0 mL/min, $\lambda = 254$ nm, RT = 15.5(minor) and 20.0(minor) min).

**tert-Butyl 3,3-dimethyl-5-(naphthalen-2-ylmethyl)pyrazolidine-1-carboxylate (V-33a).** A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with Pd$_2$(dba)$_3$ (3.7 mg, 2 mol % complex, 4 mol % Pd), chiral ligand (6 mol %), 2-bromonaphthalene (50 mg, 0.24 mmol) and NaOtBu (38 mg, 0.4 mmol). The tube was purged with nitrogen, then a solution of tert-butyl 2-(2-methylpent-4-en-2-yl)hydrazone carboxylate V-32a (43 mg, 0.2 mmol) and toluene (1 mL, 0.2 M) was added via syringe. The mixture was heated to 90 °C with stirring until the starting material had been...
consumed as judged by GC or $^1$H NMR analysis (ca. 12-15 h). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH$_4$Cl (2 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.82-7.76 (m, 3 H), 7.62 (s, 1 H), 7.44 (dquint, $J = 1.5$, 7.5 Hz, 2 H), 7.34 (d, $J = 7.5$ Hz, 1 H), 4.40 (s, 1 H), 3.58 (s, 1 H), 3.29 (dd, $J = 4.0$, 13.0 Hz, 1 H), 2.89 (dd, $J = 8.5$, 13.0, 1 H), 1.95 (dd, $J = 7.5$, 12.5 Hz, 1 H), 1.52 (s, 9 H), 1.14 (s, 3 H), 0.98 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.3, 135.7, 133.4, 132.1, 127.9, 127.7, 127.6, 127.5, 125.9, 125.4, 80.0, 60.9, 59.8, 47.0, 41.0, 28.4, 25.1, 24.7 (1 peak is missing due to incidental equivalence); IR (film) 1716 cm$^{-1}$; MS (ESI) 363.2034 (363.2043 calcd for C$_{21}$H$_{28}$N$_2$O$_2$, M + Na$^+$). The enantiomeric excess for compounds V-33a in Table 5-5 was determined by chiral HPLC analysis (chiralcel OD-H, 0.46 cm x 15 cm, 5% iPrOH/hexanes, 0.5 mL/min, $\lambda = 254$ nm, RT = 6.6$^{(major)}$ and 7.6$^{(minor)}$ min).

**General Procedure for Enantioselective Pd-Catalyzed Carboetherification:**

![Diagram of 2-(Naphthalen-2-ylmethyl)tetrahydrofuran (V-44a)](image)

**2-(Naphthalen-2-ylmethyl)tetrahydrofuran (V-44a).** A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with Pd(OAc)$_2$ (2.2 mg, 2 mol % Pd), chiral ligand (4 mol %), 2-bromonaphthalene (124 mg, 0.24 mmol) and NaO$^t$Bu (58 mg, 0.6 mmol). The tube was purged with nitrogen, then a solution of 4-penten-1-ol V-43a (43 mg, 0.5 mmol) and THF (2 mL, 0.25 M) was added via syringe. The mixture was heated to 65 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis (ca. 12 h). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH$_4$Cl (2 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica...
gel to afford the title compound as a pale yellow oil. Spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{31a} The enantiomeric excess for compounds V-44a in Tables 5-6 and 5-7 were determined by chiral HPLC analysis (chiralcel OJ-H, 0.46 cm x 25 cm, 1% iPrOH/hexanes, 2.0 mL/min, $\lambda = 254$ nm, RT = 11.8\textsuperscript{(major)} and 14.3\textsuperscript{(minor)} min).

\textbf{2,2-Dimethyl-5-(naphthalen-2-ylmethyl)tetrahydrofuran (V-44b).} A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with charged with Pd$_2$(dba)$_3$ (2.3 mg, 1 mol % complex, 2 mol % Pd), chiral ligand (4 mol %), 2-bromonaphthalene (104 mg, 0.5 mmol) and NaOtBu (48 mg, 0.5 mmol). The tube was purged with nitrogen, then a solution of 2-methylhex-5-en-2-ol V-43b and THF (1 mL, 0.25 M) was added via syringe. The mixture was heated to 65 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis (ca. 12 h). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH$_4$Cl (2 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel to afford the title compound as a pale yellow oil. Spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{31a} The enantiomeric excess for compounds V-44b in Tables 5-8, 5-9 and 5-10 were determined by chiral HPLC analysis (chiralcel OJ-H, 0.46 cm x 25 cm, 2% iPrOH/hexanes, 1.0 mL/min, $\lambda = 254$ nm, RT = 6.7\textsuperscript{(major)} and 7.4\textsuperscript{(minor)} min).
References:


Chiral phosphtite ligands \((V-L_9 \text{ – } V-L_{13})\) were synthesized and generously provided by Josh Neukom.


32 Dr. Qifei Yang, unpublished results.


