Carboamination Methodology to the Synthesis of 2,5-*trans*-Pyrrolidines and Isoxazolidines

by

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Dedication

To Mom and Dad: I can make tents very well!

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Ac ..... acyl
AIBN..... 2,2′-Azobis(2-methylpropionitrile)
Ar.....aryl
BINAP .....2,2'-bis(diphenylphosphino)-1,1'-biphenyl
BHT 3,5-Di-*tert*-4-butylhydroxytoluene
Bn ..... benzyl
Boc..... *tert*-butyl carbamate
bpy .....2,2′-Bipyridyl
Bt .....benzotriazole
n-Bu .....butyl
t-Bu ..... *tert*-butyl
CBZ .....benzyl carbamate
CDI ..... 1,1′-Carbonyldiimidazole
Cp*..... pentamethylcyclopentadienyl
18-crown-6..... 1,4,7,10,13,16-Hexaoxacyclooctadecane
Cy .....cyclohexyl
d.....days
dba ..... dibenzylidene acetone
DIAD .....Diisopropyl azodicarboxylate
DPE-Phos.....(oxydi-2,1-phenylene)bis(diphenylphosphine)
DBU .....1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF ..... N,N-dimethylformamide
dppb .....1,2-bis(diphenylphosphinyl)butane
dppe .....1,2-bis(diphenylphosphinyl)ethane
dppf ..... 1,1′-Bis(diphenylphosphino)ferrocene
dr.....diastereomeric ratio
EDCI.....N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
ee.....enantiomeric excess
EI .....electron impact
eq ..... equation
equiv ..... equivalence
ESI .....electrospray
EWG .....electron withdrawing group
GC..... gas chromatography
h .....hours
HPLC ..... high performance liquid chromatography
IBX ..... 2-iodoxybenzoic acid
IR ..... infrared spectrometry
L_n .....ligand

M.....molarity
Me.....methyl
MS.....mass spectrometry
Ms.....mesyl
MTPA.....α-Methoxy-α-(trifluoromethyl)phenylacetic acid
NMR.....nuclear magnetic resonance
nOe.....nuclear Overhauser effect
Ns.....nosyl
OAc.....acetate
OEt.....ethoxide
OMe.....methoxide
Ot-Bu.....*tert*-butoxide
PG.....protecting group
PMP.....para-methoxyphenyl
Ph.....phenyl
i-Pr.....isopropyl
rt.....room temperature
RT.....retention time
RuPhos.....2-dicyclohexylphosphino-2',6'-di-iso-propoxy-1,1'-biphenyl
S-Phos.....2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl
TBAF.....tetrabutylammonium fluoride
TEA.....triethylamine
THF.....tetrahydrofuran
TLC.....thin layer chromatography
TMSCl.....chlorotrimethylsilane
o-tol.....*ortho*-tolyl
TFA.....trifluoroacetic acid
Ts.....tosyl
Xantphos.....4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Abstract

This thesis details the development of new methods for the synthesis of four classes of biologically relevant heterocycles: 2,5-*trans*-pyrrolidines, benzofused 1-azabicyclo[3.3.0]octanes, benzofused 1-azabicyclo[4.3.0]nonanes, and 3,5-*cis* and 4,5-*trans* isoxazolidines. This methodology inolves palladium-catalyzed carboamination reactions of alkenes bearing pendant heteroatom nucleophiles with aryl/alkenyl halides. The scope and limitations of these new methods are described; models for the stereochemical outcome of these transformations are presented.

The synthesis of 2,5-*trans*-disubstituted pyrrolidines is accomplished via Pd-catalyzed carboamination reactions of 4-(but-3-en-1-yl)oxazolidin-2-ones. The requisite substrates are synthesized in 5 to 8 steps from serine methyl ester, and can be generated in enantiopure form from the nonracemic amino acid. The carboamination reactions between these substrates and aryl or alkenyl halides afford tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one products with up to three stereocenters in excellent diastereoselectivity. The oxazolidinone can be cleaved to yield 2,5-*trans*-disubstitued pyrrolidines via either reduction or hydrolysis. These heterocyclic products contain an alcohol side-chain, which could be used for further synthetic manipulations.

A tandem intramolecular *N*-arylation/carboamination process allows for the generation of benzofused 1-azabicyclo[3.3.0]octanes and benzofused 1-azabicyclo[4.3.0]nonanes from 1-(2-bromophenyl)hex-5-en-2-amine and 1-(2-bromophenyl)hept-6-en-3-amine derivatives. A straightforward one-pot reaction with a

single catalyst effects the tandem coupling of these substrates with a variety of aryl chlorides. This affords tricyclic products in moderate to good yield and diastereoselectivity. These transformations illustrate the influence of amine nucleophilicity on the relative rates of carbon nitrogen bond forming reductive elmination vs. alkene aminopalladation of palladium(aryl)(amido) complexes.

Finally, the synthesis of substituted isoxazolidines via Pd-catalyzed carboamination reactions of *O*-butenyl hydroxylamines is described. These reactions afford *cis*-2,5-disubstitued products in excellent diastereoselectivities (up to >20:1), which are considerably higher than those obtained in related carboetherification reactions of *N*-butenyl hydroxylamines. Studies on the influence of the nitrogen subsituent on the stereochemical outcome of both the carboamination and the carboetherication reactions are described, along with experiments that have led to an expansion in scope of previously described carboetherification reactions of *N*-butenyl hydroxylamines.

Chapter 1

Previous Carboamination Reactions for the Synthesis of Pyrrolidines and Isoxazolidines

1.1 Importance of Alkaloids and Heterocycles

Alkaloids and heterocyclic structures are found in a variety of natural products.[1] As such, these scaffolds have been synthetic targets for organic chemists as they sought to understand the chemistry of naturally occurring molecules.[2] Additionally, many pharmaceuticals are derived from or inspired by natural products.[1,3] As chemists sought to simplify synthetic structures for pharmaceutical leads, alkaloids and heterocycles have remained important targets.[4] Thus, new methods for their synthesis have the potential lead to novel pharmaceuticals which could treat conditions which are not currently curable.

1.2 Previous Carboamination Reactions for the Synthesis of Pyrrolidines

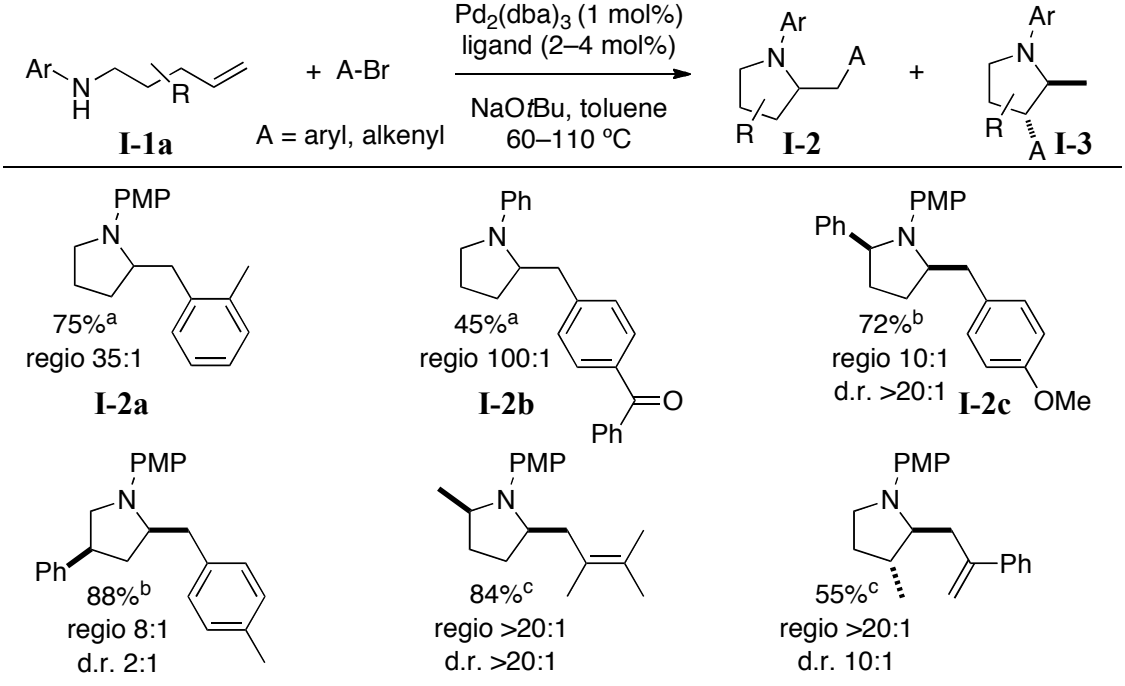
Carboamination methodology is an area of synthesis which has been developed over the last 15 years.[5] Reactions of this type require an amine with a pendent alkene and generate a new nitrogen containing ring or alkaloid. In the course of the reaction the olefin π-bond is broken and a new C-N and a new C-C bond are formed. These reactions can be catalyzed by either palladium or copper complexes.[5,6] A variety of heterocycles can be synthesized using this methodology; however, this thesis will detail work related

to the synthesis of pyrrolidines and isoxazolidines with only the relevant examples from the literature being discussed. Other methods for the synthesis of these heterocycles will be discussed in later chapters.

1.2.1 N-Aryl Pyrrolidines

In 2004, the Wolfe group first reported the palladium catalyzed carboamination reaction of γ-(*N*-arylamino) alkenes with aryl bromides (Scheme 1-1).[7] The use of $Pd_2(dba)_3$ as a precatalyst with dppe or dppb as the supporting phosphine ligand allowed for successful generation of pyrrolidine products.[8] This work was later extended to the use of alkenyl bromides and aryl chlorides as coupling partners.[9] Appropriately substituted pentenyl amine substrates lead to 2,5-*cis*-pyrrolidines (**I-2c,e**) or 2,3-*trans*-pyrrolidines (**I-2f)** with good diastereocontrol. However, 2,4-disubstituted pyrrolidines (**I-2d**) were generated with low stereocontrol. In addition, some products were formed as mixtures of regioisomers (**I-2a,c,d**) due to competing β-hydride elimination processes.

Scheme 1-1: Representative Examples of *N*-Aryl Pyrrolidines



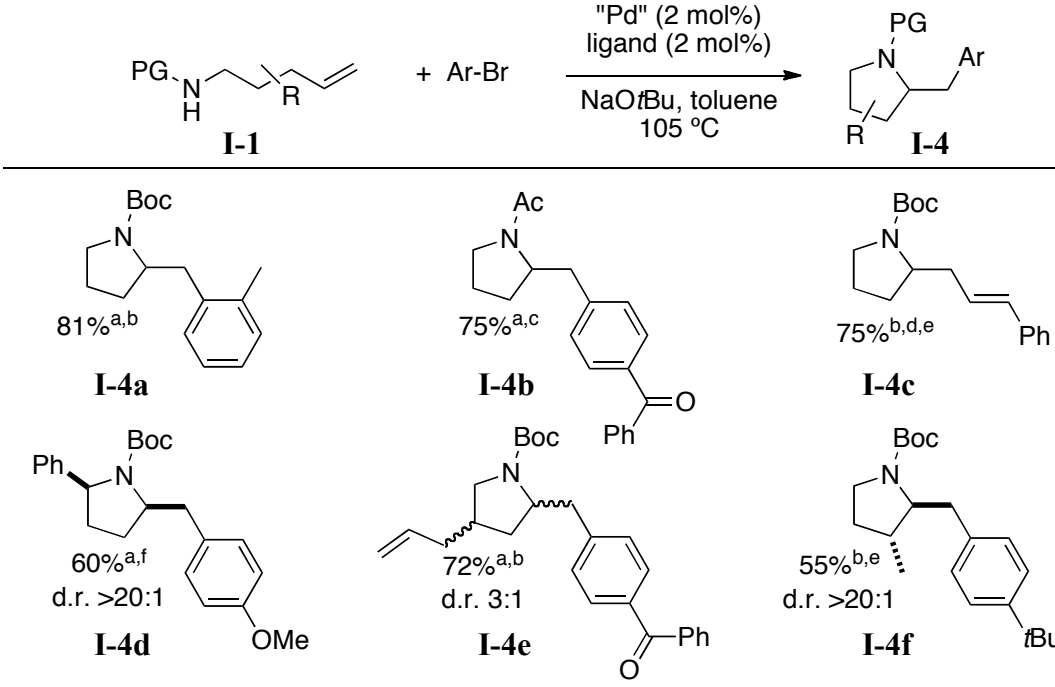
I-2d **I-2e** **I-2f**

[a] Reaction conducted at 60 ºC with dppb. [b] Reaction conducted at 100 ºC with dppe. [c] Reaction conducted at 110 ºC with P(2-furyl)$_3$.

1.2.2 N-Boc and N-Acyl Pyrrolidines

The palladium-catalyzed carboamination method was expanded to include pentenyl amine substrates which had cleavable nitrogen protecting groups, as most *N*-aryl substituents are not readily removed.[10] As a result, carbamate and acyl protecting groups on the cyclizing nitrogen were investigated to improve the synthetic utility of this process. In addition, the regioisomer observed in the synthesis of *N*-aryl pyrrolidines via carboamination was not observed with *N*-Boc or *N*-acyl pentenyl amine carboamination. Use of a palladium precatalyst and a bidentate ligand led to the same stereochemical outcome, with 2,5-*cis* and 2,3-*trans* pyrrolidines being generated (Scheme 1-2). Similarly, 2,4-disubstituted pyrrolidines (**I-4e**) were generated in low stereoselectivity (3:1 dr).

Scheme 1-2: Representative Examples of N-Boc and N-Acyl Pyrrolidines

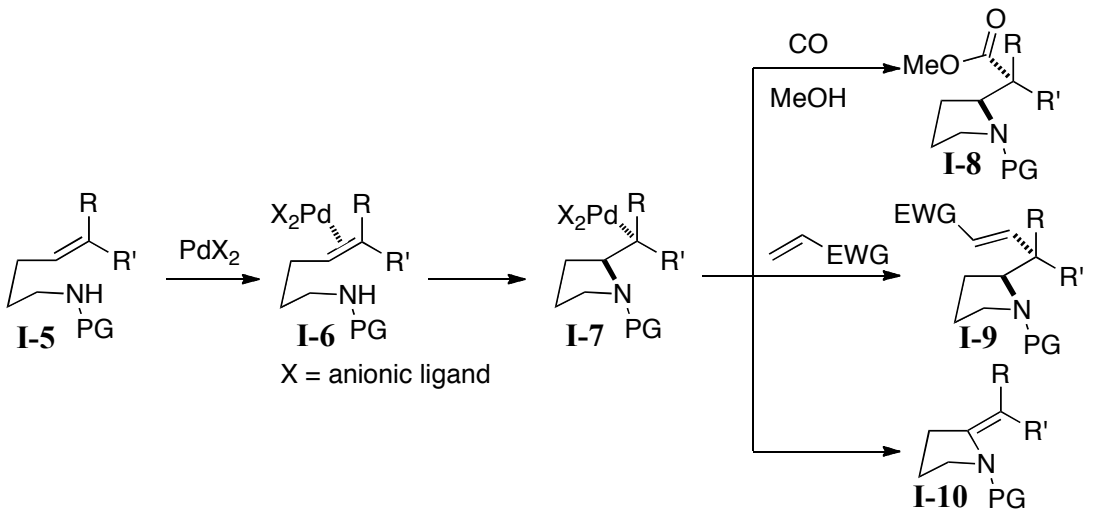


[a] Reaction conducted with 1 mol% $Pd_2(dba)_3$. [b] Reaction conducted with DPE-Phos. [c] Reaction conducted with dppe. [d] Reaction conducted at 60 ºC. [e] Reaction conducted with $Pd(OAc)_2$. [f] Reaction conducted with dppb.

1.3 Mechanism for Palladium Catalyzed Carboamination Reaction

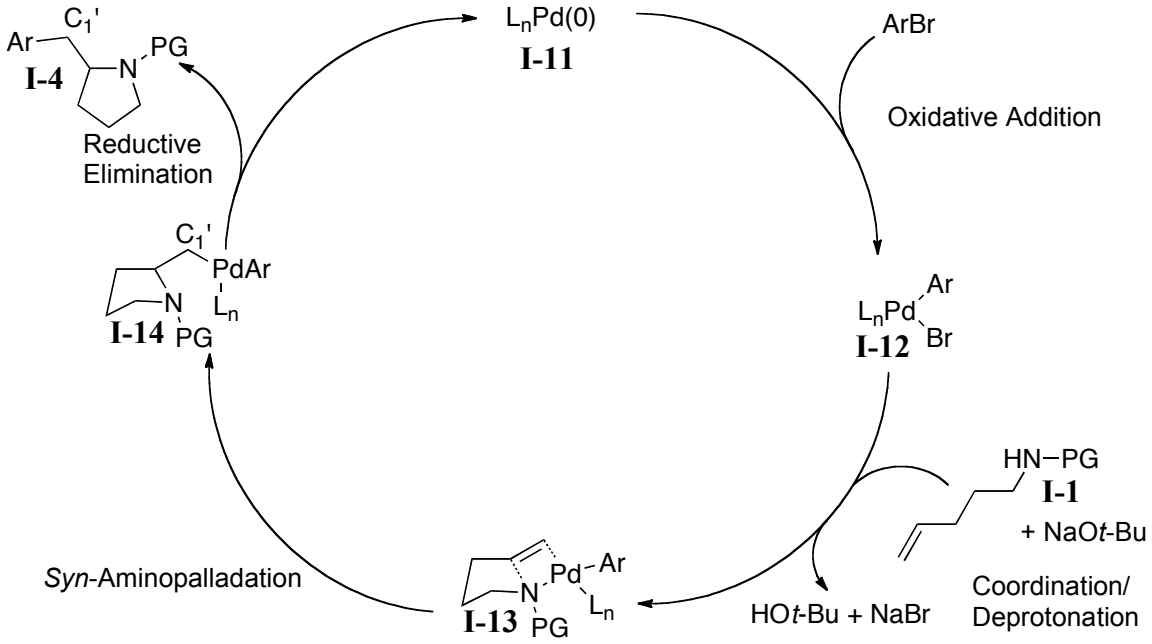
Two basic types of mechanisms operate in palladium catalyzed carboamination reactions.[5] The first type involves an *anti* attack of the amine group onto an olefin which is coordinated to a palladium (II) species (Scheme 1-3). The palladium alkyl intermediate can then be used in a number of ways to generate a new C-C bond (i.e. **I-8** and **I-9**); simple β-hydride elimination leads to a new olefinic product (**I-10**).[11]

Scheme 1-3: Anti-Aminopalladation and Representative Uses of the Pd-Alkyl Intermediate



In contrast, the second mechanism involves palladium amido species **I-13** (Scheme 1-4).[5] The catalytic cycle begins with the oxidative addition of **I-11** into an aryl bromide to generate **I-12**. Amine coordination and deprotonation generates **I-13**, a species that undergoes migratory insertion into the pendant olefin to generate heterocycle **I-14** with a palladium alkyl species at C_1'. Reductive elimination affords **I-4**.

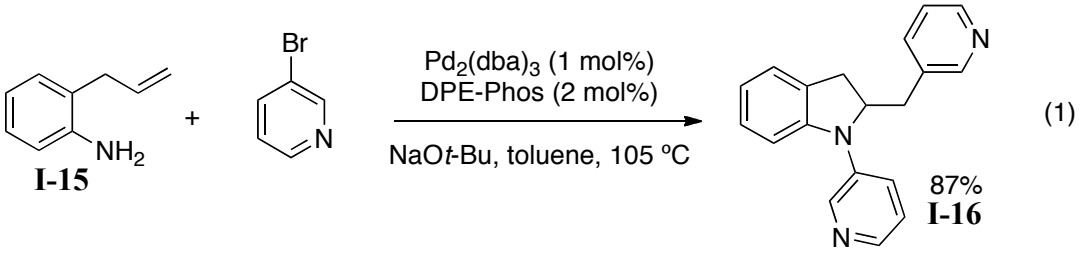
Scheme 1-4: Mechanism of *Syn*-Aminopalladation Carboamination



1.4 Tandem N-Arylation/Carboamination

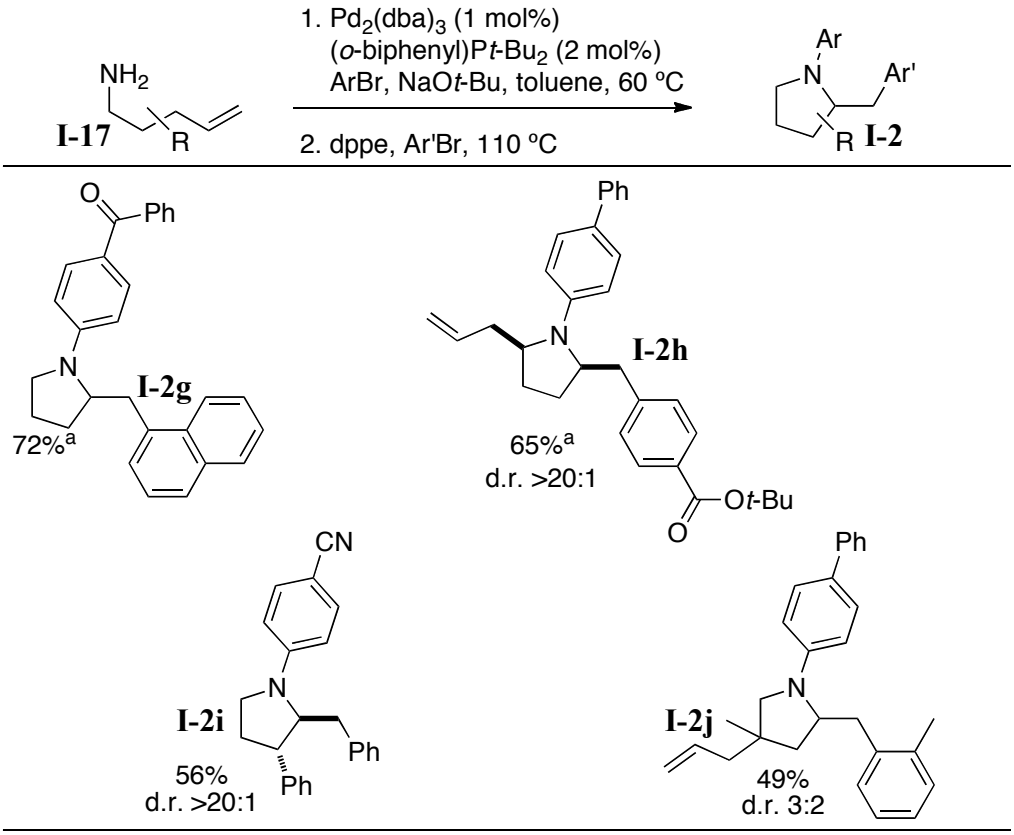
Once our group had demonstrated that *N*-aryl pentenyl amines were viable substrates for palladium catalyzed carboamination reactions (see above), we wanted to investigate if these substrates could be generated *in situ* and then cyclized in a tandem process. This strategy was found to be successful for the generation of indoline and pyrrolidine products via an intermolecular *N*-arylation/carboamination process.[12] If the same aryl group was added to both the nitrogen and the C_1' carbon, a single catalyst composed of $Pd_2(dba)_3$/DPE-Phos could be used (eq 1). Alternatively, the monodentate (*o*-biphenyl)P(*t*Bu)$_2$ ligand could be used to generate the *N*-arylated product. Once this reaction was complete as determined by GC analysis, the bidentate dppe could be added to the reaction mixture, stirred with the catalyst to effect ligand exchange and a second aryl bromide then added to afford the carboamination product (Scheme 1-5). This process

generated the desired product in moderate to good yields with a variety of aryl bromide coupling partners.



(1)

Scheme 1-5: Representative Products of Tandem Intermolecular *N*-Arylation/Carboamination

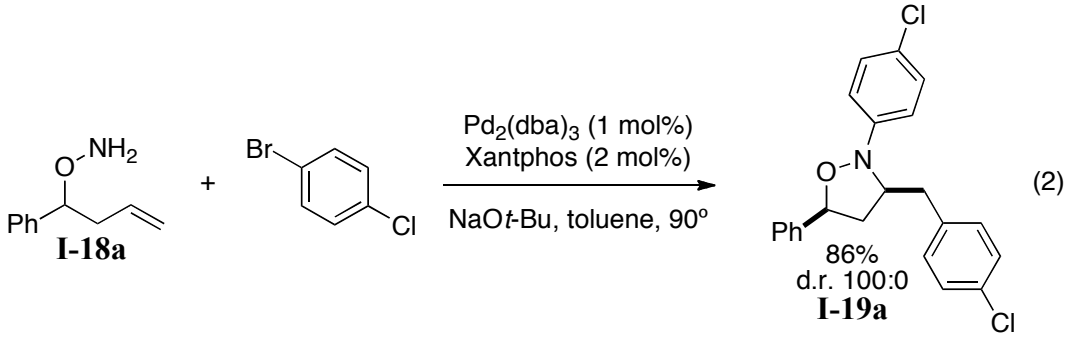


[a] This product contained a small amount (ca. 5–10%) of an inseparable regioisomer.

1.5 Previous Carboamination Reactions for the Synthesis of Isoxazolidines

Two different carboamination processes have been developed for the synthesis of isoxazolidines. One proceeds via a *syn*-aminopalladation, while the other proceeds via an

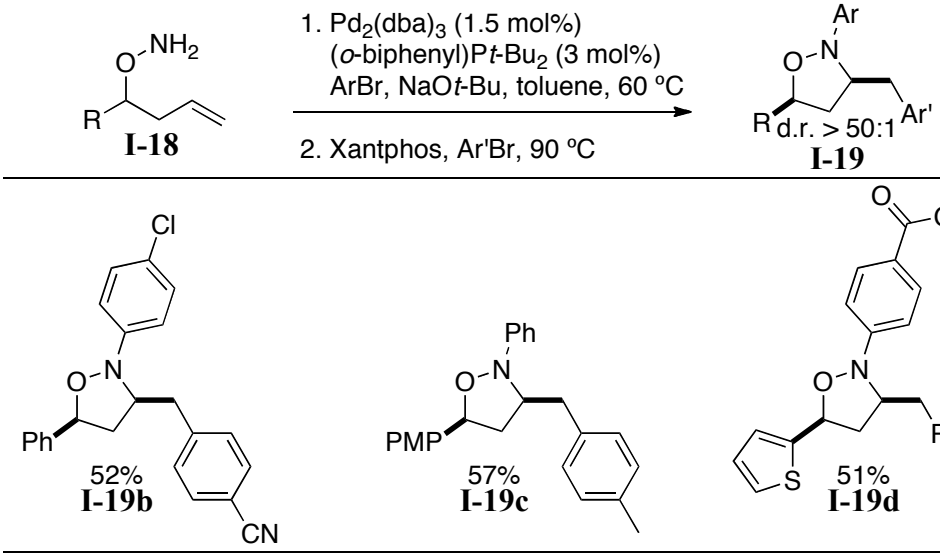
anti-aminopalladation mechanism. Other methods for the synthesis of isoxazolidines will be discussed in chapters 2 and 3.



(2)

N-aryl isoxazolidines have been synthesized via a tandem *N*-arylation/carboamination reaction very similar to the route discussed above for the synthesis of *N*-aryl pyrrolidines.[13] This method has allowed for the synthesis of 3,5-*cis* *N*-aryl isoxazolidines in good yield. A palladium catalyst, with Xantphos as the supporting ligand, efficiently generates an isoxazolidine with the same aryl bromide added to both the nitrogen and the C_1' position (eq 2).[13a] If two different aryl bromides are used, use of two different ligands for each step (*N*-arylation versus carboamination) is required to generate the desired product (Scheme 1-6).[13b] This carboamination process proceeds via an analogous mechanism to that shown in Scheme 1-4.

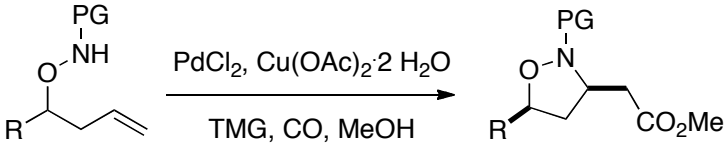
Scheme 1-6: Representative Examples of *N*-Aryl Isoxazolidine Formation



I-18 **I-19** **I-19b** **I-19c** **I-19d**

An example which proceeds via an *anti*-aminopalladation mechanism has been reported by Bates and coworkers.[14] They have shown that *O*-butenyl hydroxylamines can be cyclized using a palladium catalyst under a carbon monoxide atmosphere to afford an isoxazolidine with a methyl ester side chain (Scheme 1-7). While this method works well for adding a methyl ester side chain to the isoxazolidine, it does require a stoichiometric copper oxidant for the reaction to achieve catalytic turnover.

Scheme 1-7: Palladium Catalyzed Synthesis of Isoxazolidines Under CO Atmosphere



I-20
PG = CO_2Me, Ns, CBZ, Boc
TMG = tetramethylguanidine

30 - 79% **I-21**
all cis isomer when PG = CO_2Me, CBZ, Boc
5:1 dr when PG = Ns

1.6 Limitations of Syn-*Carboamination Methodology in 2007*

When the work that is detailed in this thesis was initiated, there were some key limitations to the generation of heterocycles via *syn*-aminopalladation. In the generation of pyrrolidines, while the diastereoselectivity was high for 2,5-*cis* and 2,3-*trans* cases, this also meant that access to the opposite diastereomer (ie 2,5-*trans* or 2,3-*cis*) was not possible.[7,10] As chapter 3 details, the 2,5-*trans* pyrrolidines are now accessible, however, access to the 2,3-*cis* pyrrolidines remains a challenge for this methodology.

Another area which had not been explored using this carboamination methodology is the generation of fused polycyclic heterocycles. This is an area which has now been addressed in the group. These studies are noted in chapters 4 and 5.

When we began our carboamination approach to isoxazolidines, the previous carboamination routes suffered from low yield or low diastereoselectivity (see section 1.5). In addition, traditional methods using dipolar cycloaddition with nitrones also gave low stereoselectivity (see section 6.2). During the course of these studies, we found that choice of ligand had a large influence on the diastereoselectivity of the reaction, which had not previously been seen in other carboamination reactions.

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[5] For reviews of the palladium catalyzed carboamination reactions, see: (a) Wolfe, J. P. *Synlett*, **2008**, 2913–2937. (b) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571–582.

[6] For copper catalyzed carboaminations, see: (a) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896–3905. (b) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949. (c) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573–1575.

[7] Ney, J. E.; Wolfe, J. P. *Angew. Chem. Int. Ed*. **2004**, *43*, 3605–3608.

[8] dppe = 1,2-bis(diphenylphosphinyl)ethane; dppb = 1,4-bis(diphenylphosphinyl)butane

[9] (a) Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614–1620. (b) Rosen, B. R.; Ney, J. E.; Wolfe, J. P. *J. Org. Chem.* **2010**,

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[12] (a) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906–13907. (b) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575–2578.

[13] (a) Peng, J.; Lin, W.; Yuan, S.; Chen, Y. *J. Org. Chem.*, **2007**, *72*, 3145–3148. (b) Peng, J.; Jiang, D.; Lin, W.; Chen, Y. *Org. Biomol. Chem.* **2007**, *5*, 1391–1396.

[14] Bates, R. W.; Kanicha, S. *Org. Lett.* **2002**, *4*, 4225–4227.

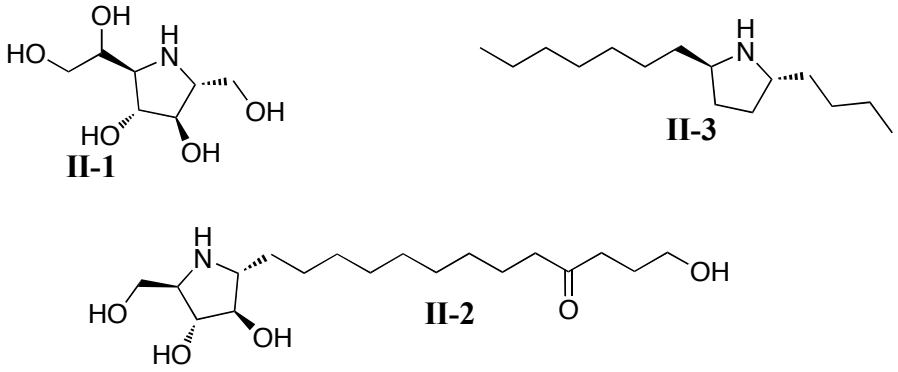
Chapter 2

Literature Examples of 2,5-*trans* Pyrrolidines Synthesis

*2.1 Biological Activity of 2,5-*trans *Pyrrolidines*

2,5-*trans* disubstituted pyrrolidines are found in a variety of natural products which have interesting biological activity. For example, many polyhydroxylated pyrrolidines are glycosidase inhibitors. These compounds have been used in anti-tumor, anti-viral, and diabetes treatment.[1] Compound **II-1** has been isolated from the bulb of *Scilla sibirica*, which is in the lily family (Figure 2-1).[1] It has also been found in the extracts of *Hyacinthoides non-scripta*, more commonly known as bluebells.[2] Compound **II-1** has been shown to have activity against the β-glucosidase enzyme.[1] Bluebells are known to cause livestock poisoning; **II-1** and related compounds are believed to be the reason for this.[2] The broussonetine class of compounds have been isolated from *Broussonetia kazinoki* Siebold (Moraceae), a tree used for herbal medicine in Japan and China.[3] This class of compounds contains around 30 members, of which broussonetine C (**II-2**) has been the most synthesized. In addition, **II-3** has been isolated from the culture broth of the bacteria *Streptomyces longispororuber* #525.[4] This compound has been shown to bind to σ receptors, which are found in the central nervous system. Given their location, these receptors are thought to be interesting targets for treatment of neurological disorders, but their exact function is not well understood.[5]

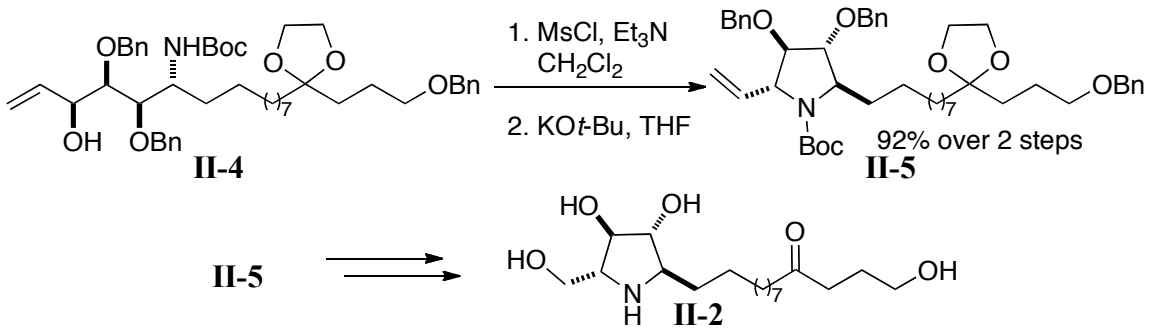
Figure 2-1: Natural Products Containing a 2,5-*trans* Pyrrolidine Core



2.2 Synthesis of Broussonetines

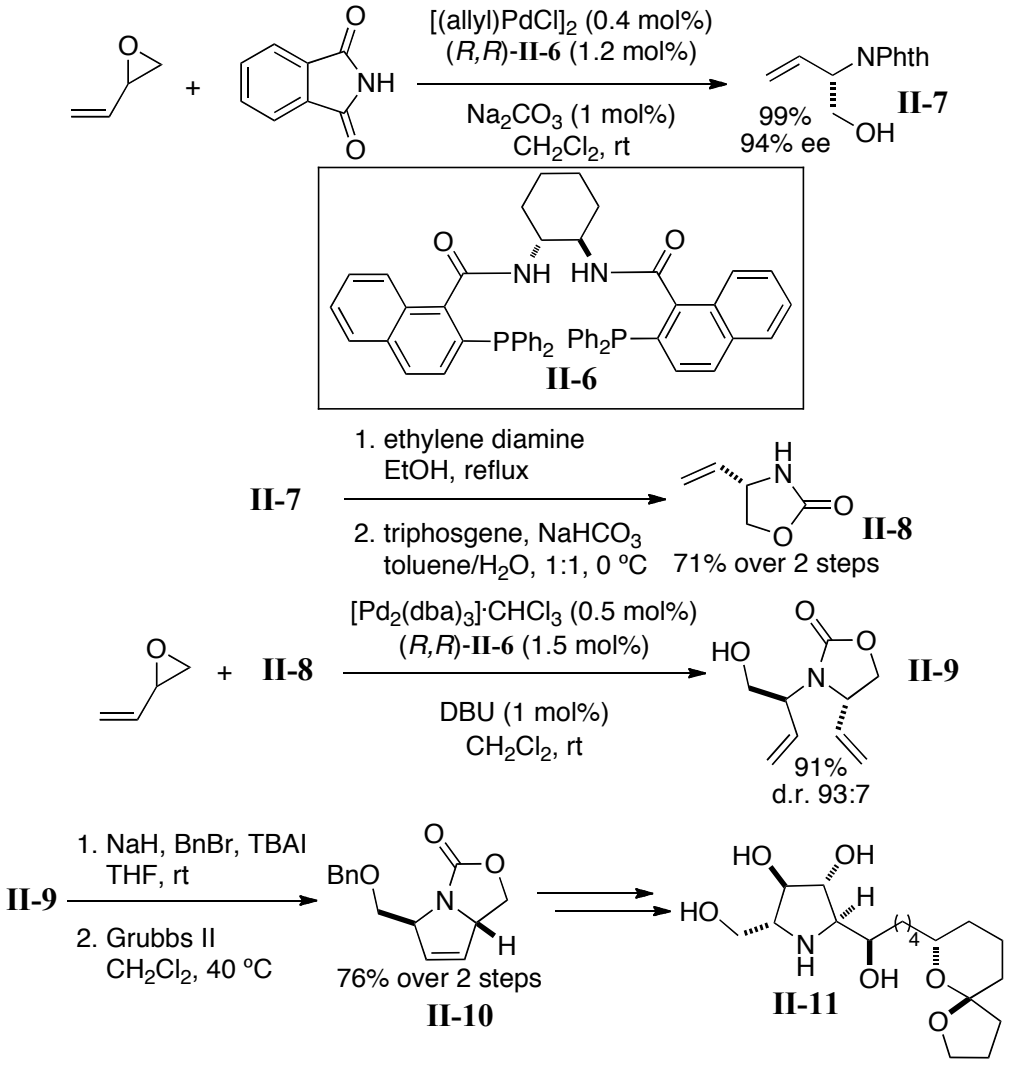
Due to the biological activity of the broussonetine alkaloids, several groups have synthesized various members of this class of compounds. The first synthesized was broussonetine C and was reported in 1999.[6] This synthesis began with *D*-tartaric acid, which was converted to **II-4** in 16 steps. An intramolecular S_N2 reaction generated the 2,5-*trans* pyrrolidine **II-5** in good yield (Scheme 2-1). Broussonetine C was generated in four additional steps from **II-5**, for a total of 22 steps. In 2003, the second synthesis of broussonetine C was reported starting from *D*-arabinose.[7] This protocol also used an intramolecular S_N2 reaction to install the 2,5-*trans* pyrrolidine core and was a total of 20 linear steps.

Scheme 2-1: First Total Synthesis of Broussonetine C



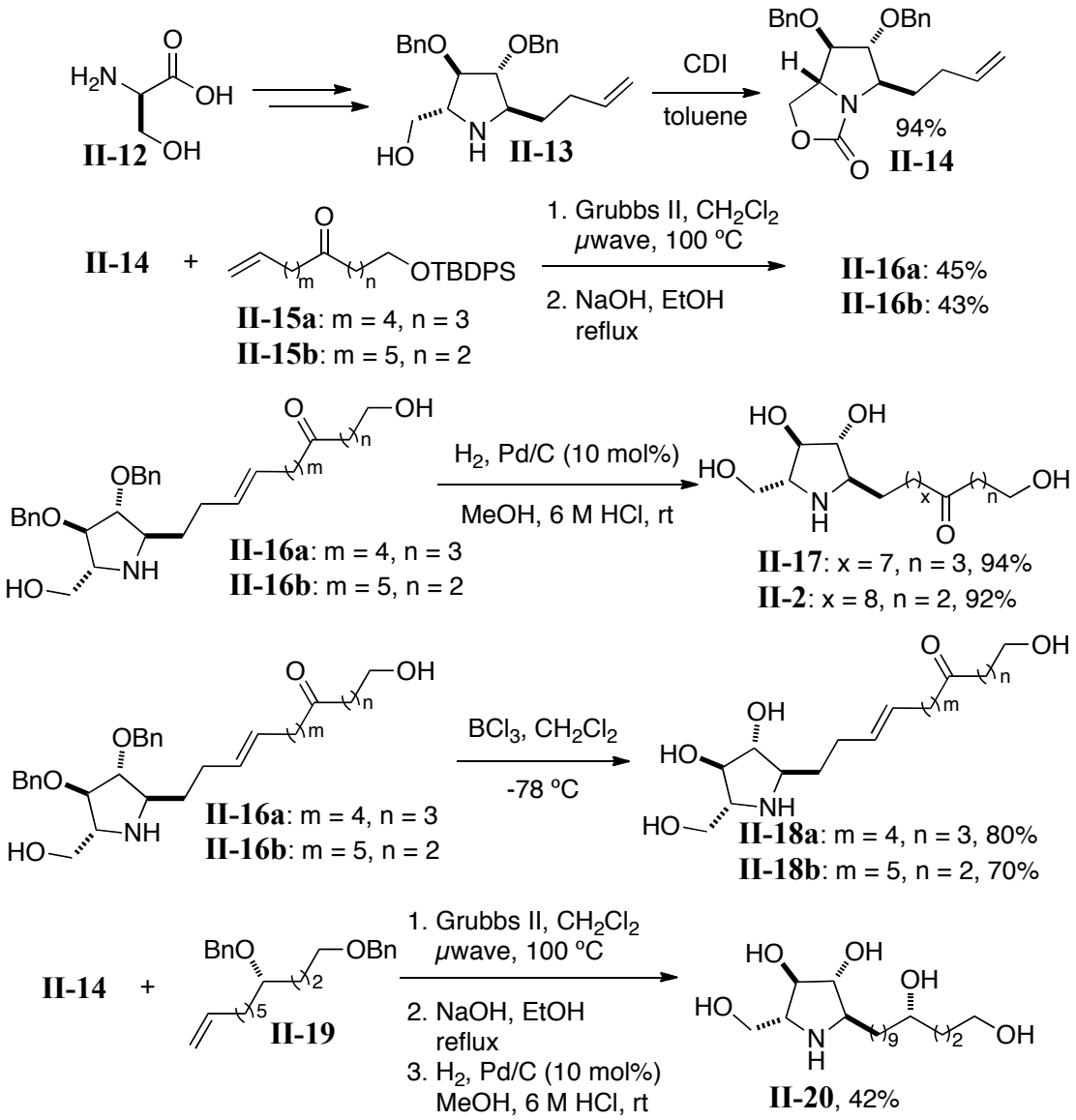
Trost and coworkers used a dynamic kinetic asymmetric transformation (DYKAT) to set the stereocenters at what became the 2 and 5 positions of the pyrrolidine ring in their synthesis of broussonetine G (Scheme 2-2).[8] This was followed by ring closing metathesis to generate **II-10**. This pyrroline (**II-10**) was converted to broussonetine G (**II-11**) over an additional 9 steps. In the course of their studies, Trost and coworkers were able to confirm the absolute stereochemistry of **II-11** by the synthesis of other diastereomers.

Scheme 2-2: Total Synthesis of Broussonetine G



Broussonetines C, D, M, O, and P were synthesized via a convergent synthesis.[9] The key pyrrolidine core **II-13** was generated from *D*-serine in 12 steps (Scheme 2-3). This was then transformed to common intermediate **II-14**. The side chains were installed via cross-metathesis with either **II-15** or **II-19**, which resulted in both the desired products as well as homo-coupled products. Deprotection of the protecting groups and hydrogenation of the alkene afforded broussonetines C (**II-2)**, D (**II-17**) and M (**II-20**). Broussonetines O (**II-18b**) and P (**II-18a**) have the alkene functionality present in the side chain, so E/Z isomers had to be separated and then the alcohols unmasked to afford the natural products.

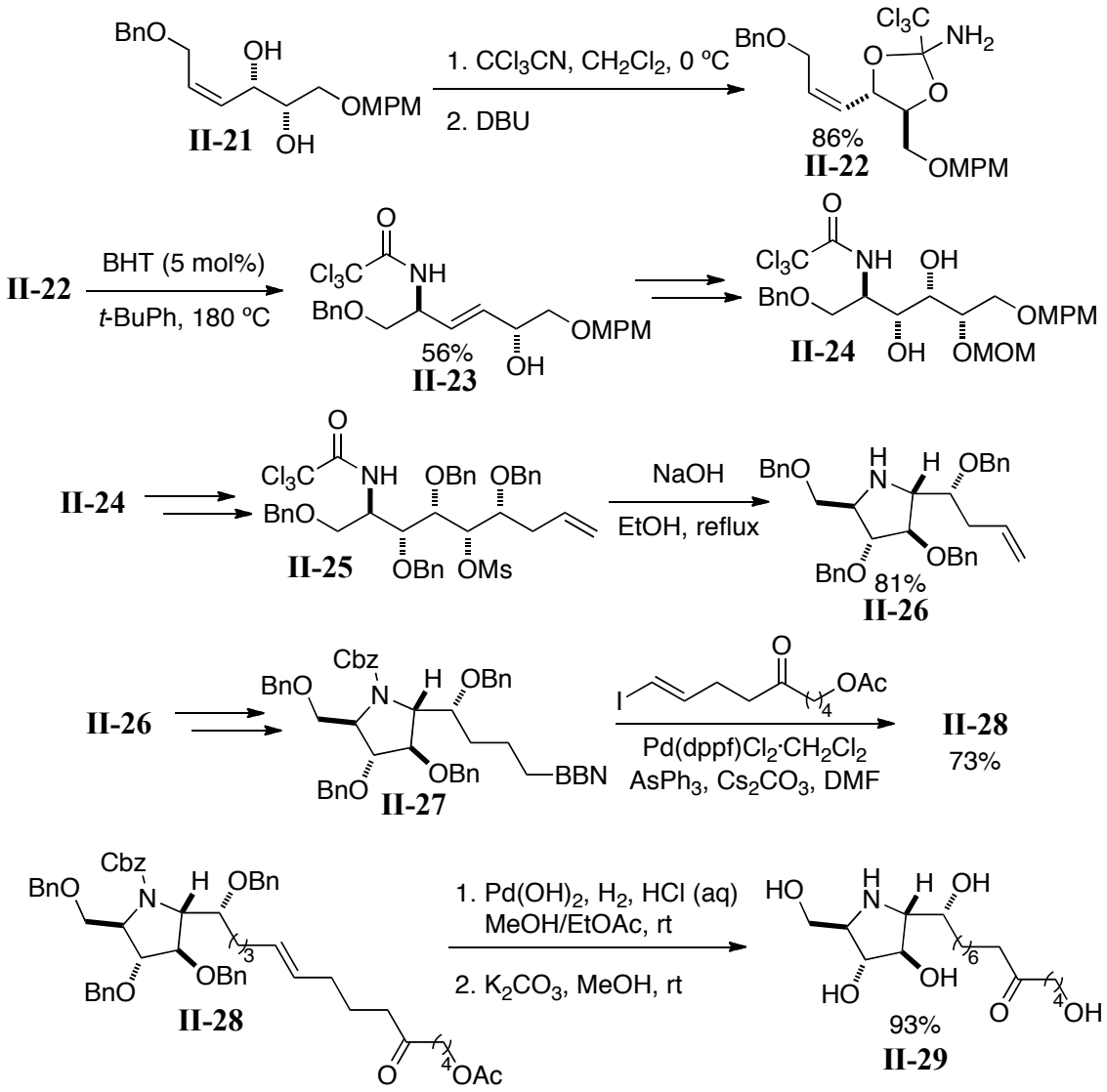
Scheme 2-3: Total Synthesis of Broussonetines C, D, M, O and P



Chida and coworkers have reported the total synthesis of broussonetine F (**II-29**), which utilized an orthoamide Overman rearrangement to set the stereocenters at the 2 and 5 positions of the pyrrolidine ring (Scheme 2-4).[10] Allylic diol **II-21** was transformed into the necessary cyclic orthoamide **II-22**. The optimized conditions allowed for the synthesis of **II-23** in 56%. Sharpless asymmetric dihydroxylation afforded **II-24**. Further transformations generated **II-25**. The pyrrolidine ring was constructed via an

intramolecular S_N2 reaction (**II-25** to **II-26**). Hydroboration of the alkene generated **II-27** and allowed for Suzuki–Miyaura coupling to install the side chain. Finally, hydrogenation of **II-28** and removal of all protecting groups afforded broussonetine F (**II-29**).

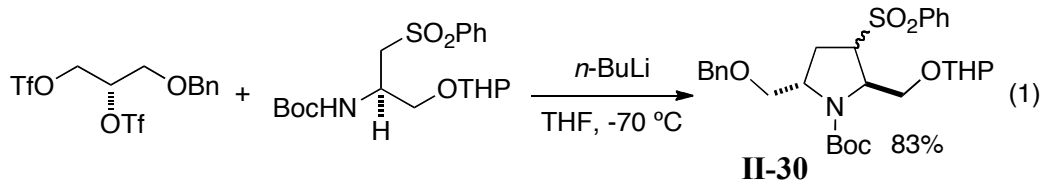
Scheme 2-4: Total Synthesis of Broussonetine F



*2.3 Synthesis of Other 2,5-*trans *Pyrrolidines*

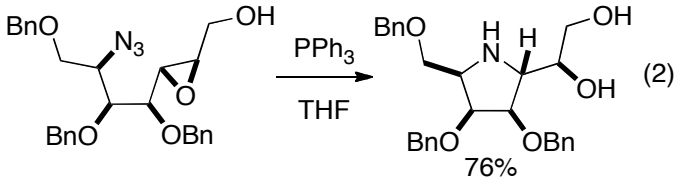
2.3.1 Methods Requiring Two Preformed Stereocenters

Many of the methods for the synthesis of 2,5-*trans* pyrrolidines require that the relative stereochemistry be preinstalled prior to ring formation, instead of one stereocenter controlling the formation of the second in the cyclization. Trost and coworkers used an elegant strategy to install these two stereocenters of broussonetine G (**II-11**).[8] However, they did need to be established prior to the ring closing metathesis and dihydroxylation reaction. As shown above in the synthesis of broussonetines C (**II-2**) and F (**II-29**), an intramolecular S_N2 reaction can also be used to generate the pyrrolidine ring.[6,10] A related method which has been developed requires a double anion in order to have both an inter- and an intramolecular S_N2 reaction occur (eq 1).[11] This method does work well, but requires cleavage of a carbon sulfur bond of **II-32** if access to most natural products is desired. Thus, the advantage gained by beginning with two components each having one stereocenter is lost by the need to remove an unnecessary functional group.



II-30 (1)

Reductive cyclization of an azide onto an epoxide affords the pyrrolidine ring in good yield (eq 2). Wong and coworkers used this strategy to synthesize a diastereomer of **II-1** in the course of their study of iminocyclitols and pseudodisaccarides.[12]



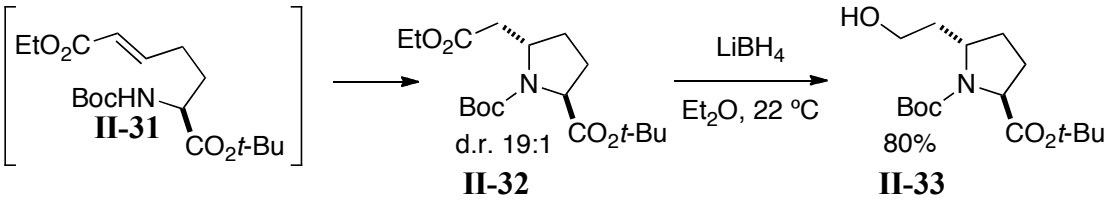
(2)

2.3.2 Methods Requiring One Initial Stereocenter

While these methods discussed do generate the pyrrolidine ring, they do not allow for an existing stereocenter to control the generation of the second stereocenter. This need for two preformed stereocenters requires more complex synthetic routes prior to the cyclization reaction. Thus, routes which do allow for a diastereoselective cyclization to occur would allow for more rapid build up of molecular complexity.

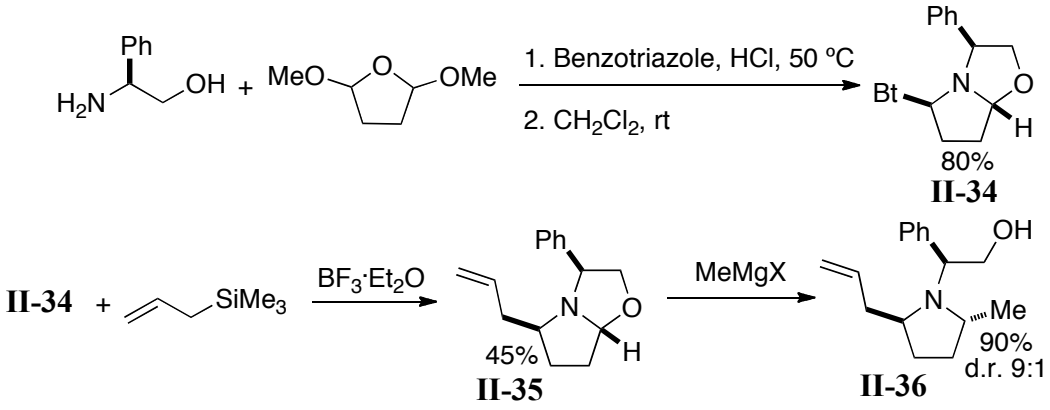
One such method is an intramolecular Michael addition followed by reduction of the ester to the alcohol (Scheme 2-5).[13] **II-31** is generated as an intermediate via a Horner-Wadsworth-Emmons reactions and the nitrogen immediately cyclizes onto the enoate to generate **II-32**. The cyclization occurs in good diastereoselectivity. After the reduction, the two diastereomers of **II-33** are separable.

Scheme 2-5: Intramolecular Michael Addition to Generate 2,5-*trans* Pyrrolidines



Katritzky and coworkers have demonstrated that (*S*)-phenylglycinol can be used as a chiral auxiliary to generate a benzotriazole substituted pyrrolidine ring which can be further functionalized (Scheme 2-6).[14] Once **II-34** is formed, an allyl silane can displace the benzotriazole to generate **II-35**. Grignard addition into the hemiaminal is preferred from the bottom face of the ring, leading the 2,5-*trans* pyrrolidine **II-36** in modest diastereoselectivity. The chiral auxiliary can then be removed by hydrogenation. While this method works well, it is limited by its modest diastereoselectivity and the low yield for the addition of the allyl silane.

Scheme 2-6: Synthesis of Chiral 2,5-*trans* Pyrrolidines



As can be seen from these examples, there is still room to develop other methods which control diastereoselectivity in the cyclization to generate pyrrolidine rings. In addition, a method which could install functionality that can be further utilized in organic synthesis would be desirable. Our efforts towards this area will be discussed in the next chapter.

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[9] (a) Ribes, C.; Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Org. Biomol. Chem.* **2009**, *7*, 1355–1360. (b) Ribes, C.; Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron* **2009**, *65*, 10612–10616.

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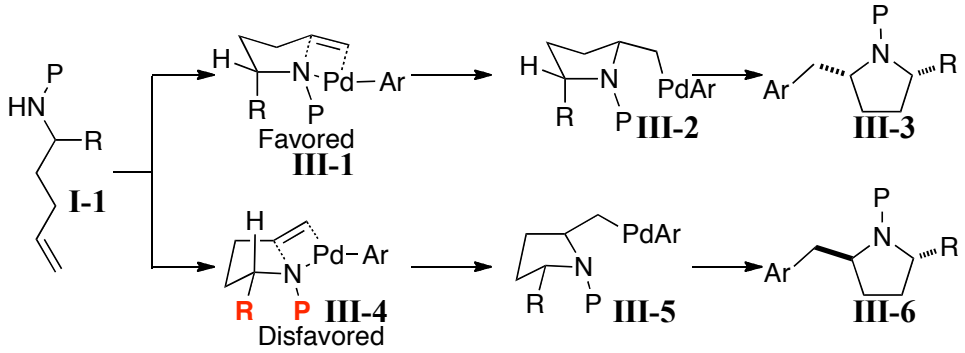
Chapter 3

Synthesis of 2,5-trans-Pyrrolidines via a Carboamination Reaction[1]

3.1 Introduction

Carboaminations of *N*-aryl, *N*-Boc, and *N*-acyl pentenyl amines have been successfully used to generate 2,5-*cis* disubstituted pyrrolidines (see Chapter 1).[2,3,4] Although this methodology works well, access to both diastereomers is desirable, as some biologically active pyrrolidines have a 2,5-*trans* substitution pattern. Analysis of the transition states suggest that transition state **III-1**, which minimizes allylic strain leads to the 2,5-*cis* product (Figure 3-1). One logical way to reduce allylic strain in **III-1** is to have an unprotected amine (P = H). However, attempts to generate 2,5-*trans* pyrrolidines via the carboamination of a primary pentenyl amine lead to *N*-arylation of the substrate.[5]

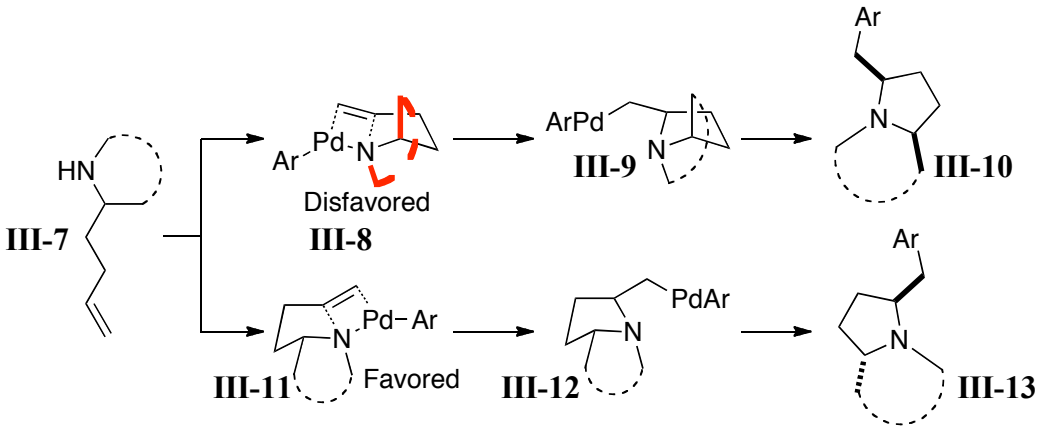
Figure 3-1: Stereochemical Rationale for 2,5-*cis* Pyrrolidine Formation



Thus, we sought another way to minimize allylic strain. In considering the transition states, we hypothesized that if we tethered the side chain to the nitrogen (**III-7**),

transition state **III-11** should be favored (Figure 3-2). Transition state **III-8**, which leads to the 2,5-*cis* pyrrolidine product **III-10**, would be disfavored due to ring strain.

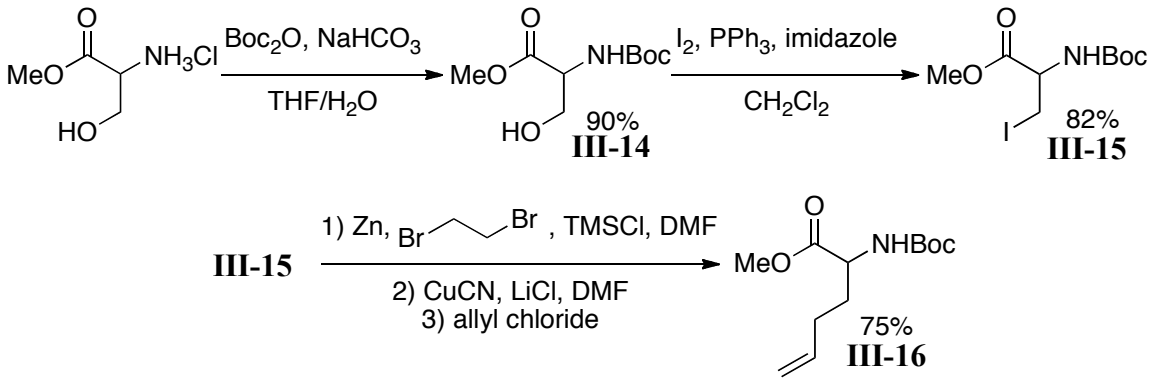
Figure 3-2: Stereochemical Rationale for 2,5-*trans* Pyrrolidine Formation



3.2 Substrate Synthesis

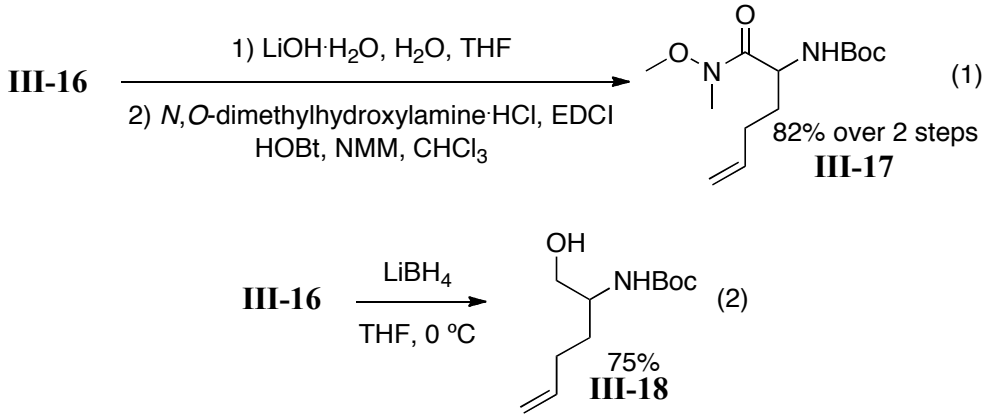
In order to test our hypothesis, it was necessary to synthesize substrates that had a nitrogen containing heterocycle. In order to have a monocyclic pyrrolidine product, a cleavable linker between the nitrogen and the side-chain was also necessary. Thus, we opted to synthesize oxazolidinone substrates, as previous carboamination methodology was successful with carbamates.[3b,d,e]

Scheme 3-1: Generation of III-16

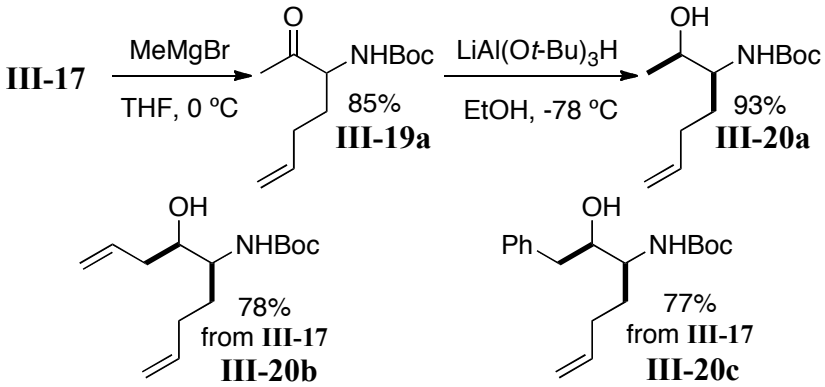


Most of the substrates were generated from serine methyl ester (**III-14**) via common intermediate **III-16** (Scheme 3-1). The methyl ester was then either converted to

the Weinreb amide (**III-17**) or reduced directly to the alcohol (**III-18**) (eqs 1–2). Grignard addition to **III-17** led to a variety of ketones (**III-20a–c**), which could be reduced with high diastereocontrol using lithium tri *tert*-butoxyaluminum hydride in dry ethanol at -78 ºC to afford **III-21a–c** (Scheme 3-2). Attempts to reduce the ketones to the opposite diastereomer with good stereocontrol were unsuccessful.

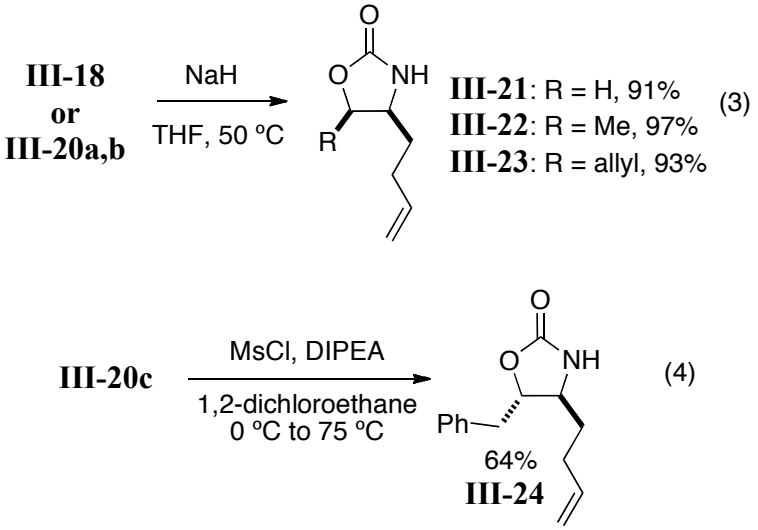


Scheme 3-2: Conversion of III-17 to Amino Alcohols

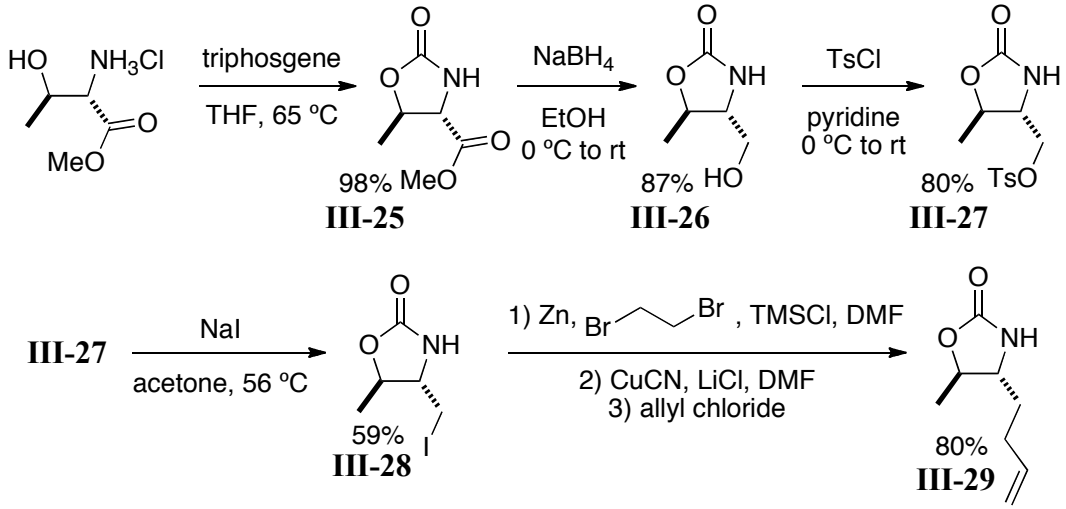


Using two different reaction conditions, the oxazolidinone substrates could be generated as either diastereomer from the same amino alcohol. Simple deprotonation of the alcohol (**III-18**, **III-20a,b**) with sodium hydride allowed for cyclization onto the *tert*-butyl carbamate with retention of the alcohol stereocenter to generate **III-21–23** (eq 3). Alternatively, treatment of **III-20c** with mesyl chloride and Hünig's base promoted

oxazolidone formation via intramolecular S_N2 reaction with inversion of stereochemistry to afford **III-24** (eq 4).[6]



Scheme 3-3: Synthesis of III-29 from Threonine Methyl Ester



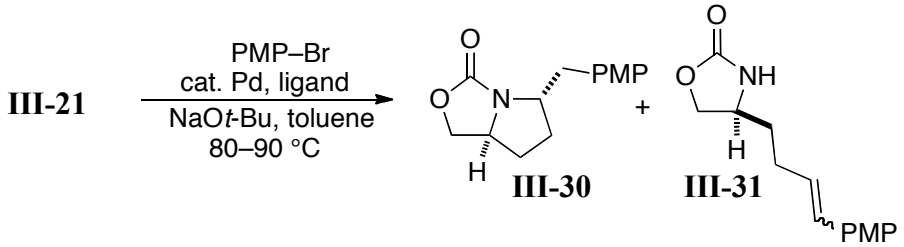
Additionally, threonine methyl ester could also be used as the initial starting material for substrate synthesis (Scheme 3-3). Formation of the oxazolidinone using triphosgene afforded **III-25** in high yield, and the methyl ester was then reduced to the alcohol (**III-26**). Direct conversion of the alcohol to the iodide led to decomposition, thus a two step sequence including conversion to the tosylate and displacement with iodide

afforded **III-28** in modest yield. Finally, conversion of the iodide to the cuprate via the alkyl zinc reagent followed by alkylation with allyl chloride afforded **III-29**.

3.3 Reaction Optimization

With substrates in hand, it was necessary to find conditions that allowed for the successful cyclization of the oxazolidinone nitrogen onto the pendent alkene. Initial studies demonstrated that the use of conditions that were previously successful with *N*-Boc-pent-4-enylamine derivatives were unsuccessful for the cyclization of these substrates (Table 3-1).[3b,d,e] After much optimization, it was found that Buchwald's RuPhos was the best ligand when electron neutral and electron rich aryl bromides were used as coupling partners (Table 3-1).[7] Either palladium acetate or palladium allyl chloride dimer could be used as the palladium source; however, the use of palladium acetate required premixing of palladium and ligand prior to the addition of the other reagents. Thus, palladium allyl chloride dimer allowed for simplified reaction set-up and was preferred over palladium acetate.

Table 3-1: Optimization of Reaction Conditions[a]



palladium source[b,c]	ligand[8]	conversion (%)	yield **III-30** (%)[d]	yield **III-31** (%)[d]
$Pd(OAc)_2$	dppe	27	0	8
$Pd(OAc)_2$	DPE-Phos	15	2	9
$Pd(OAc)_2$	S-Phos	70	57	3
$Pd(OAc)_2$	PCy_2(*o*-biphenyl)	17	<1	2
$Pd(OAc)_2$	RuPhos	92	87	3
$[(allyl)PdCl]_2$	RuPhos	92	79	4
$[(allyl)PdCl]_2$	RuPhos	96[e]	81 (80)[f]	3

[a] Conditions: 1.0 equiv **III-21**, 1.2 equiv 4-bromoanisole, 1.2 equiv NaO*t*-Bu, 2 mol% Pd, 4 mol% monodentate ligand/2 mol% bidentate ligand, NaO*t*-Bu, toluene (0.25 M), 80–90 °C. Product **III-30** was formed with >20:1 dr in all experiments. [b] Experiments with the dinuclear palladium complex $[(allyl)PdCl]_2$ were conducted using 1 mol% of the dimer (2 mol% total Pd). [c] When $Pd(OAc)_2$ was employed, the ligand and palladium source were stirred at rt in toluene for 5 min prior to addition of the substrate and other reagents. [d] Yields for optimization studies were determined by ^{1}H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard. [e] The reaction was conducted using benzene as solvent. [f] Isolated yield (average of two or more experiments).

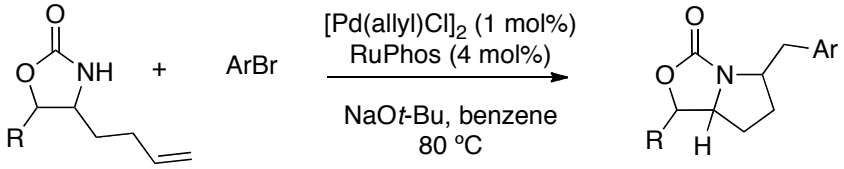
3.4 Scope and Limitations

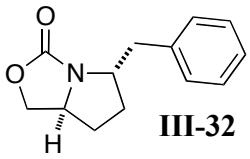
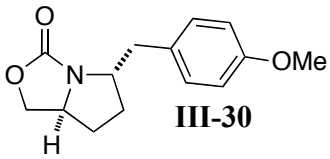
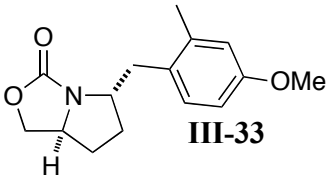
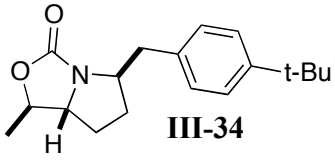
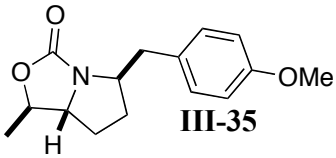
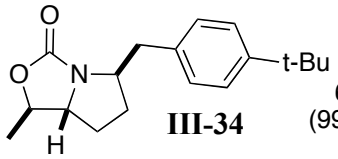
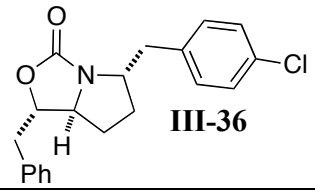
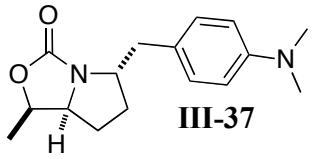
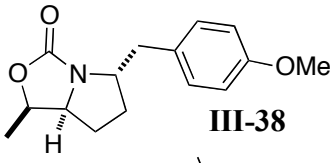
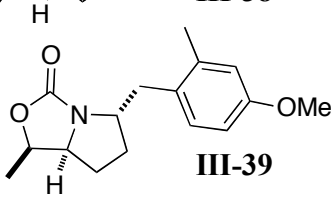
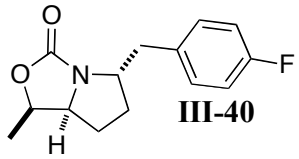
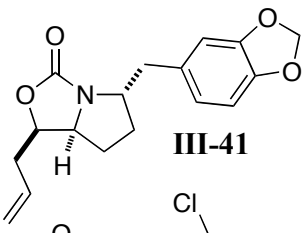
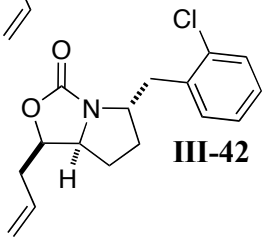
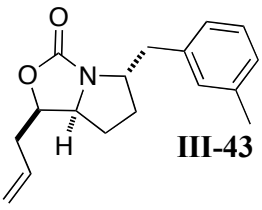
3.4.1 Examples

As can be seen in Table 3-2, a variety of electron rich and electron neutral aryl bromides were successful coupling partners in the carboamination reaction. Methyl substitution in the *ortho* position led to reduced yield due to competing Heck arylation (entries 3 and 10). Electron deficient aryl bromide coupling partners proved to be more

challenging than those that were electron rich. With 4-bromobenzophenone, competing *N*-arylation was problematic. Modestly electron deficient aryl bromides were viable coupling partners when PCy_2(*o*-biphenyl) was used as the ligand. With more electron poor aryl bromides, increased catalyst loading and PCy_2(*o*-biphenyl) as the ligand were required to afford the desired product in moderate to good yield (entries 7, 11 and 13). Additionally, the use of enantiopure starting materials led to enantiopure products (entries 6 and 14).

Table 3-2: Examples of Oxazolidinone Carboamination



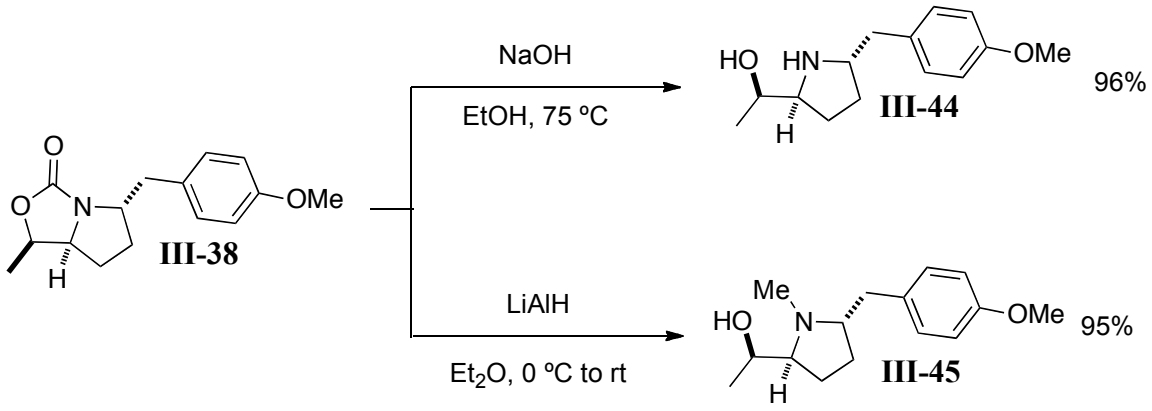
Entry	Substrate	Product	Yield[a]
1	**III-21**	 **III-32**	80%
2	**III-21**	 **III-30**	80%
3	**III-21**	 **III-33**	66%
4	**III-29** (rac)	 **III-34**	63%
5[c]	**III-29**	 **III-35**	83%
6	**III-29** (chrial)	 **III-34**	69% (99% ee)
7	**III-24**	 **III-36**	63%
8[b]	**III-22**	 **III-37**	70%
9	**III-22**	 **III-38**	84%
10	**III-22**	 **III-39**	61%
11[d]	**III-22**	 **III-40**	77%
12[b]	**III-23** (rac)	 **III-41**	78%
13[d]	**III-23**	 **III-42**	61%
14	**III-23** (chrial)	 **III-43**	79% (97% ee)

[a] Isolated yield (average of two or more experiments). All products formed in >20:1 dr. [b] The reaction was conducted with 2 mol% $Pd(OAc)_2$. [c] The reaction was conducted with 2 mol% $[Pd(allyl)Cl]_2$ and 8 mol% RuPhos. [d]The reaction was conducted with 2.5 mol% $[Pd(allyl)Cl]_2$ and 10 mol% PCy_2(*o*-biphenyl)

3.4.2 Derivatization of Products

Cleavage of the oxazolidinone linker to the free N-H or the N-methyl 2,5-*trans* pyrrolidine was facile. Treatment of the bicyclic oxazolidinone with sodium hydroxide in ethanol afforded the free N-H pyrrolidine **III-44** in 96% yield (Scheme 3-4). Alternatively, reduction of the carbamate with lithium aluminum hydride generated the N-methyl pyrrolidine **III-45** cleanly in 95% yield (Scheme 3-4).

Scheme 3-4: 2,5-*trans*-Pyrrolidine Formation



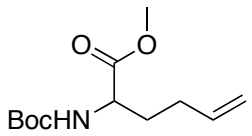
3.5 Conclusion

In conclusion, we developed a novel method for the generation of tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-ones and 2,5-*trans* disubstituted pyrrolidines. We have shown that multiple products with up to 3 stereocenters can be generated in excellent diastereoselectivity and in a convergent manner. Additionally, as these products are initially derived from either serine methyl ester or threonine methyl ester, they can be generated as single enantiomers from a cheap chiral starting material. This method can be used in the future to generate natural products.

3.6 Experimental

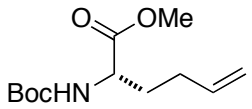
General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. $Pd(OAc)_2$, $[(allyl)PdCl]_2$, and all phosphine ligands were purchased from Strem Chemical Co. or Aldrich Chemical Co. and used without further purification. All aryl bromides and common reagents were obtained from commercial sources and were used as obtained, with the exception of 4-bromo-1,2-(methylenedioxybenzene), which was filtered through a plug of silica gel plug prior to use. Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate[9] (**III-15**), (±)-2-[(*tert*-butoxycarbonyl)amino]hex-5-enoic acid[10] and (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate[11] (**III-17**) were synthesized according to literature procedures. Toluene, diethyl ether, methylene chloride, and THF were purified using a GlassContour solvent purification system. Benzene was freshly distilled from calcium hydride. Ethanol was distilled from magnesium turnings activated with iodine and stored over activated molecular sieves. $[(allyl)PdCl]_2$ and NaO*t*-Bu were stored in a nitrogen-filled glovebox, removed just prior to use, and were weighed outside of the glovebox. Ratios of diastereomers were determined by ^{1}H NMR analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Table 2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 2.

3.6.1 Preparation and Characterization of Substrates

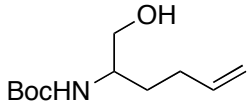


(±)-Methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (III-16).[12] An oven-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with zinc dust (11.9 g, 182 mmol). The flask was purged with nitrogen, then DMF (20 mL) and 1,2-dibromoethane (0.79 mL, 9.1 mmol) were added. The resulting mixture was heated to 90 ºC for 20 min, then cooled to rt and stirred for 5 min. Chlorotrimethylsilane (0.24 mL, 1.9 mmol) was added, and the reaction mixture was stirred at rt for 30 min. A solution of methyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate (**III-15**) (10.0 g, 30.4 mmol) in DMF (20 mL) was added, and the mixture was stirred at rt until the iodide had been completely consumed as determine by TLC analysis (ca 25 min). The reaction mixture was cooled to –60 ºC and a solution of anhydrous lithium chloride (2.58 g, 60.8 mmol) and copper (I) cyanide (2.72 g, 30.4 mmol) in DMF (40 mL) was added via cannula over 15 min. The resulting mixture was warmed to 0 ºC and stirred for 20 min. The mixture was then cooled to –60 °C and allyl chloride (5.0 mL, 60.8 mmol) was added in one portion. The resulting mixture was warmed to –10 ºC and stirred for 3 h. The reaction was then quenched slowly with saturated aqueous ammonium chloride (80 mL). The mixture was transferred to a separatory funnel an extracted with 1:1 ethyl acetate/hexanes (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound as a clear oil (5.76 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84–5.74 (m,

1 H), 5.08–4.98 (m, 3 H), 4.36–4.28 (m, 1 H), 3.74 (s, 3 H), 2.18–2.04 (m, 2 H), 1.95–1.86 (m, 1 H), 1.76–1.66 (m, 1 H), 1.45 (s, 9 H).

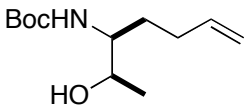


(–)-(*S*)-Methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (III-16). (–)-(*S*)-Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate (5.383 g, 16.35 mmol) was converted to the title compound using a procedure analogous to that described above. This procedure afforded the title compound as a clear oil (2.71 g, 68%), $[\alpha]^{20}_{D}$ –20.7 (*c* 0.97, MeOH). [lit.[13] $[\alpha]^{23}_{D}$ –22.43 (*c* 1.0, MeOH)]. ^{1}H NMR data were identical to those reported above for (±)-**III-16**.



(±)-*tert*-Butyl 1-hydroxyhex-5-en-2-ylcarbamate (III-18).[14] An oven-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (±)-methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (**III-16**) (4.95 g, 20.3 mmol). The flask was purged with nitrogen, then THF (200 mL) was added and the resulting solution was cooled to 0 °C. Lithium borohydride (665 mg, 30.5 mmol) was added in one portion, the reaction mixture was stirred at 0 ºC for 5 min, then warmed to rt and stirred for 11.5 h. Saturated aqueous ammonium chloride (150 mL) was added slowly and the resulting mixture was transferred to a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 x 75 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was

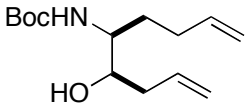
purified by flash chromatography on silica gel to afford the title compound as a clear oil (3.70 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86–5.77 (m, 1 H), 5.07–4.97 (m, 2 H), 4.62 (s, br, 1 H), 3.72–3.61 (m, 2 H), 3.59–3.53 (m, 1 H), 2.26–2.07 (m, 3 H), 1.66–1.48 (m, 2 H), 1.45 (s, 9 H).



(±)-(2*R,3*S**)-*tert*-Butyl 2-hydroxyhept-6-en-3-ylcarbamate (III-20a).** An oven-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate[11] (**III-17**) (2.0 g, 7.34 mmol). The flask was purged with nitrogen, THF (49 mL) was added, and the resulting solution was cooled to 0 °C. Methylmagnesium bromide (6 mL, 18 mmol, 3 M in Et_2O) was added via syringe over 2 min, and the reaction mixture was stirred at 0 ºC for 4.5 h. The reaction mixture was carefully poured into saturated aqueous ammonium chloride (50 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate (**III-19a**) as a clear oil (1.37 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.73 (m, 1 H), 5.24–5.14 (m, 1 H), 5.09–4.98 (m, 2 H), 4.38–4.30 (m, 1 H), 2.21 (s, 3 H), 2.20–1.90 (m, 3 H), 1.66–1.55 (m, 1 H), 1.45 (s, 9 H).

A portion of the (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate (**III-19a**) was converted to the title compound using the following procedure. An oven-dried round

bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with anhydrous ethanol (20 mL). The flask was cooled to –78 °C and stirred for 1 h, then solid lithium tri-*tert*-butoxyaluminum hydride (1.526 g, 6.0 mmol) was added, the flask was purged with nitrogen, and the resulting ethanolic solution of $LiAl(O\textit{t}\text{-}Bu)_3H$ was maintained at –78 °C. A separate oven-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate (682 mg, 3.0 mmol, 1 equiv) and anhydrous ethanol (10 mL) then cooled to –78 ºC and stirred for 1 h. The solution of (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate was added to the solution of $LiAl(O\textit{t}Bu)_3H$ dropwise via cannula over 30 min. The resulting mixture was stirred at –78 ºC for 1.5 h, then 10% aqueous citric acid (20 mL) was added, the mixture was warmed to rt, and stirred for 1 h. The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Benzene (20 mL) was added, and the mixture was again concentrated *in vacuo* to facilitate removal of ethanol. The resulting crude product was purified by flash chromatography on silica gel to afford 649 mg (93%) of the title compound as white solid, mp 77–79 ºC. This material was obtained with >20:1 dr as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86–5.76 (m, 1 H), 5.07–4.97 (m, 2 H), 4.60–4.50 (m, 1 H), 3.90–3.81 (m, 1 H), 3.66–3.58 (m, 1 H), 2.56 (d, J = 4.5 Hz, 1 H), 2.24–2.14 (m, 1 H), 2.14–2.04 (m, 1 H), 1.65–1.56 (m, 1 H), 1.49–1.39 (m, 10 H), 1.14 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 137.8, 115.1, 79.6, 70.4, 55.6, 30.4, 29.0, 28.3, 18.3; IR (film) 3352, 2978, 1689 cm^{-1}. MS (ESI) 252.1579 (252.1576 calcd for $C_{12}H_{23}NO_3$, M + Na^+).



(±)-(4*R,5*S**)-*tert*-Butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (III-20b).** An oven-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate **III-17** (1.0 g, 3.67 mmol). The flask was purged with nitrogen, THF (26 mL) was added, and the resulting solution was cooled to –78 ºC. Allylmagnesium bromide (11 mL, 11 mmol, 1 M in Et_2O) was added dropwise over 40 min, and the resulting mixture was stirred at –78 ºC for 4 h. The reaction mixture was carefully poured into saturated aqueous ammonium chloride (25 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford (±)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (**III-19b**) as a clear oil (792 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97–5.86 (m, 1 H), 5.85–5.73 (m, 1 H), 5.24–5.10 (m, 3 H), 5.08–4.99 (m, 2 H), 4.42–4.34 (m, 1 H), 3.35–3.21 (m, 2 H), 2.18–1.90 (m, 3 H), 1.65–1.54 (m, 1 H), 1.44 (s, 9 H).

A portion of (±)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (**III-19b**) (792 mg, 3.1 mmol) was converted to the title compound using a procedure analogous to that described above for the conversion of (±)-*tert*-butyl (2-oxohept-6-en-3-yl)carbamate to (±)-(2*R**,3*S**)-*tert*-butyl 2-hydroxyhept-6-en-3-ylcarbamate. This procedure afforded 739 mg (92%) of the title compound as a white solid, mp 99–101 ºC. This product was

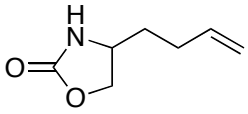
obtained with >20:1 dr as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.76 (m, 2 H), 5.18–5.11 (m, 2 H), 5.08–5.01 (m, 1 H), 5.01–4.96 (m, 1 H), 5.68 (d, *J* = 8.4 Hz, 1 H), 3.73–3.55 (m, 2 H), 2.46 (d, *J* = 4.0 Hz, 1 H), 2.34-2.00 (m, 4 H), 1.74–1.62 (m, 1 H), 1.54–1.38 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 137.9, 134.8, 118.1, 115.1, 79.5, 73.5, 54.4, 38.2, 30.3, 28.6, 28.4; IR (film) 3352, 3079, 1684 cm^{-1}; MS 278.1740 (278.1732 calcd for $C_{14}H_{25}NO_3$, M + Na^+).

(–)-(4*R*,5*S*)-*tert*-Butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (III-20b). (+)-(*S*)-*tert*-Butyl (1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate[11] (**III-17**) (2.00 g, 7.34 mmol) was converted to (+)-(S)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (1.478 g, 79%, clear oil, 90% purity) using a procedure analogous to that employed above for the synthesis of the racemic compound. $[\alpha]^{20}_D$ +54.5 (*c* 0.99, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for the racemic compound.

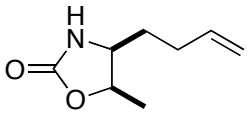
(+)-(*S*)-*tert*-butyl (4-oxonona-1,8-dien-5-yl)carbamate (1.458g mg, 5.76 mmol) was converted to the title compound using a procedure analogous to that employed above for the synthesis of the racemic compound. This procedure afforded 1.216 g (83%) of the title compound as a white solid, mp 115–117 ºC. This product was obtained with >20:1 dr as judged by ^{1}H NMR analysis. $[\alpha]^{20}_D$ –21.7 (*c* 1.07, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for (±)-**III-20b**.

General Procedure 1: Synthesis of 4-(but-3-en-1-yl)oxazolidin-2-one derivatives. An oven-dried round bottom flask was cooled under a stream of nitrogen and charged with

the appropriate Boc-protected amino alcohol (1 equiv), THF (10 mL/mmol), and sodium hydride (60% dispersion in mineral oil, 1.2 equiv). The flask was equipped with a reflux condenser and purged with nitrogen. The reaction mixture was then heated to reflux with stirring until the starting material had been completely consumed as judged by TLC analysis. The mixture was cooled to rt, quenched with saturated aqueous ammonium chloride, and transferred to a separatory funnel. The mixture was extracted with CH_2Cl_2 (3x), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

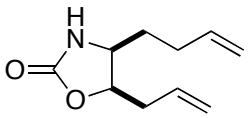


(±)-4-(But-3-en-1-yl)oxazolidin-2-one (III-21).[15] The reaction of (±)-*tert*-butyl 1-hydroxyhex-5-en-2-ylcarbamate (**III-18**) (1.50 g, 6.97 mmol) was conducted according to General Procedure 1 for 2.75 h to afford 957 mg (97%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83–5.74 (m, 1 H), 5.38 (s, br, 1 H), 5.11–5.02 (m, 2 H), 4.50 (t, J = 8.5 Hz, 1 H), 4.04 (dd, J = 6.5, 8.5 Hz, 1 H), 3.93–3.86 (m, 1 H), 2.16–2.10 (m, 2 H), 1.77–1.65 (m, 2 H).



(±)-(4*S,5*R**)-4-(But-3-en-1-yl)-5-methyloxazolidin-2-one (III-22).** The reaction of (±)-(2*R**,3*S**)-*tert*-butyl 2-hydroxyhept-6-en-3-ylcarbamate (**III-20a**) (649 mg, 2.83 mmol)

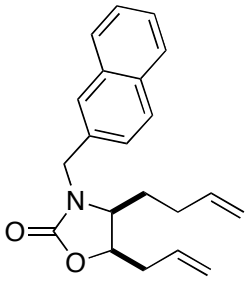
was conducted according to General Procedure 1 for 1 h to afford 424 mg (97%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84–5.75 (m, 1 H), 5.40 (s, br, 1 H), 5.12–5.03 (m, 2 H), 4.81–4.75 (m, 1 H), 3.82–3.76 (m, 1 H), 2.21–2.04 (m, 2 H), 1.64–1.59 (m, 2 H), 1.36 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 136.9, 115.9, 76.1, 55.1, 30.2, 29.0, 14.8; IR (film) 3267, 2942, 1748 cm^{-1}. MS (ESI) 178.0847 (178.0844 calcd for $C_8H_{13}NO_2$, M + Na^+).



(±)-(4*S,5*R**)-5-Allyl-4-(but-3-en-1-yl)oxazolidin-2-one (III-23)**. The reaction of (±)-(4*R**,5*S**)-*tert*-butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (**III-20b**) (670 mg, 2.62 mmol) was conducted according to General Procedure 1 for 2 h to afford 440 mg (93%) of the title compound as a white solid, mp 40–42 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88–5.74 (m, 2 H), 5.34 (s, br, 1 H), 5.21–5.14 (m, 2 H), 5.12–5.04 (m, 2 H), 4.66 (ddd, J = 5.5, 8.0, 8.5 Hz, 1 H), 3.80 (dt, J = 5.0, 8.0 Hz, 1 H), 2.59–2.51 (m, 1 H), 2.41–2.34 (m, 1 H), 2.22–2.04 (m, 2 H), 1.67–1.61 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 136.8, 132.7, 118.3, 116.1, 79.3, 55.0, 33.6, 30.1, 28.9; IR (film) 3265, 2932, 1748 cm^{-1}. MS (ESI) 204.1002 (204.1000 calcd for $C_{10}H_{15}NO_2$, M + Na^+).

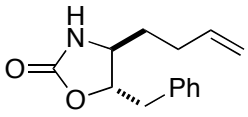
(+)-(4*S*,5*R*)-5-Allyl-4-(but-3-en-1-yl)oxazolidin-2-one (III-23). The reaction of (–)-(4*R*,5*S*)-*tert*-butyl 4-hydroxynona-1,8-dien-5-ylcarbamate (1.017 mg, 3.98 mmol) was conducted according to General Procedure 1 for 7 h to afford 629 mg (87%) of the title compound as a white solid, mp 34–35 ºC. $[\alpha]^{23}_D$ +5.48 (*c* 10.2, CH_2Cl_2). ^{1}H NMR data

were identical to those reported above for (±)-**III-23**. The enantiomeric purity of this compound was determined to be 99% ee by conversion to **III-46** and analysis by chiral HPLC as described below.



(+)-(4*S*,5*R*)-5-Allyl-4-(but-3-en-1-yl)-3-(naphthalen-2-ylmethyl)oxazolidin-2-one (III-46). An oven dried test tube equipped with a stir bar was cooled under a stream of nitrogen and charged with (+)-**III-23** (50 mg, 0.28 mmol) and sodium hydride (12 mg, 0.30 mmol). The tube was purged with nitrogen and anhydrous DMF (0.40 mL) was added. The resulting mixture was stirred at rt for 25 min, then a solution of 2-(bromomethyl)naphthalene (62 mg, 0.28 mmol) in DMF (0.15 mL) was added in one portion. The reaction mixture was stirred at rt for 24.5 h, then was quenched with saturated aqueous ammonium chloride (2 mL). The resulting mixture was transferred to a separatory funnel and extracted with ethyl acetate (5 x 2 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound as a clear oil (49 mg, 55%). The enantiopurity was determined to be 99% ee by chiral HPLC analysis [(*R*,*R*)-Whelk-O-1 5100, 0.46 cm x 25 cm, 13% isopropanol/hexanes, 2.0 mL/min, RT= 23.8 and 33.3 min]. $[\alpha]^{23}_{D}$ +36.8 (*c* 2.27, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.79 (m, 3 H), 7.72–7.70 (m, 1 H), 7.53–

7.46 (m, 2 H), 7.43–7.39 (m, 1 H), 5.90–5.79 (m, 1 H), 5.75–5.63 (m, 1 H), 5.20–5.12 (m, 2 H), 5.03–4.93 (m, 2 H), 4.49 (ddd, J = 4.8, 7.6, 8.8 Hz, 1 H), 4.22 (d, J = 15.6 Hz, 1 H), 3.60 (dt, J = 4.4, 7.2 Hz, 1 H), 2.59–2.49 (m, 1 H), 2.40–2.31 (m, 1 H), 2.08–2.00 (m, 2 H), 1.80–1.65 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 136.6, 133.6, 133.3, 132.9, 132.7, 128.8, 127.7, 126.9, 126.4, 126.2, 125.7, 118.5, 115.7, 77.1, 56.5, 46.5, 33.6, 29.4, 26.3 (one carbon signal is absent due to incidental equivalence); IR (film) 3056, 2936, 1749 cm^{-1}. MS (ESI) 344.1614 (244.1626 calcd for $C_{21}H_{23}NO_2$, M + Na^+).



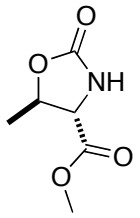
(±)-(4*S,5*S**)-5-benzyl-4-(but-3-en-1-yl)oxazolidin-2-one (III-24).** An oven-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl 1-methoxy(methyl)amino-1-oxohex-5-en-2-ylcarbamate **III-17** (1.91 g, 7.00 mmol). The flask was purged with nitrogen, THF (19 mL) was added, and the resulting solution was cooled to 0 ºC. Benzylmagnesium bromide (14 mL, 21 mmol, 1.5 M in THF) was added dropwise over 3 min, and the resulting mixture was slowly warmed from 0 ºC to rt over 4 h. The reaction was then quenched slowly with 1 M HCl (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 1.89 g (89%) of (±)-*tert*-butyl (2-oxo-1-phenylhept-6-en-3-yl)carbamate (**III-19c**) as a white solid, mp 61–65 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 3 H), 7.22–7.18 (m, 2 H), 5.80–5.67 (m,

1 H), 5.20–5.10 (m, 1 H), 5.04–4.96 (m, 2 H), 4.48–4.40 (m, 1 H), 3.86–3.74 (m, 2 H), 2.13–1.85 (m, 3 H), 1.65–1.53 (m, 1 H), 1.44 (s, 9 H).

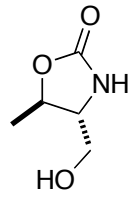
A flame-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with anhydrous ethanol (40 mL). The flask was cooled to –78 °C and stirred for 1 h, then solid lithium tri-*tert*-butoxyaluminum hydride (3.06 g, 12.0 mmol) was added, the flask was purged with nitrogen, and the resulting ethanolic solution of $LiAl(OtBu)_3H$ was maintained at –78 °C. A separate flame-dried round bottom flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl (2-oxo-1-phenylhept-6-en-3-yl)carbamate (**III-19c**) (1.83 g, 6.0 mmol, 1 equiv) and anhydrous ethanol (20 mL). The resulting mixture was cooled to 0 ºC and stirred for 30 min. The solution of (±)-*tert*-butyl (2-oxo-1-phenylhept-6-en-3-yl)carbamate was then added to the solution of $LiAl(Ot\text{-}Bu)_3H$ dropwise via cannula over 15 min. The resulting mixture was stirred at –78 ºC for 3 h, then 10% aqueous citric acid (20 mL) was added, the mixture was warmed to rt, and stirred for 1 h. The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. To remove ethanol, the product was dissolved in benzene (40 mL), and the resulting solution was concentrated *in vacuo*. This was repeated three additional times to afford 1.58 g (86%) of *tert*-butyl [(2S^*,3R^*)-2-hydroxy-1-phenylhept-6-en-3-yl]carbamate (**III-20c**) as a white solid, mp 120–124 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2 H), 7.26–7.21 (m, 3 H), 5.88–5.79 (m, 1 H), 5.08–5.03 (m, 1 H), 5.02–4.98 (m, 1 H), 4.68 (d, J = 9.0 Hz, 1 H), 3.91–3.85 (m, 1 H), 3.71–3.63 (m, 1

H), 2.85–2.80 (m, 1 H), 2.67 (dd, *J* = 10.0, 14.0 Hz, 1 H), 2.27–2.17 (m, 2 H), 2.15–2.06 (m, 1 H), 1.79–1.70 (m, 1 H), 1.59–1.50 (m, 1 H), 1.45 (s, 9 H).

A flame-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with *tert*-butyl [(2*R**,3*S**)-2-hydroxy-1-phenylhept-6-en-3-yl]carbamate (**III-20c)** (1.58 g, 1.6 mmol, 1 equiv). The flask was purged with nitrogen, 1,2-dichloroethane (26 mL, 5 mL/mmol) was added, and the resulting mixture was cooled to 0 ºC. Methane sulfonylchloride (0.60 mL, 888 mg, 7.8 mmol) and N,N-diisopropylethylamine (2.7 mL, 2.0 g, 15.5 mmol) were added, and the mixture was warmed to rt and stirred for 1 h. The mixture was heated to 75 ºC for 30 h, then cooled to rt. Saturated aqueous ammonium chloride (20 mL) was added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 0.701 g (59%) of the title compound as a brown solid, mp 48–51 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5 H), 6.13 (s, br, 1 H), 5.73–5.61 (m, 1 H), 5.01–4.94 (m, 2 H), 4.44–4.38 (m, 1 H), 3.54 (td, *J* = 5.2, 7.6 Hz, 1 H), 3.10 (dd, *J* = 6.4, 14.0 Hz, 1 H), 2.91 (dd, *J* = 6.4, 14.0 Hz, 1 H), 2.03–1.96 (m, 2 H), 1.60–1.41 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.7, 135.2, 129.5, 128.7, 127.1, 116.0, 82.5, 56.4, 40.5, 34.2, 29.5; IR (film) 3260, 2925, 1750 cm^{-1}. MS (ESI) 254.1160 (254.1157 calcd for $C_{14}H_{17}NO_2$, M + Na^+).

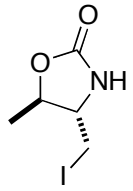


(+)-(4*S*,5*R*)-Methyl 5-methyl-2-oxooxazolidine-4-carboxylate (III-25).[16] An oven-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with triphosgene (3.50 g, 11.8 mmol) and L-threonine methyl ester hydrochloride (2.00 g, 11.8 mmol). The flask was equipped with a reflux condenser and purged with nitrogen. THF was added and the resulting mixture was heated to reflux for 1 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 1.85 g (98%) of the title compound as a clear oil. $[\alpha]^{23}_{D}$ +27.5 (*c* 1.18, CH_2Cl_2) [lit.[16] $[\alpha]^{20}_{D}$ +30.5 (*c* 0.12, CH_2Cl_2)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, br, 1 H), 4.80–4.72 (m, 1 H), 3.99 (d, *J* = 5.2 Hz, 1 H), 3.82 (s, 3 H), 1.57 (d, *J* = 6.4 Hz, 3 H).



(+)-(4*R*,5*R*)-4-(Hydroxymethyl)-5-methyloxazolidin-2-one (III-26).[17] An oven-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged dry flask was charged with **(+)-**(4*S*,5*R*)-methyl 5-methyl-2-oxooxazolidine-4-carboxylate (**III-25**) (1.85g, 11.6 mmol). The flask was purged with nitrogen, anhydrous ethanol (23 mL) was added, and the resulting mixture was cooled to 0 °C. Sodium borohydride (461 mg, 12.2 mmol) was added, the mixture was stirred at 0 ºC for 5 min,

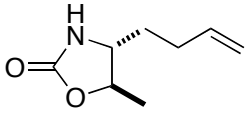
then warmed to rt and stirred for 1.5 h. Saturated aqueous ammonium chloride (2 mL) was added and the resulting mixture was stirred at rt for 45 min. The reaction mixture was then filtered, and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the 1.32 g (87%) of title compound as a white solid, mp 81–84 ºC, $[\alpha]^{23}_{D}$ +65.4 (*c* 1.14, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, br, 1 H), 4.52–4.45 (m, 1 H), 3.76–3.70 (m, 1 H), 3.66–3.59 (m, 1 H), 3.58–3.53 (m, 1 H), 2.00 (s, br, 1 H), 1.47 (d, *J* = 6.5 Hz, 3 H).



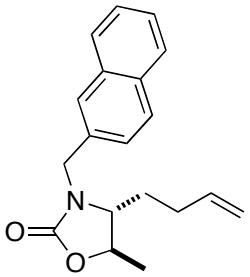
(+)-(4*S*,5*R*)-4-(Iodomethyl)-5-methyloxazolidin-2-one (III-28). An oven-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (+)-(4*R*,5*R*)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (**III-26**) (1.29 g, 9.8 mmol). The flask was purged with nitrogen, pyridine (3.6 mL) was added, and the mixture was cooled to 0 ºC. Tosyl chloride (2.81 g, 14.7 mmol) was added, the flask was purged with nitrogen, and the reaction mixture was warmed to rt and stirred for 18 h. The mixture was diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and washed with 1 M hydrochloric acid (3 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 2.23 g (80%) of (4*R*,5*R*)-5-methyl-2-oxooxazolidin-4-ylmethyl 4-methylbenzenesulfonate (**III-27**) as a white solid, mp 105–106 ºC. $[\alpha]^{23}_{D}$ +31.9 (*c* 1.65, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2 H),

7.41–7.37 (m, 2 H), 5.17 (s, br, 1 H), 4.39–4.33 (m, 1 H), 4.04 (dd, *J* = 5.0, 10.5 Hz, 1 H), 3.97 (dd, *J* = 6.5, 10.5 Hz, 1 H), 3.73–3.68 (m, 1 H), 2.48 (s, 3 H), 1.45 (d, *J* = 6.5 Hz, 3 H).

A portion of the (+)-(4*R*,5*R*)-(5-methyl-2-oxooxazolidin-4-yl)methyl 4-methylbenzenesulfonate (**III-28**) was converted to the title compound using the following procedure. An oven-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with (4*R*,5*R*)-5-methyl-2-oxooxazolidin-4-ylmethyl 4-methylbenzenesulfonate (2.22 g, 7.8 mmol), sodium iodide (5.47 g, 36.5 mmol), and anhydrous acetone (32 mL). The flask was equipped with reflux condenser, purged with nitrogen, and the reaction mixture was heated to reflux for 6 h. The mixture was then cooled to rt, filtered, and concentrated *in vacuo*. The crude product was dissolved in ethyl acetate (15 mL) and washed with saturated sodium sulfite (2 x 15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 1.51 g (59%) of the title compound as a pale yellow solid, mp 45–47 ºC, $[\alpha]^{23}_{D}$ +3.70 (*c* 1.06, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.55 (s, br, 1 H), 4.41–4.36 (m, 1 H), 3.65–3.61 (m, 1 H), 3.23–3.18 (m, 2 H), 1.49 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 78.9, 60.0, 20.8, 7.3; IR (film) 3288, 2926, 1744 cm^{-1}. MS (ESI) 263.9498 (263.9494 calcd for $C_5H_8INO_2$, M + Na^+).



(+)-(4*R*,5*R*)-4-(But-3-en-1-yl)-5-methyloxazolidin-2-one (III-29). The conversion of (+)-(4*S*,5*R*)-4-(iodomethyl)-5-methyloxazolidin-2-one (**III-28**) (1.45 g, 6.02 mmol) to the title compound was accomplished using a procedure identical to that described above for the preparation of (±)-methyl 2-[(*tert*-butoxycarbonyl)amino]hex-5-enoate (**III-16**). This procedure afforded 748 mg (80%) of the title compound as a clear oil, $[\alpha]^{23}_{D}$ +70.5 (*c* 1.12, CH_2Cl_2). The enantiomeric purity of this compound was determined to be 99% ee by conversion to **III-47** and analysis by chiral HPLC as described below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, br, 1 H), 5.84–5.72 (m, 1 H), 5.11–5.00 (m, 2 H), 4.29 (app quint, *J* = 6.0 Hz, 1 H), 3.45–3.39 (m, 1 H), 2.22–2.06 (m, 2 H), 1.65 (q, *J* = 7.2 Hz, 2 H), 1.42 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 136.8, 115.9, 78.9, 59.2, 33.9, 29.7, 20.1; IR (film) 3275, 2932, 1751 cm^{-1}. MS (EI): 155.0946 (155.0946 calcd for $C_8H_{13}NO_2$, M^+).



(+)-(4*R*,5*R*)-4-(But-3-en-1-yl)-5-methyl-3-(naphthalen-2-ylmethyl)oxazolidin-2-one (III-47)

The conversion of (+)-**III-29** (43 mg, 0.28 mmol) to the title compound was accomplished using a procedure analogous to that described above for the preparation of **III-46**. This procedure afforded the title compound as a clear oil (57 mg, 70%). The enantiopurity was determined to be 99% ee by chiral HPLC analysis [Chiracel OJ-H, 0.46 cm x 25 cm, 15% isopropanol/hexanes, 2.0 mL/min, RT= 8.5 and 17.0 min]. $[\alpha]^{23}_{D}$

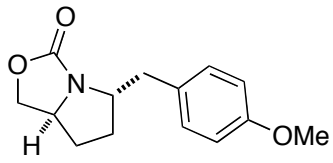
+30.0 (*c* 1.07, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.80 (m, 3 H), 7.72–7.69 (m, 1 H), 7.53–7.46 (m, 2 H), 7.43–7.39 (m, 1 H), 5.75–5.63 (m, 1 H), 5.01–4.93 (m, 3 H), 4.34–4.26 (m, 1 H), 4.21 (d, *J* = 15.2 Hz, 1 H), 3.13 (ddd, *J* = 3.2, 5.2, 8.4 Hz, 1 H), 2.10–1.89 (m, 2 H), 1.82–1.72 (m, 1 H), 1.66–1.55 (m, 1 H), 1.30 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 136.6, 133.5, 133.2, 132.9, 128.8, 127.7, 126.9, 126.4, 126.2, 125.8, 115.8, 75.1, 60.5, 46.1, 30.4, 28.0, 20.9 (one carbon signal is absent due to incidental equivalence); IR (film) 3053, 2926, 1744 cm^{-1}. MS (ESI) 318.1458 (318.1470 calcd for $C_{19}H_{21}NO_2$, M + Na^+).

3.6.2 Preparation and Characterization of Products

General Procedure 2: Pd-catalyzed Synthesis of Tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one derivatives Using $Pd(OAc)_2$ as the Precatalyst. An oven-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol%) and RuPhos (4 mol%). The tube was evacuated and refilled with nitrogen three times, then benzene (1 mL/mmol, substrate) was added and the resulting yellow solution was stirred at rt for 20 min to provide a red solution. Solid NaO*t*-Bu (1.2 equiv) was added, the tube was purged with nitrogen, then a solution of the substrate (1 equiv) and the aryl bromide (1.2 equiv) in benzene (2 mL/mmol substrate) was added. The sides of the Schlenk tube were rinsed with additional benzene (1 mL/mmol substrate), then the reaction mixture was immersed in an 80 ºC oil bath and stirred until the starting material was consumed as determined by ^{1}H NMR analysis of a small aliquot removed from the mixture. The reaction mixture was cooled to rt and saturated aqueous ammonium chloride (2 mL) and ethyl acetate (5 mL) were added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The

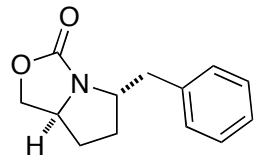
combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

General Procedure 3: Pd-catalyzed Synthesis of Tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one derivatives Using [(allyl)Pd(Cl)]$_2$ as the Precatalyst. An oven dried Schlenk tube was cooled under a stream of nitrogen and charged with [(allyl)Pd(Cl)]$_2$ (1 mol% complex, 2 mol% Pd), RuPhos (4 mol%), and NaO*t*-Bu (1.2 equiv). The tube was evacuated and refilled with nitrogen three times, then a solution of the substrate (1 equiv) and the aryl halide (1.2 equiv) in benzene (4 mL/mmol substrate) was added. The reaction mixture was immersed in an 80 ºC oil bath and stirred until the starting material was consumed as determined by ^{1}H NMR analysis of a small aliquot removed from the mixture. The reaction mixture was cooled to rt and saturated aqueous ammonium chloride (2 mL) and ethyl acetate (5 mL) were added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

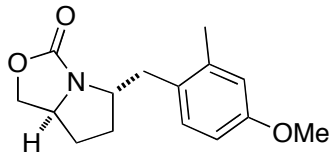


(±)-(5*S,7a*S**)-5-(4-Methoxybenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-30).** The reaction of **III-21** (71 mg, 0.50 mmol) with 4-bromoanisole (75 μL, 0.60 mmol) was conducted at 80 ºC for 20.5 h according to General Procedure 3. This procedure

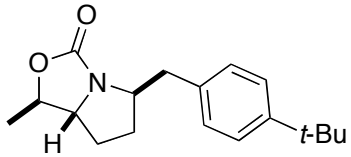
afforded 102 mg (82%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.14 (m, 2 H), 6.86–6.82 (m, 2 H), 4.50 (dd, *J* = 7.5, 8.5 Hz, 1 H), 4.16–4.09 (m, 2 H), 3.79 (s, 3 H), 3.77–3.70 (m, 1 H), 2.92 (dd, *J* = 5.5, 14.0, 1 H), 2.76 (dd, *J* = 7.5, 13.5 Hz, 1 H), 2.11 (dtd, *J* = 1.5, 8.0, 13.0 Hz, 1 H), 2.00–1.93 (m, 1 H), 1.68 (tdd, *J* = 7.0, 11.5, 13.5 Hz, 1 H), 1.52–1.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 158.2, 130.5, 129.6, 113.8, 67.6, 59.5, 59.0, 55.2, 40.6, 31.6, 31.4; IR (film) 2932, 1748 cm^{-1}. MS (ESI) 270.1108 (270.1106 calcd for $C_{14}H_{17}NO_3$, M + Na^+).



(±)-(5*S,7a*S**)-5-Benzyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-32).** The reaction of **III-21** (71 mg, 0.50 mmol) with bromobenzene (63 μL, 0.60 mmol) was conducted at 80 ºC for 21 h according to General Procedure 3. This procedure afforded 87 mg (80%) of the title compound as a pale yellow amorphous solid, mp 39–41 °C. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H), 7.26–7.21 (m, 3 H), 4.46 (dd, *J* = 8.0, 8.5 Hz, 1 H), 4.20–4.10 (m, 2 H), 3.79–3.72 (m, 1 H), 3.00 (dd, *J* = 5.5, 13.5 Hz, 1 H), 2.80 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.12 (dtd, *J* = 1.2, 8.0, 13.0 Hz, 1 H), 2.01–1.94 (m, 1 H), 1.69 (tdd, *J* = 7.5, 11.5, 13.0 Hz, 1 H), 1.52–1.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 137.5, 129.5, 128.3, 126.4, 67.5, 59.4, 58.9, 41.5, 31.7, 31.4; IR (film) 2967, 1749 cm^{-1}. MS (ESI) 240.1008 (240.1000 calcd for $C_{13}H_{15}NO_2$, M + Na^+).



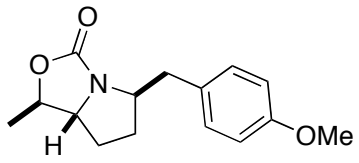
(±)-(5*S,7a*S**)-5-(4-Methoxy-2-methylbenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-33)**. The reaction of **III-21** (71 mg, 0.50 mmol) with 2-bromo-5-methoxytoluene (85 μL, 0.60 mmol) was conducted at 80 ºC for 4 h according to General Procedure 2. This procedure afforded 83 mg (64%) of the title compound as a pale yellow solid, mp 65–69 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 3.0 Hz, 1 H), 6.68 (dd, *J* = 2.5, 8.5 Hz, 1 H), 4.47 (dd, *J* = 8.0, 9.0 Hz, 1 H), 4.15–4.08 (m, 2 H), 3.89–3.82 (m, 1 H), 3.78 (s, 3 H), 3.00 (dd, *J* = 6.0, 14.5 Hz, 1 H), 2.69 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.35 (s, 3 H), 2.13 (dtd, *J* = 2.0, 8.0, 13.5 Hz, 1 H), 2.05–1.98 (m, 1 H), 1.69 (tdd, *J* = 7.5, 11.5, 13.0 Hz, 1 H), 1.52–1.42 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.1, 138.0, 130.9, 128.2, 115.9, 111.0, 67.6, 59.0, 58.9, 55.1, 38.2, 32.1, 31.5, 20.0; IR (film) 2926, 1750 cm^{-1}. MS (ESI) 284.1261 (284.1263 calcd for $C_{14}H_{17}NO_3$, M + Na^+).



(±)-(1*R,5*R**,7a*R**)-5-[4-(*tert*-Butyl)benzyl]-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-34).** The reaction of **(±)-III-29** (78 mg, 0.50 mmol) with 4-bromo-1-*tert*-butylbenzene (105 μL, 0.60 mmol) was conducted at 80 ºC for 27 h according to General Procedure 3. This procedure afforded 88 mg (61%) of the title compound as a tan solid,

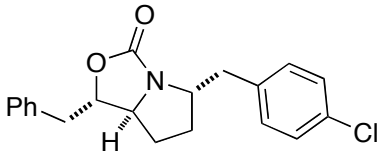
mp 89–94 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) 7.33–7.29 (m, 2 H), 7.18–7.15 (m, 2 H), 4.38 (dq, *J* = 4.0, 6.5 Hz, 1 H), 4.16–4.09 (m, 1 H), 3.36 (ddd, *J* = 2.5, 5.5, 9.5 Hz, 1 H), 3.01 (dd, *J* = 5.0, 13.5 Hz, 1 H), 2.71 (dd, *J* = 8.5, 13.5 Hz, 1 H), 2.09 (dtd, *J* = 2.0, 5.0, 13.0 Hz, 1 H), 2.01–1.94 (m, 1 H), 1.67 (tdd, *J* = 7.5, 11.0, 13.0 Hz, 1 H), 1.49–1.38 (m, 4 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.9, 149.3, 134.5, 129.2, 125.2, 65.8, 59.1, 41.0, 34.4, 31.8, 31.4, 31.0, 21.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2963, 1750 cm^{-1}. MS (ESI) 310.1785 (310.1783 calcd for $C_{18}H_{25}NO_2$, M + Na^+).

(+)-(1*R*,5*R*,7a*R*)-5-[4-(*tert*-Butyl)benzyl]-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-34). The reaction of **(+)-III-29** (78 mg, 0.50 mmol) with 4-bromo-1-*tert*-butylbenzene (105 μL, 0.60 mmol) was conducted at 80 ºC for 27 h according to General Procedure 3. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. This procedure afforded 102 mg (71%) of the title compound as a tan solid, mp 81–84 ºC. The enantiopurity was determined to be 99% ee by chiral HPLC analysis [(*R*,*R*)-Whelk-O-1 5100 0.46 cm x 25 cm, 7% isopropanol/hexanes, 1.0 mL/min, RT= 26.8 and 31.7 min]. $[\alpha]^{23}_D$ +52.2 (*c* 1.06, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for (±)-**III-34**.



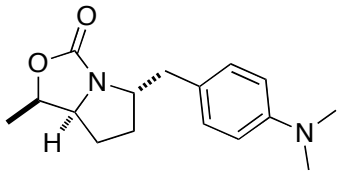
(±)-(1*R,5*R**,7a*R**)-5-(4-Methoxybenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-**

3(1*H*)-one (III-35). The reaction of **(±)-III-29** (78 mg, 0.50 mmol) with 4-bromoanisole (75 μL, 0.60 mmol) was conducted at 80 ºC for 6.5 h according to General Procedure 3. This procedure afforded 106 mg (81%) of the title compound as a pale yellow solid, mp 87–89 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.12 (m, 2 H), 6.86–6.81 (m, 2 H), 4.36 (dq, *J* = 4.0, 6.4 Hz, 1 H), 4.08 (dt, *J* = 4.8, 7.6 Hz, 1 H), 3.79 (s, 3 H), 3.30 (ddd, *J* = 4.0, 5.2, 9.6 Hz, 1 H), 2.92 (dd, *J* = 4.4, 13.6 Hz, 1 H), 2.73 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.08 (dtd, *J* = 2.4, 8.4, 12.8 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.65 (tdd, 7.6, 10.8, 12.8 Hz, 1 H), 1.48–1.37 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.2, 130.6, 129.6, 113.7, 76.6, 65.8, 59.2, 55.2, 40.4, 31.5, 31.0, 21.2; IR (film) 2930, 1749 cm^{-1}. MS (ESI) 284.1259 (284.1263 calcd for $C_{15}H_{19}NO_3$, M + Na^+).

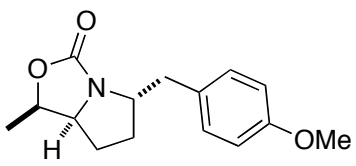


(±)-(1*S,5*S**,7a*S**)-1-Benzyl-5-(4-chlorobenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-36).** The reaction of **III-24** (58 mg, 0.25 mmol) with 4-bromochlorobenzene (57 mg, 0.30 mmol) was conducted at 80 ºC for 15 h according to General Procedure 3 except using 2.5 mol% $[Pd(allyl)(Cl)]_2$ and 10 mol% 2-(dicyclohexylphosphino)biphenyl as ligand. This procedure afforded 58 mg (68%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 7 H), 7.07–7.02 (m, 2 H), 4.49 (ddd, *J* = 3.6, 6.4, 6.8 Hz, 1 H), 4.10–4.02 (m, 1 H), 3.39 (ddd, *J* = 4.0, 5.6, 10.0 Hz, 1 H), 3.11 (dd, *J* = 6.0, 14.0 Hz, 1 H), 2.94 (dd, *J* = 7.2, 14.0 Hz, 1 H), 2.85–2.73 (m, 2

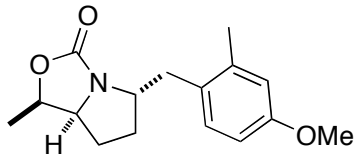
H), 2.08 (dtd, J = 1.6, 8.0, 12.8 Hz, 1 H), 1.83–1.75 (m, 1 H), 1.62–1.51 (m, 1 H), 1.45–1.33 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 135.9, 135.3, 132.4, 131.0, 129.5, 128.7, 128.4, 127.1, 80.4, 63.2, 58.9, 40.9, 40.5, 31.5, 31.3; IR (film) 3029, 1750 cm^{-1}. MS (ESI) 364.1065 (364.1080 calcd for $C_{20}H_{20}ClNO_2$, M + Na^+).



(±)-(1*R,5*S**,7a*S**)-5-[4-(Dimethylamino)benzyl]-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-37).** The reaction of **III-22** (78 mg, 0.50 mmol) with 4-bromo-*N,N*-dimethylaniline (120 mg, 0.60 mmol) was conducted at 80 ºC for 7 h according to General Procedure 2. This procedure afforded 96 mg (70%) of the title compound as an orange solid, mp 97–100 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.08 (m, 2 H), 6.70–6.66 (m, 2 H), 4.75 (app quint, J = 6.8 Hz, 1 H), 4.17–4.09 (m, 1 H), 3.63 (ddd, J = 4.4, 7.2, 10.8 Hz, 1 H), 2.93–2.86 (m, 7 H), 2.70 (dd, J = 8.0, 14.0 Hz, 1 H), 2.12–2.04 (m, 1 H), 1.68–1.57 (m, 2 H), 1.55–1.41 (m, 1 H), 1.34 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 149.3, 130.2, 125.4, 112.6, 72.1, 63.0, 59.8, 40.7, 31.0, 25.8, 15.6 (one carbon signal is absent due to incidental equivalence); IR (film) 2926, 1749 cm^{-1}. MS (ESI) 297.1572 (297.1579 calcd for $C_{16}H_{22}N_2O_2$, M + Na^+).

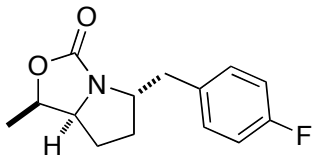


(±)-(1*R,5*S**,7a*S**)-5-(4-Methoxybenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-38).** The reaction of **III-22** (78 mg, 0.50 mmol) with 4-bromoanisole (75 μL, 0.60 mmol) was conducted at 80 ºC for 22 h according to General Procedure 3. This procedure afforded 111 mg (85%) of the title compound as peach colored solid, mp 91–93 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.13 (m, 2 H), 6.86–6.80 (m, 2 H), 4.76 (app quint, *J* = 6.8 Hz, 1 H), 4.13 (dq, *J* = 5.6, 7.2 Hz, 1 H), 3.71 (s, 3 H), 3.67–3.60 (m, 1 H), 2.90 (dd, *J* = 5.2, 14.0 Hz, 1 H), 2.75 (dd, *J* = 7.6, 13.6 Hz, 1 H), 2.15–2.06 (m, 1 H), 1.67–1.55 (m, 2 H), 1.54–1.42 (m, 1 H), 1.34 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 158.2, 130.6, 129.6, 113.7, 72.1, 63.1, 59.7, 55.2, 40.8, 31.1, 25.8, 15.6; IR (film) 2926, 1749 cm^{-1}. MS (ESI) 284.1266 (284.1263 calcd for $C_{15}H_{19}NO_3$, M + Na^+).

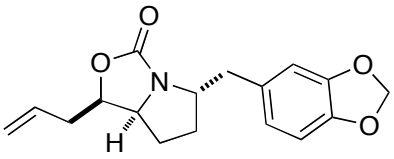


(±)-(1*R,5*S**,7a*S**)-5-(4-Methoxy-2-methylbenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-39).** The reaction of **III-22** (78 mg, 0.50 mmol) with 2-bromo-5-methoxytoluene (85 μL, 0.60 mmol) was conducted at 80 ºC for 4 h according to General Procedure 3. This procedure afforded 85 mg (61%) of the title compound as a pale yellow solid, mp 85–88 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 1 H), 6.73–6.66 (m, 2 H), 4.78 (app quint, *J* = 7.0 Hz, 1 H), 4.16–4.09 (m, 1 H), 3.80–

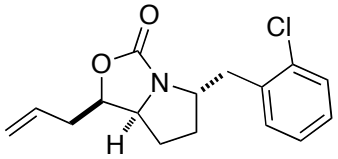
3.73 (m, 4 H), 2.98 (dd, J = 5.5, 14.0 Hz, 1 H), 2.69 (dd, J = 8.0, 14.0 Hz, 1 H), 2.35 (s, 3 H), 2.16–2.09 (m, 1 H), 1.71–1.57 (m, 2 H), 1.55–1.46 (m, 1 H), 1.35 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.1, 138.0, 130.8, 128.2, 115.8, 110.9, 72.2, 63.0, 59.2, 55.1, 38.4, 31.6, 25.9, 20.0, 15.7; IR (film) 2932, 1749 cm^{-1}. MS (ESI) 298.1421 (298.1419 calcd for $C_{16}H_{21}NO_3$, M + Na^+).



(±)-(1*R,5*S**,7a*S**)-5-(4-Fluorobenzyl)-1-methyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-40).** The reaction of **III-22** (78 mg, 0.50 mmol) with 4-bromofluorobenzene (70 μL, 0.60 mmol) was conducted at 80 ºC for 17 h according to General Procedure 3 except using 2.5 mol% $[Pd(allyl)(Cl)]_2$ and 10 mol% 2-(dicyclohexylphosphino)biphenyl as ligand. This procedure afforded 97 mg (78%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.18 (m, 2 H), 7.01–6.96 (m, 2 H), 4.80–4.73 (m, 1 H), 4.17–4.10 (m, 1 H), 3.64 (ddd, J = 5.5, 8.0, 11.0 Hz, 1 H), 2.91 (dd, J = 5.5, 13.5 Hz, 1 H), 2.79 (dd, J = 7.5, 14.0 Hz, 1 H), 2.16–2.10 (m, 1 H), 1.69–1.62 (m, 1 H), 1.62–1.45 (m, 2 H), 1.35 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 134.5 Hz), 160.5, 133.3 (d, J = 3.9 Hz), 130.9 (d, J = 7.8), 115.1 (d, J = 21.6 Hz), 72.1, 63.1, 59.7, 41.0, 31.3, 25.9, 15.6. IR (film) 2980, 2939, 1748 cm^{-1}. MS (ESI) 272.1071 (272.1063 calcd for $C_{14}H_{16}FNO_2$, M + Na^+).



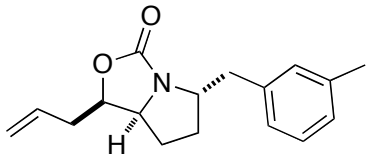
(±)-(1*R,5*S**,7a*S**)-1-Allyl-5-(benzo[*d*][1,3]dioxol-5-ylmethyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-41).** The reaction of **(±)-III-23** (91 mg, 0.50 mmol) with 4-bromo-1,2-(methylenedioxy)benzene (121 mg, 0.60 mmol) was conducted at 80 ºC for 8 h according to General Procedure 2. This procedure afforded 96 mg (70%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75–6.72 (m, 2 H), 6.69–6.66 (m, 1 H), 5.93 (s, 2 H), 5.84–5.72 (m, 1 H), 5.20–5.12 (m, 2 H), 4.66 (q, *J* = 9.0 Hz, 1 H), 4.13–4.05 (m, 1 H), 3.69 (ddd, *J* = 4.8, 7.2, 10.8 Hz, 1 H), 2.87 (dd, *J* = 7.0, 17.5 Hz, 1 H), 2.71 (dd, *J* = 9.5, 17.5 Hz, 1 H), 2.61–2.52 (m, 1 H), 2.37–2.28 (m, 1 H), 2.16–2.07 (m, 1 H), 1.76–1.69 (m, 1 H), 1.65–1.45 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 147.5, 146.1, 132.2, 131.3, 122.5, 118.6, 109.9, 108.1, 100.8, 75.2, 62.5, 59.6, 41.5, 34.7, 31.1, 25.9; IR (film) 2939, 1750 cm^{-1}. MS (ESI) 324.1200 (324.1212 calcd for $C_{17}H_{19}NO_4$, M + Na^+).



(±)-(1*R,5*S**,7a*S**)-1-Allyl-5-(2-chlorobenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-42)**

The reaction of **(±)-III-23** (91 mg, 0.50 mmol) with 2-bromochlorobenzene (70 μL, 0.60 mmol) was conducted at 80 ºC for 17 h according to General Procedure 3 except using

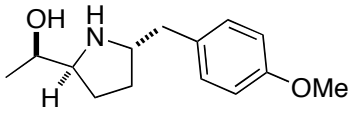
2.5 mol% $[Pd(allyl)(Cl)]_2$ and 10 mol% 2-(dicyclohexylphosphino)biphenyl as ligand. This procedure afforded 77 mg (53%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2 H), 7.23–7.14 (m, 2 H), 5.84–5.72 (m, 1 H), 5.21–5.12 (m, 2 H), 4.67 (dd, *J* = 7.6, 14.4 Hz, 1 H), 4.24 (app quint, *J* = 7.2 Hz, 1 H), 3.79 (ddd, *J* = 5.2, 7.2, 11.2 Hz, 1 H), 3.07 (dd, *J* = 7.2, 14.0 Hz, 1 H), 2.95 (dd, *J* = 6.4, 14.0 Hz, 1 H), 2.63–2.53 (m, 1 H), 2.38–2.30 (m, 1 H), 2.23–2.14 (m, 1 H), 1.81–1.74 (m, 1 H), 1.71–1.48 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 135.7, 134.4, 132.2, 131.3, 129.4, 127.9, 126.7, 118.6, 75.2, 62.2, 58.7, 38.9, 34.7, 31.4, 25.8; IR (film) 3073, 2938, 1752 cm^{-1}. MS (ESI) 314.0923 (314.0924 calcd for $C_{16}H_{18}ClNO_2$, M + Na^+).



(–)-(1*R,5*S**,*7aS**)-1-Allyl-5-(3-methylbenzyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (III-43).** The reaction of **(+)-III-23** (91 mg, 0.50 mmol) with 3-bromotoluene (73µL, 0.60 mmol) was conducted at 80 ºC for 7 h according to General Procedure 3. This procedure afforded 108 mg (80%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed with >20:1 dr, $[\alpha]^{23}_D$ –10.6 (*c* 1.23, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.6 Hz, 1 H), 7.07–7.01 (m, 3 H), 5.84–5.72 (m, 1 H), 5.20–5.11 (m, 2 H), 4.65 (q, *J* = 7.2 Hz, 1 H), 4.19–4.10 (m, 1 H), 3.70 (ddd, *J* = 5.2, 7.2, 11.2 Hz, 1 H), 2.98 (dd, *J* = 5.6, 13.6 Hz, 1 H), 2.72 (dd, *J* = 8.4, 13.6 Hz, 1 H), 2.61–2.51 (m, 1 H), 2.38–2.28 (m, 4 H), 2.14–2.05 (m, 1 H), 1.75–1.68 (m, 1 H), 1.66–1.44 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3,

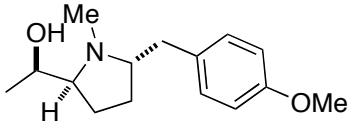
137.9, 137.5, 132.2, 130.4, 128.2, 127.2, 126.5, 118.6, 75.2, 62.4, 59.4, 41.9, 34.8, 31.3, 25.9, 21.4; IR (film) 2940, 1753 cm^{-1}. MS (ESI) 294.1460 (294.1470 calcd for $C_{17}H_{21}NO_2$, M + Na^+).

3.6.3 Conversion of Oxazolidinone Products to trans-*2,5-Disubstituted Pyrrolidines*



(1'*R,2*S**,5*S**)-1-[5-(4-Methoxybenzyl)pyrrolidin-2-yl]ethanol (III-44).** An oven-dried test tube equipped with a stir bar was cooled under a stream of nitrogen and charged with **III-38** (50 mg, 0.19 mmol) and freshly ground sodium hydroxide (56 mg, 1.4 mmol). The tube was capped with a rubber septum and purged with nitrogen. Dry ethanol (0.55 mL) was added and the resulting mixture was heated in a 75 ºC oil bath for 17 h. The mixture was then cooled to rt and 1 M HCl was added slowly until the solution had reached pH = 8. The mixture was transferred to a separatory funnel and extracted with methylene chloride (4 x 2 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 43 mg (96%) of the title compound as a white solid, mp 114–116 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12–7.07 (m, 2 H), 6.87–6.83 (m, 2 H), 3.79 (s, 3 H), 3.70–3.64 (m, 1 H), 3.41 (app quint, *J* = 7.0 Hz, 1 H), 3.25 (dt, *J* = 2.8, 6.4 Hz, 1 H), 2.68–2.60 (m, 2 H), 2.20 (s, br, 2 H), 1.93–1.85 (m, 1 H), 1.81–1.73 (m, 1 H), 1.72–1.62 (m, 1 H), 1.49–1.41 (m, 1 H), 1.11 (d, *J* = 5.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 131.5, 129.9, 113.9, 68.1, 61.8, 59.9, 55.2, 41.6, 31.8, 23.8, 18.7; IR (film) 3415, 3260, 2925 cm^{-1}. MS (ESI) 236.1651 (236.1651 calcd

for $C_{14}H_{21}NO_2$, M + Na^+).



(1'*R,2*S**,5*S**)-1-[5-(4-Methoxybenzyl)-1-methylpyrrolidin-2-yl]ethanol (III-45).**

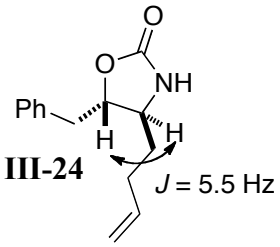
A flame-dried flask equipped with a stir bar was cooled under a stream of nitrogen and charged with **III-38** (50 mg, 0.19 mmol) and ether (3.2 mL). The resulting suspension was cooled to 0 °C and $LiAlH_4$ (0.57 mL, 0.57 mmol, 1 M in Et_2O) was added. The resulting mixture was warmed to rt and stirred for 14 h. The mixture was then diluted with ether (4 mL) and cooled to 0 °C. Water (0.04 mL) was added, followed by a solution of 10 M NaOH (0.02 mL), and additional water (0.04 mL). The flask was warmed to rt and stirred for 2 h. The solution was then decanted, dried over anhydrous sodium sulfate, filtered through Celite, and concentrated *in vacuo* to afford 45 mg (95%) of the title compound as white solid, mp 80–83 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) 7.07–7.02 (m, 2 H), 6.86–6.81 (m, 2 H), 3.88 (dq, *J* = 2.4, 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.39–3.31 (m, 1 H), 3.05–2.93 (m, 2 H), 2.57 (ddd, *J* = 2.4, 6.0, 8.8 Hz, 1 H), 2.47 (s, 3 H), 2.17 (dd, *J* = 11.2, 13.2 Hz, 1 H), 1.88–1.72 (m, 2 H), 1.59–1.49 (m, 2 H), 1.13 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 132.2, 130.0, 113.8, 66.8, 66.5, 64.0, 55.2, 34.7, 31.8, 27.3, 21.6, 18.3; IR (film) 3404, 2927 cm^{-1}. MS (ESI) 250.1811 (250.1807 calcd for $C_{15}H_{23}NO_2$, M + Na^+).

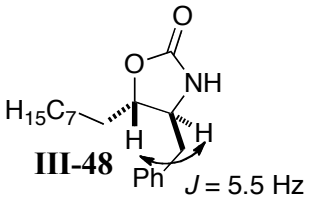
3.6.4 Assignment of Stereochemistry

Stereochemistry of 4,5-Disubstituted Oxazolidin-2-ones

The stereochemistry of **III-24** was assigned based on a vicinal coupling constant of 5.5

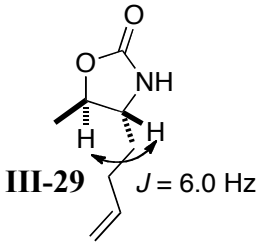
Hz between the protons on C4 and C5, which was determined by ^{1}H NMR decoupling experiments. This coupling constant is identical to that previously reported for oxazolidin-2-one **III-48**.[18]

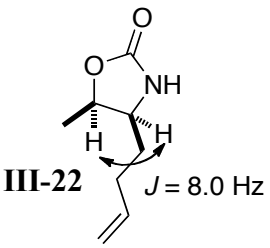




From Ref. 18

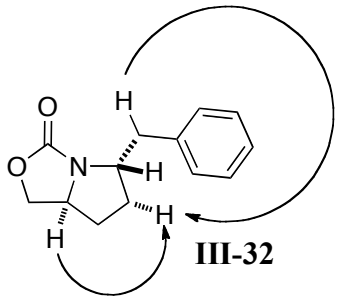
The threonine derived *trans*-4,5-disubstituted oxazolidin-2-one (**III-29**) displayed a vicinal coupling constant of 6.0 Hz between the C4 and C5 hydrogen atoms. In contrast, the *cis*-4,5-disubstituted analog (**III-22**) exhibited a vicinal coupling constant of 8.0 Hz (the coupling constants were determined via ^{1}H NMR decoupling experiments). The stereochemistry of the threonine substrate was assigned based on both the stereochemistry of threonine and by coupling constant comparison.[18] Substrate **III-23** was assigned based on analogy to **III-22**.





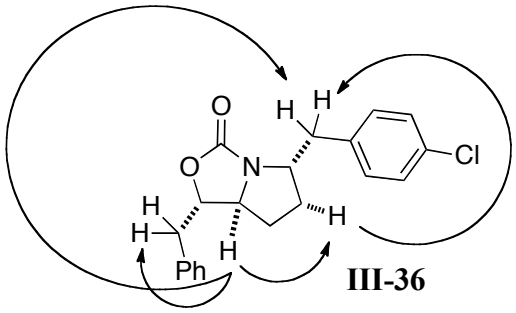
Stereochemistry of Tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-ones

The stereochemistry of **III-32** was assigned through a ^{1}H NMR 2D-NOESY experiment as depicted below. The stereochemistry of **III-30** and **III-33** were assigned based on analogy to **III-32**.



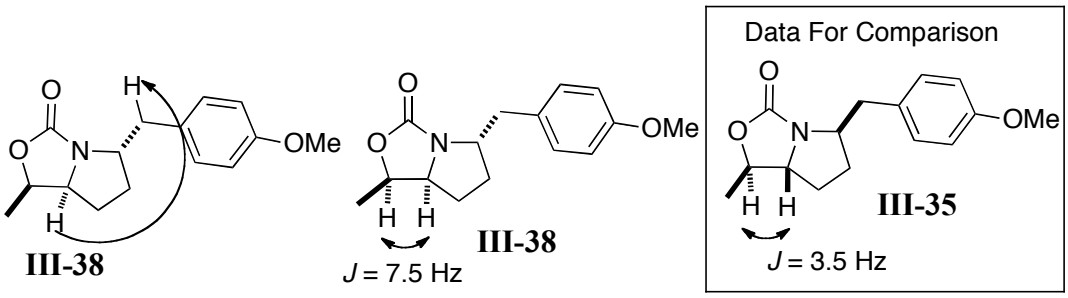
III-32

The stereochemistry of **III-36** was assigned through a ^{1}H NMR 2D-NOESY experiment as depicted below. The stereochemistry of **III-34** and **III-35** were assigned based on analogy to **III-36**.



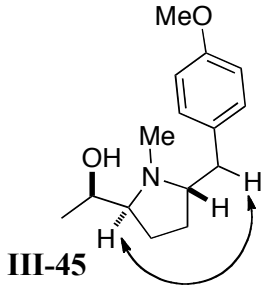
III-36

The stereochemistry of **III-38** was assigned through a combination of a ^{1}H NMR 2D-NOESY experiment and analysis of coupling constants (obtained by ^{1}H NMR decoupling experiments). As shown below, nOe data indicated that the substituents on C2 and C5 of the pyrrolidine ring are in a *trans*-orientation. The vicinal coupling constant between C4 and C5 of the oxazolidin-2-one ring was measured to be 7.5 Hz, which is considerably larger than the 3.5 Hz coupling of the C4 and C5 hydrogen atoms on isomer **III-35** (characterized as noted above). The stereochemistry of **III-37**, **III-39**, **III-40**, **III-41**, **III-42** and **III-43** were assigned based on analogy to **III-38**.



Stereochemistry of *trans*-Disubstituted Pyrrolidines

The stereochemistry around the pyrrolidine ring in III-45 was assigned through a ^{1}H NMR nOe experiment as depicted below, and the stereochemistry hydroxyl-bearing carbon atom was assigned based on the configuration of the oxazolidinone starting material (III-38). The stereochemistry of III-44 was assigned based on analogy to III-45.



[1] Reproduced in part with permission from Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 2322–2325. Copyright 2010 American Chemical Society.

[2] Reviews: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (b) Wolfe, J. P. *Synlett* **2008**, 2913.

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[8] dppe = 1,2-*bis*-(diphenylphosphino)ethane; DPE-Phos = *bis*(2-diphenylphosphinophenyl)ether; S-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl; RuPhos = 2-dicyclohexylphosphino-2',6'-di-*iso*-propoxy-1,1'-biphenyl.

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Chapter 4

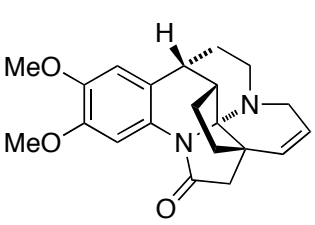
Examples and Synthesis of Benzofused 1-Azabicyclo[3.3.0]octanes and 1-Azabicyclo[4.3.0]nonanes

4.1 Natural Products

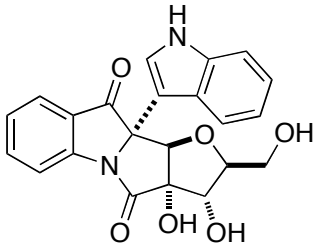
Benzofused 1-azabicyclo[4.3.0]nonane or 1-azabicyclo[3.3.0]octane cores are found in natural products, such as isoschizogamine (**IV-1**) and isatisine A (**IV-2**) (Figure 4-1).[1] Other natural products, such as mitocycin A (**IV-3**) and gephyrotoxin (**IV-4**), have been synthesized using benzofused intermediates.[2]

These compounds exhibit an array of biological activity. For example, **IV-2** is derived from *Isatis indigotica* Fort. (Cruciferae), a plant commonly used in Chinese herbal medicine for the treatment of viral infections.[1b] Mitomycin C (**IV-5**) has been used to treat cancer and is also an antibiotic (Figure 4-2).[3] **IV-4** is derived from the skin of poisonous dart frogs.[4]

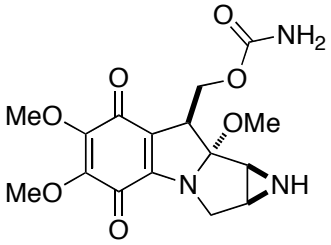
Figure 4-1: Natural Products Containing or Derived from Benzofused 1-Azabicyclo[3.3.0]octanes and 1-Azabicyclo[4.3.0]nonanes



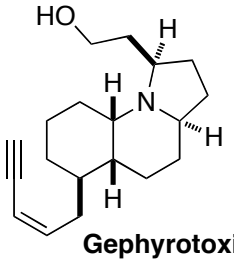
Isoschizogamine
IV-1



Isatisine A
IV-2

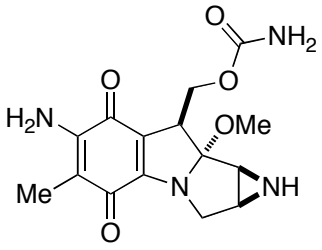


Mitomycin A
IV-3



Gephyrotoxin
IV-4

Figure 4-2: Mitomycin C



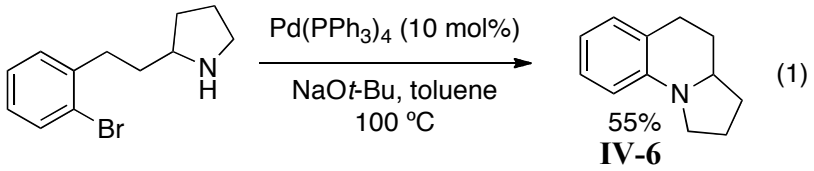
IV-5

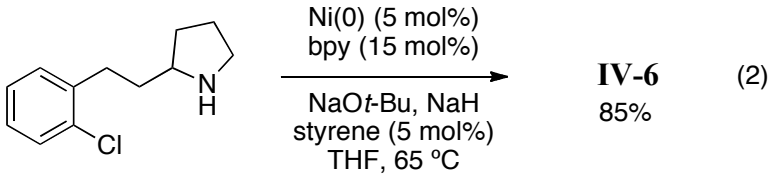
4.2 Synthesis of Benzofused 1-Azabicyclo[3.3.0]octanes and 1-Azabicyclo[4.3.0]nonanes

Given the interesting biological activity of these compounds and their ability to be reduced to saturated tricyclic structures, many groups have sought to develop methods for their synthesis. Some of these routes generate one ring at a time, while others involve tandem processes that generate both non-aryl rings in a single reaction sequence.

4.2.1 Non-tandem Processes

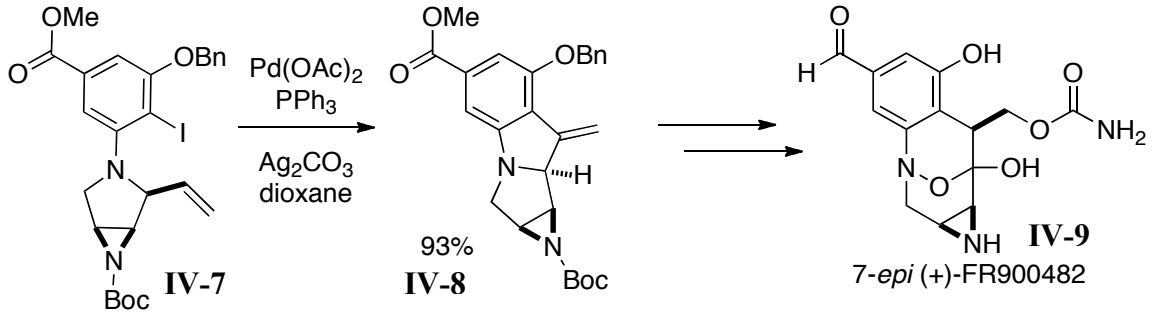
Non-tandem processes require a nitrogen containing heterocycle to be present prior to the final cyclization. For example, an intramolecular *N*-arylation of a pyrrolidine tethered to an aryl halide with either a palladium or nickel catalyst affords **IV-6** (eqs 1 and 2).[5] The nickel catalyzed process afforded a much higher yield than the palladium catalyzed process.



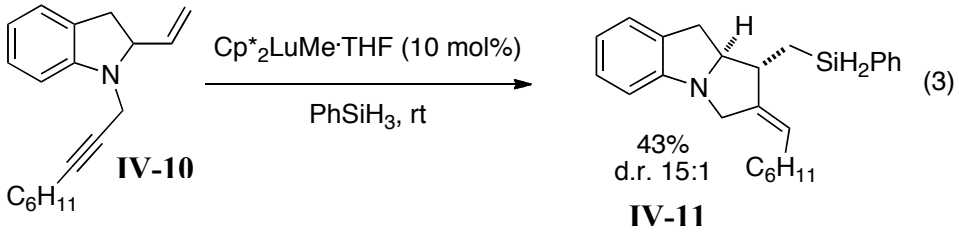


Trost and coworkers have demonstrated that benzofused 1-azabicyclo[3.3.0]octane **IV-8** which contains an exocyclic double bond, can be synthesized via an intramolecular Heck reaction from **IV-7** (Scheme 4-1).[6] This was carried on to generate 7-*epi* (+)-FR900482 (**IV-9**), which has anti-cancer activity.

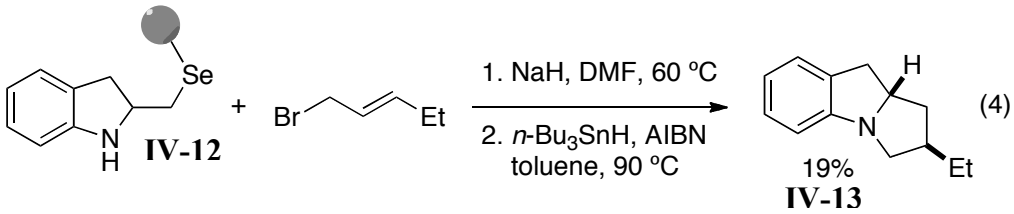
Scheme 4-1: Synthesis of 7-*epi* (+)-FR900482



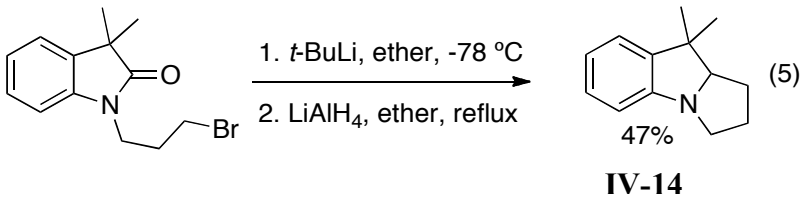
Another method used to generate a benzofused 1-azabicyclo[3.3.0]octane with an exocyclic double bond was developed by Molander and coworkers.[7] Treatment of **IV-10** with a lutetium catalyst afforded **IV-11** in modest yield and good diastereoselectivity (eq 3).



Nicolaou and coworkers have demonstrated that a radical cleavage from a selenium tethered indole (**IV-12**) can generate **IV-13**, albeit in low yield (eq 4).[8]



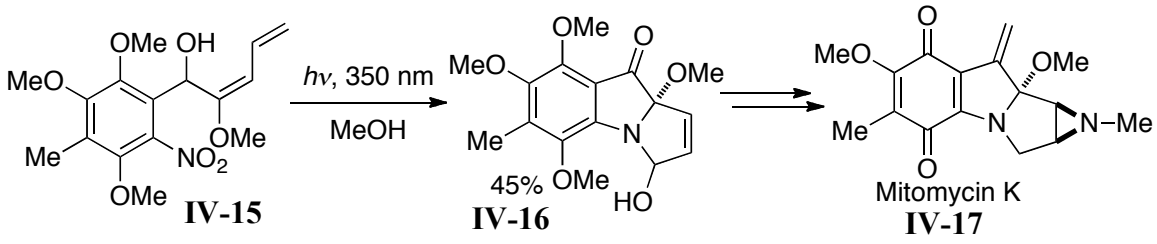
Organolithium addition into indol-2(3*H*)-ones has been shown to be an effective method of cyclizing the final ring of **IV-14** (eq 5).[2a] Reduction of the resulting hemiaminal affords **IV-14**, however, the yield of this process was modest.



4.2.2 Tandem Reactions

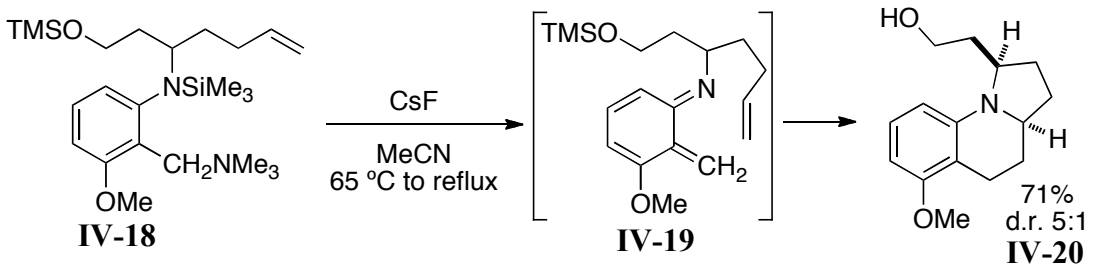
A variety of tandem methods have been used to convert benzene derivatives with linear side-chains into tricyclic systems. Some of these processes are metal mediated, while others are not. These methods allow for the rapid build up of molecular complexity. Danishefsky and coworkers achieved an intramolecular double cyclization of **IV-15** via a photo-redox protocol (Scheme 4-2).[9] They further functionalized benzofused 1-azabicyclo[3.3.0]octane **IV-16** to produce mitomycin K (**IV-17**).

Scheme 4-2: Key Step in Mitomycin K Synthesis

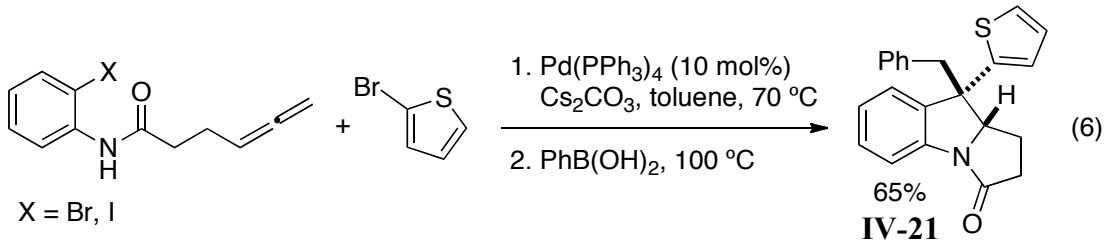


In their formal synthesis of **IV-4**, Saegusa and coworkers used an intramolecular Diels-Alder reaction to generate the tricyclic core (**IV-20**) (Scheme 4-3).[2b] Simple fluoride treatment of **IV-18** cleaved the silicon-nitrogen bond, which lead to the elimination of trimethylamine. Intermediate **IV-19** could then undergo an intramolecular Diels-Alder reaction. Further transformations were performed to synthesize gephyrotoxin.

Scheme 4-3: Diels-Alder Generation of the Gephyrotoxin Core



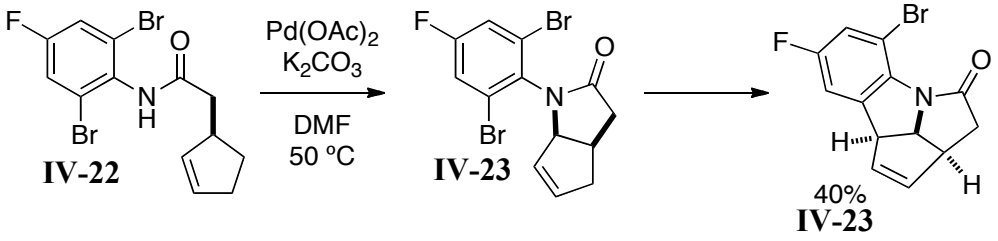
Grigg and coworkers used a palladium catalyzed process to generate **IV-21** in good yield.[10] This "zipper" type cascade involves the formation of one new carbon-nitrogen bond and three new carbon-carbon bonds in a single reaction process (eq 6).



(6)

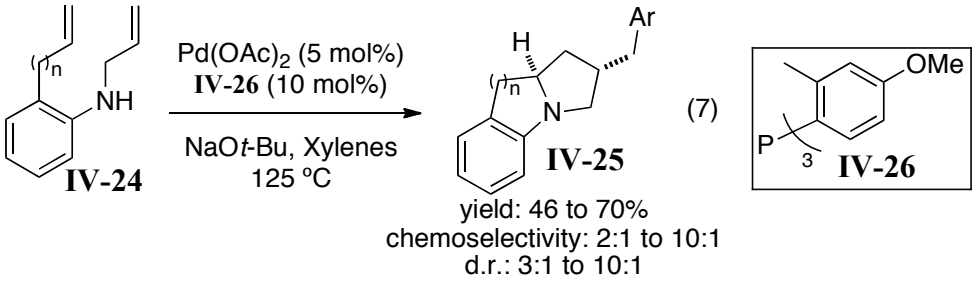
Two processes that involve a Heck reaction in a tandem reaction sequence have been developed. The first was reported by Campos and coworkers.[11] In this work, they demonstrated that oxidative cyclization of **IV-22** mediated by Pd (II) could be employed to generate the first cycle, **IV-23** (Scheme 4-4). Pd(0) could then catalyze an intramolecular Heck reaction. However, this reaction suffers from low yield of **IV-24**, and stoichiometric amounts of palladium must be used.

Scheme 4-4: Tandem Oxidative Cyclization/Heck Process

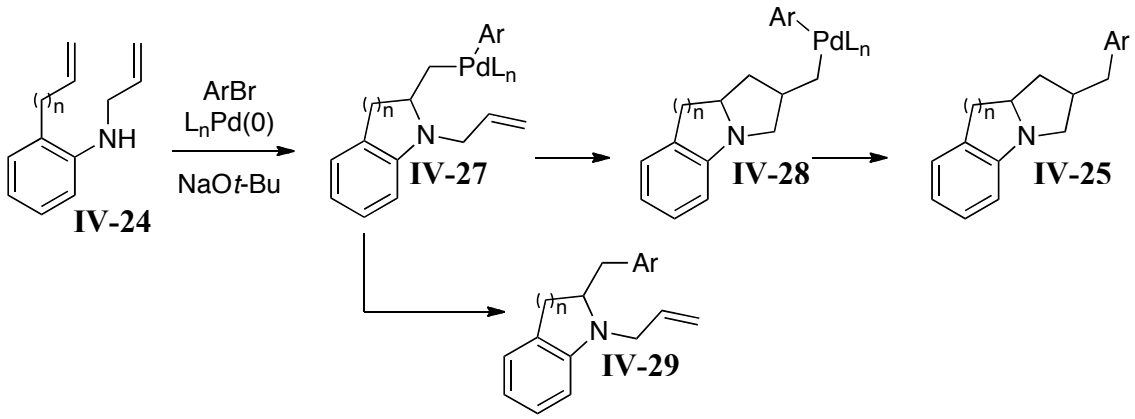


Our group has demonstrated that both benzofused 1-azabicyclo[4.3.0]nonanes or 1-azabicyclo[3.3.0]octanes **IV-25** can be synthesized via a cascade aminopalladation/carbopalladation reaction sequence of aniline diene derivatives **IV-24** (eq 7).[12] The palladium alkyl intermediate **IV-27**, which is generated after aminopalladation, reacts with the second olefin to generate **IV-28** (Scheme 4-5). Reductive elimination then affords **IV-25**. However, reductive elimination can occur

from **IV-27**, thus the chemoselectivity of this reaction is low to moderate (2:1 to 10:1). However, a variety of aryl bromide coupling partners can be used and many different of analogs can be easily synthesized.



Scheme 4-5: Mechanism of Aminopalladation/Carbopalladation Process



Although many methods have been developed for the synthesis of benzofused 1-azabicyclo[4.3.0]nonanes or 1-azabicyclo[3.3.0]octanes, given their importance, new methods for their synthesis must be developed. In the following chapter, a tandem intramolecular *N*-arylation/carboamination process that allows for the synthesis of these compounds will be discussed.

[1] (a) Hájícek, J.; Taimr, J.; Budesínsky, M. *Tetrahedron Lett.* **1998**, *39*, 505–508. (b) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127–4129.

[2] (a) Jones, K.; Storey, J. M. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 769–774 and references cited therein. (b) Ito, Y.; Nakajo, E.; Nakatsuka, M.; Saegusa, T. *Tetrahedron Lett.* **1983**, *24*, 2881–2884.

[3] Tomasz, M. *Chem. Biol.* **1995**, *2*, 575–579 and references cited therein.

[4] Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 4197–4198.

[5] (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546. (b) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311–2314.

[6] Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369–1372.

[7] Molander, G. A.; Corrette, C. P. *J. Org. Chem.* **1999**, *64*, 9697–9703.

[8] Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 2966–2697.

[9] Benbow, J. W.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 12305–12314.

[10] Grigg, R.; Kilner, C.; Mariani, E.; Sridharan, V. *Synlett*, **2006**, 3021–3024.

[11] Campos, K. R.; Journet, M.; Lee, S.; Grabowski, E. J. J.; Tillyer, R. D. *J. Org. Chem.* **2005**, *70*, 268–274.

[12] Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028–1031.

Chapter 5

Synthesis of Benzofused 1-Azabicyclo[3.3.0]octanes and 1-Azabicyclo[4.3.0]nonanes Via an Intramolecular *N*-Arylation/Carboamination Process

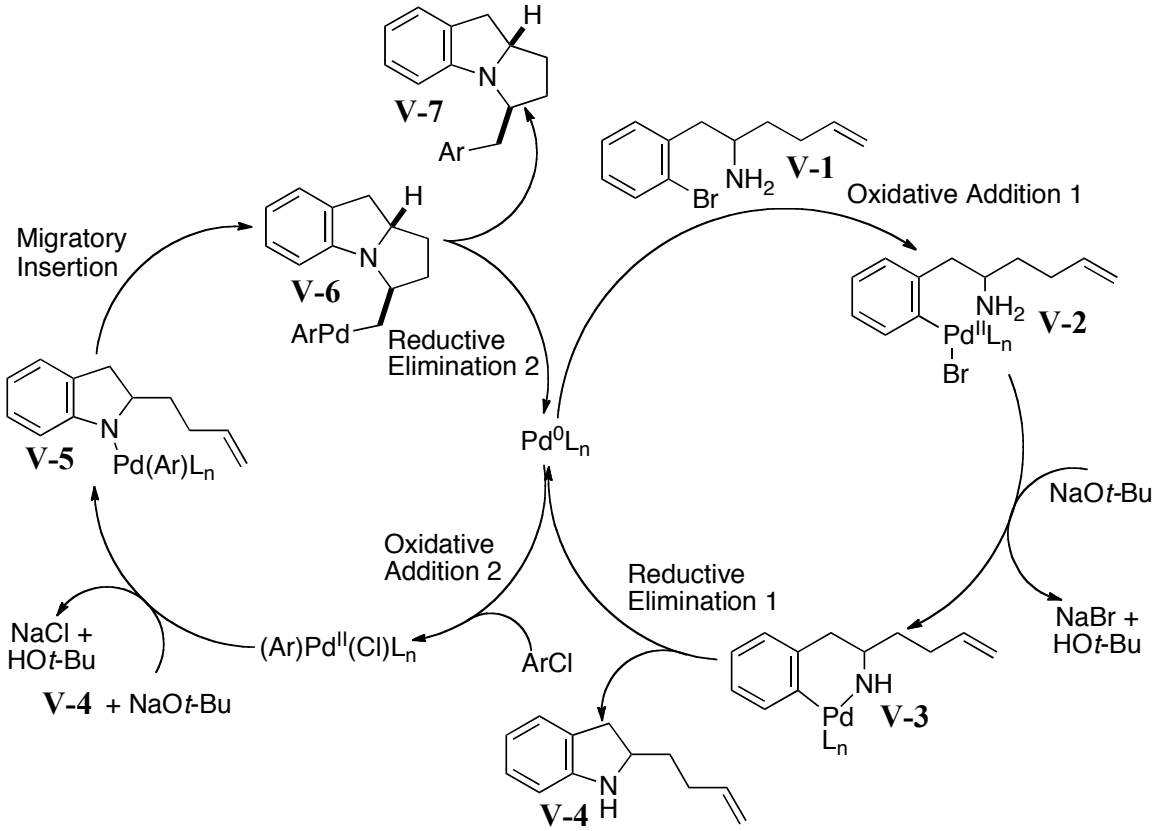
5.1 Introduction

Tandem processes interest synthetic chemists, as rapid build up of molecular complexity is achieved.[1] Another way to build molecular complexity is the generation of a cyclic structure in the molecule.[2] Thus, a reaction which could generate two rings in a single flask would be desirable.

Previously, our group has demonstrated that an *inter*molecular *N*-arylation/carboamination procedure is possible (see Chapter 1).[3] This process only generates monocyclic pyrrolidine products. However, the use of an *intra*molecular *N*-arylation/carboamination process would allow for the synthesis of a fused bicyclic system. Along with generating more complex products, we also desired to overcome the limitation of needing two different ligands for the *N*-arylation and the carboamination reactions.[3b] We sought to use a primary amine substrate with a tethered aryl bromide and use an aryl chloride as the coupling partner for the carboamination step. We rationalized that the use of a single catalyst should be possible, as the C-N reductive elimination of **V-3** should be facile, as the amine is primary (Scheme 5-1). In contrast, the nucleophilicity of the nitrogen atom of an aniline intermediate (**V-5**) after the intramolecular *N*-arylation is much lower. Thus, the C-N bond forming reductive elimination should be slowed,

which would allow for migratory insertion into the Pd-N bond of **V-5**. C-C bond forming reductive elimination from **V-6** would then generate **V-7**.

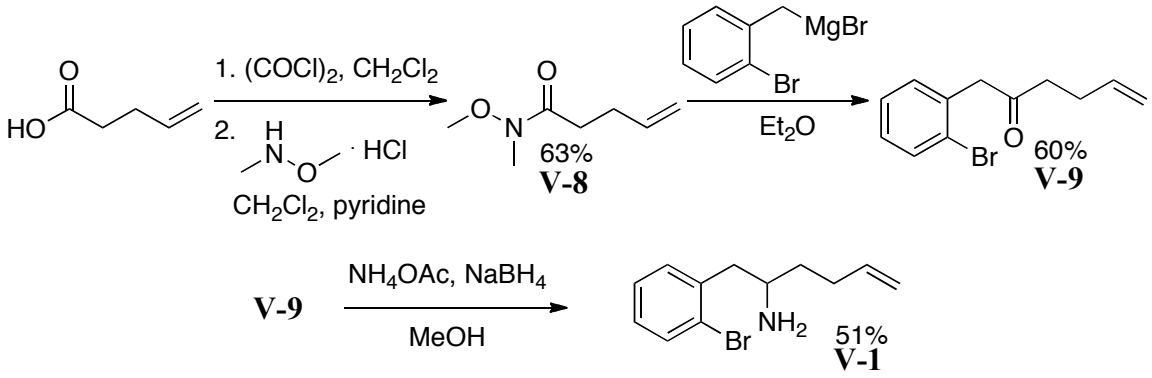
Scheme 5-1: Proposed Mechanism for Tandem *N*-Arylation/Carboamination



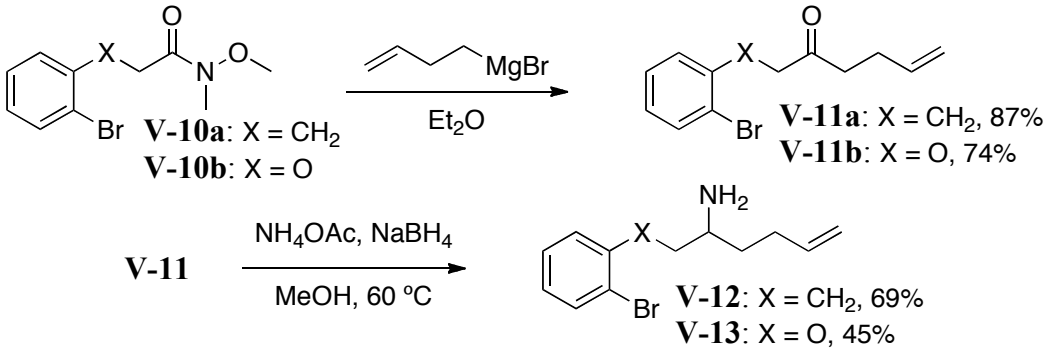
5.2 Substrate Synthesis

To begin our investigations, we synthesized a variety of primary amine substrates bearing tethered aryl bromides. Synthesis of the appropriate ketone by Grignard addition into a Weinreb amide (**V-8** to **V-9**; **V-10** to **V-11**) followed by reductive amination afforded two of the necessary substrates (Scheme 5-2 and Scheme 5-3). Generation of enantioenriched substrates was possible by Grignard addition into the *t*-butyl sulfinamide derived aldimine (Scheme 5-4). The absolute stereochemistry of the product was assigned based on models established by Ellman.[4] Acid cleavage of the nitrogen sulfur bond afforded **(+)-V-1** and **(+)-V-12**.

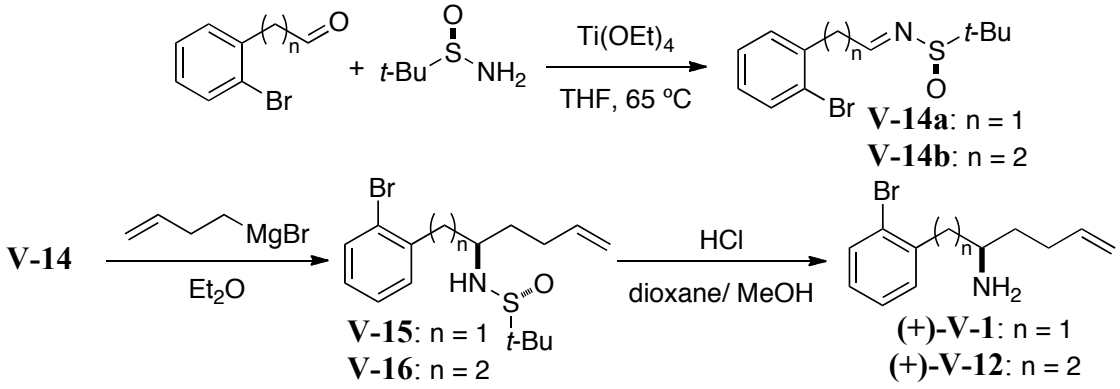
Scheme 5-2: Synthesis of V-1



Scheme 5-3: Synthesis of V-12 and V-13



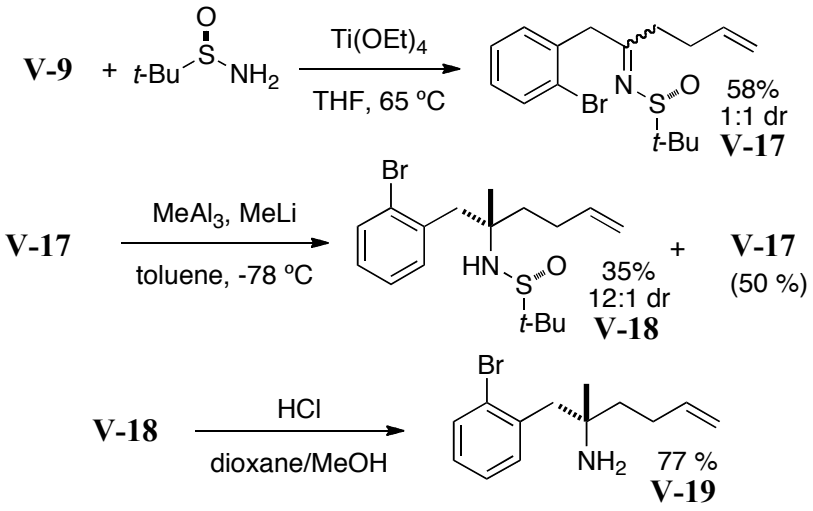
Scheme 5-4: Synthesis of (+)-V-1 and (+)-V-12



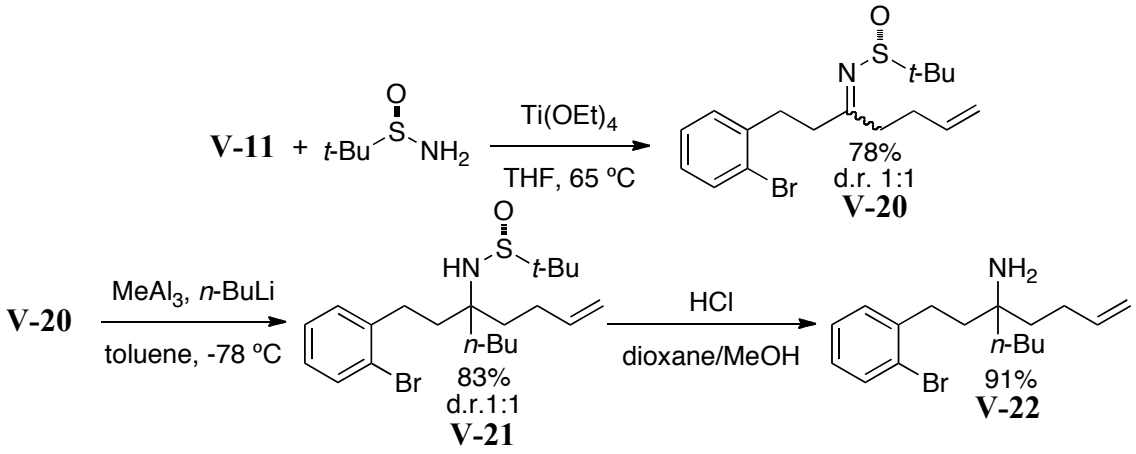
In order to make substrates which contained a quaternary center alpha to the primary amine, we synthesized the ketimines using *t*-butyl sulfinamide (**V-17** and **V-20**). Organolithium addition into these generated the sulfimine products in modest to good yield (Scheme 5-5 and Scheme 5-6). Cleavage of the sulfur afforded the primary amine.

We hypothesize that low conversion of **V-17** to **V-18** is due to competing enolization, presumably at the more acidic benzylic position, as this does not appear to be an issue in the synthesis of **V-21**. Additionally, **V-18** is formed in good diastereoselectivity (12:1) starting from a 1:1 mixture of E/Z isomers, thus suggestive of the fact that one isomer is being converted to the enolate while the other is reacting with 1,2-addition of the methyl lithium. In contrast, **V-20** is also a 1:1 mixture of E/Z isomers, but **V-21** is generated as a 1:1 mixture of diastereomers. The absolute stereochemistry of **V-19** was assigned by Mosher amide analysis.[5] Racemic **V-19** was generated by starting the synthesis with (±)-*t*-butyl sulfinamide.

Scheme 5-5: Synthesis of V-19

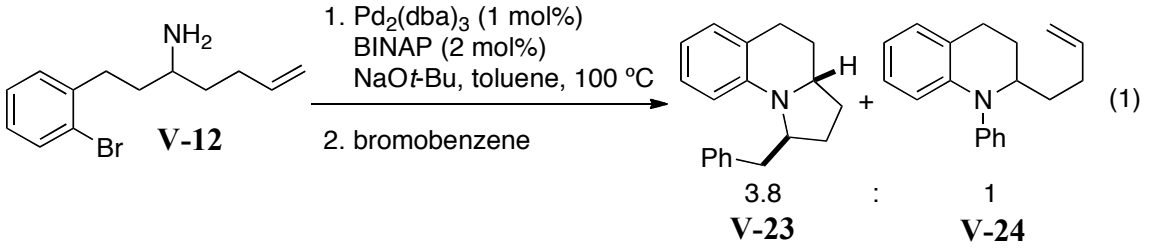


Scheme 5-6: Synthesis of V-22



5.3 Initial Studies

Initial studies focused on the intramolecular *N*-arylation of **V-12**. BINAP and dppf supported palladium catalysts are known to facilitate *N*-arylation reactions.[6,7] The reaction with BINAP afforded a cleaner product with a shorter reaction time. However, as BINAP is bidentate, ligand exchange with a second ligand was not expected to be successful. Thus, we opted to add bromobenzene into the reaction mixture after the completion of the *N*-arylation as determined by GC analysis. This resulted in a mixture of our desired product **V-23** and a bis-*N*-arylated product **V-24** (eq 1). The product ratio was determined by ^{1}H NMR analysis.



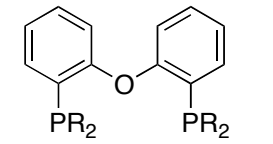
Through further screening, we found that a palladium catalyst with DPE-Phos as the supporting ligand successfully catalyzed both reactions in the sequence. However, timing the addition of the external aryl bromide was critical, as the intramolecular *N*-

arylation had to be complete. In addition, the reaction time for carboamination process varied widely between duplicate trials, presumably due to catalyst decomposition if the second aryl bromide was not added immediately upon completion of the first reaction.

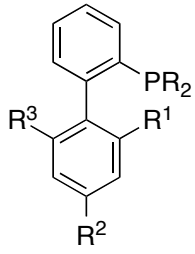
We then opted to try aryl chlorides as the external coupling partner. Oxidative addition is faster into carbon bromine bonds than into the carbon chloride bonds.[8] Thus, the intramolecular *N*-arylation should occur prior to an *inter*molecular *N*-arylation or other reaction with the aryl chloride. The presence of a second aryl halide in the system should also minimize catalyst decomposition.

For successful oxidative addition into the carbon chloride bond, a more electron rich metal center was required. We screened a variety of ligands, including several Buchwald ligands (**V-26**) (Figure 5-1).[9] Although **V-26a** is not very electron rich, it does react with chlorobenzene (Table 5-1). The reasons for this are unclear at this time. However, the best ligand appeared to be the dicyclohexyl analog of DPE-Phos, as the formation of **V-24** was minimized. Tricyclohexylphosphine was also relatively effective, but gave a mixture of minor byproducts. Additional screening revealed that palladium acetate was a better precatalyst with this ligand than $Pd_2(dba)_3$.

Figure 5-1: Ligand Structures

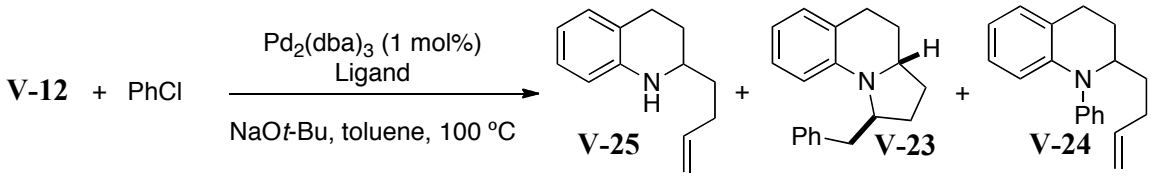


R = Ph: DPE-Phos
R = Cy: Cy_4DPE-Phos



V-26a: R=Ph; R^1=R^2=H; R^3=NMe_2
V-26b: R=*t*-Bu; R^1=R^2=R^3=H
V-26c: R=*t*-Bu; R^1=R^2=R^3=*i*-Pr
V-26d: R=Cy; R^1=R^2=H; R^3=NMe_2
V-26e: R=Cy; R^1=R^2=R^3=*i*-Pr
V-26f: R=Cy; R^1=R^3=OMe; R^2=H
V-26g: R=Cy; R^1=R^3=O*i*-Pr; R^2=H
V-26h: R=Cy; R^1=R^2=H; R^3=Me

Table 5-1: Ligand Screen with Chlorobenzene[a]



Ligand	**V-25**	**V-23**	**V-24**
DPE-Phos	100	0	0
V-26a	0	77	23
V-26b	100	0	0
V-26c	50	0	50
V-26d	0	75	25
V-26e	0	91	9
V-26f	0	93	7
V-26g	0	80	20
V-26h	0	80	20
$PCy_3 \cdot HBF_4$[b,c]	0	98	2
Cy_4DPE-Phos[b]	0	>98	2

[a]Ratios of products are listed. [b]This entry conducted with $Pd(OAc)_2$. [c]This reaction had trace amounts of multiple unidentified byproducts.

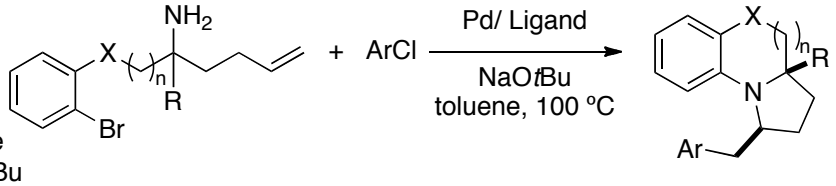
5.4 Reaction Scope

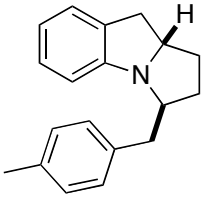
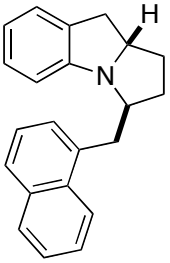
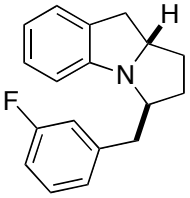
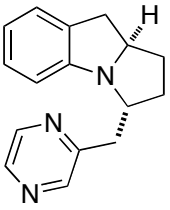
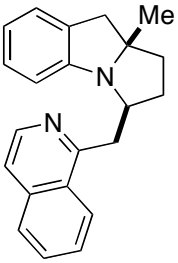
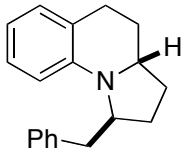
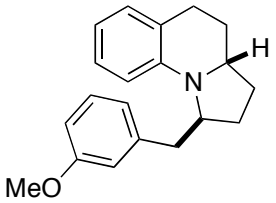
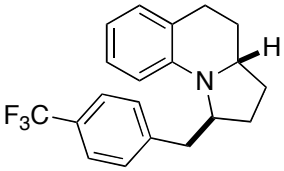
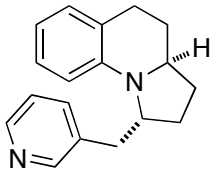
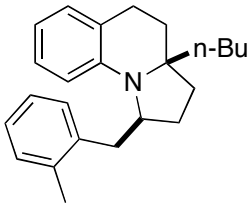
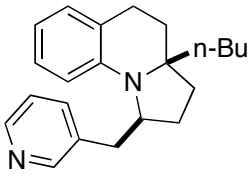
With optimized reaction conditions in hand, we explored the scope of the reaction. We found that the diastereoselectivity of the reaction was influenced by the choice of aryl chloride (Table 5-2). However, the stereochemistry was determined to be *trans* across the pyrrolidine ring, which is consistent with the stereochemical model proposed in Chapter 3 (Figure 3-2), as the intermediates **V-4** and **V-25** have the nitrogen aryl group tethered to the alkenyl side chain.

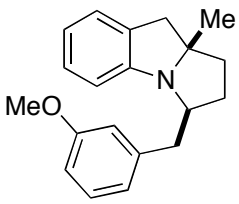
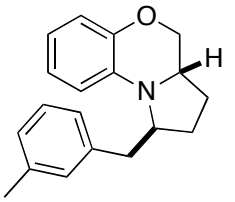
We also found that the same catalysts are competent for the formation of both [5,5] and [6,5] bis-fused ring systems. The use of enantioenriched substrates lead to enantioenriched products (Table 5-2, entries 4, 6, and 10).[10] We found that a different catalyst was necessary with electron deficient aryl chlorides, as competing bis-*N*-arylation occurred when the catalyst generated from $Pd(OAc)_2$/Cy_4DPE-Phos was used (Table 5-2). Screening revealed that a catalyst composed of $Pd_2(dba)_3$/PCy_3·HBF_4 in a 1:2 palladium to phosphine ratio was competent for this transformation. This catalyst system was also competent for nitrogen containing heteroaromatic aryl chlorides, although a 1:1 palladium to phosphine ratio afforded better yields.[11] This suggests that the heteroatom may be coordinating to the palladium at some point along the catalytic cycle. Additionally, reactions utilizing the $Pd_2(dba)_3$/PCy_3·HBF_4 system resulted in the formation of an inseparable mixture of minor byproducts, thus the yields for these transformations were diminished compared to those using the $Pd(OAc)_2$/Cy_4DPE-Phos system.

Table 5-2: Examples of Tandem *N*-Arylation/Carbomination[a]

V-1, n=0; X=CH_2; R=H
V-12, n=1; X=CH_2; R=H
V-13, n=1; X=O; R=H
V-19, n=0; X=CH_2; R=Me
V-22, n=1; X=CH_2; R=*n*-Bu



Entry	Substrate Method[a]	Product	Yield[b] d.r.
1	**V-1** A		**V-27** 76% >25:1 (20:1)
2	**V-1** A		**V-28** 78% 8:1 (5:1)
3	**V-1** C		**V-29** 42% >25:1 (5:1)
4	**(+)-V-1** 92% ee B		**V-30** 58% 8:1 (7:1) 85% ee
5	**V-19** B		**V-31** 60% 14:1 (5:1)
7	**V-12** A		**V-23** 68% 25:1 (12:1)
8	**V-12** D		**V-23** 51% 8:1 (6:1)
9	**V-12** A		**V-33** 63% 22:1 (8:1)
10	**V-12** C		**V-34** 56% 7:1 (3:1)
11	**(+)-V-12** 88% ee B		**V-35** 56% >25:1 (10:1) 92% ee
12	**V-22** A		**V-36** 79% 11:1 (12:1)
13	**V-22** B		**V-37** 47% 10:1 (7:1)

6	**(–)-V-19** 87% ee A		**V-32** 75% >25:1 (10:1) 91% ee	14	**V-13** A		**V-38** 35% 15:1 (5:1)

[a] Reaction conditions: Substrate (1.0 equiv), ArCl (1.2 equiv), Pd (4 mol%), Ligand (4 or 8 mol%), NaO*t*-Bu (2.4 equiv) and toluene (0.25 M). Method A: $Pd(OAc)_2$ (4 mol%) and Cy_4DPE-Phos (4 mol%). Method B: $Pd_2(dba)_3$ (2 mol%) and $PCy_3{\cdot}HBF_4$ (4 mol%). Method C: $Pd_2(dba)_3$ (2 mol%) and $PCy_3{\cdot}HBF_4$ (8 mol%). Method D: $Pd(OAc)_2$ (2 mol%) and $PCy_3{\cdot}HBF_4$ (4 mol%). [b] All yields are the average of two reactions. Diastereomeric ratios are isolated (crude).

5.5 Conclusion

In conclusion, we have a developed a novel method for the generation of benzofused 1-azabicyclo[3.3.0]octanes and 1-azabicyclo[4.3.0]nonanes, as well as benzofused hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazines. This transformation begins with relatively simple primary amines tethered to an aryl bromide, and through a tandem intramolecular *N*-arylation/carboamination process with an aryl chloride, molecular complexity is rapidly built. In addition, this process is procedurally simple, as all reagents are combined initially, instead of in two stages. Thus, careful monitoring of the reaction for the completion of the *N*-arylation reaction is unnecessary. Finally, this reaction proceeds via to different palladium-amido complexes. The difference in nitrogen nucleophilicity directly impacts chemoselective outcome of each step of the reaction. The use of one catalyst to facilitate two different reaction types in a single flask is area which should be further studied.

5.6 Experimental

General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. $Pd(OAc)_2$, $Pd_2(dba)_3$, and all phosphine ligands were purchased from Strem Chemical Co. or Aldrich Chemical Co. and used without further purification. All

aryl chlorides and common reagents were obtained from commercial sources and were used as received. Toluene, diethyl ether, methylene chloride, and THF were purified using a GlassContour solvent purification system. Flash chromatography was conducted using silica gel unless otherwise noted. Bulk quantities of NaO*t*-Bu were stored in a nitrogen-filled glovebox, removed prior to use, and quantities needed for individual experiment were weighed in the air. 3-(2-bromophenyl)propanal[12] and 2-(2-bromophenoxy)acetic acid[13] were synthesized according to literature procedure. Ratios of diastereomers were determined by ^{1}H NMR analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in Table 5-2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 5-2.

5.6.1 Preparation and Characterization of Substrates

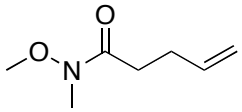
General Procedure 1: Generation of Grignard Reagents

A flame- or oven-dried flask equipped with a reflux condenser and a magnetic stir bar was cooled under a stream of nitrogen was charged with appropriate alkyl bromide (2.0 equiv relative to substrate) and diethyl ether (concentrations as listed) Freshly ground magnesium turnings were added (4.0 equiv relative to substrate) and the flask was purged with nitrogen. When self-reflux began, the reaction was placed in an ambient temperature water bath for 5 min. The reaction was removed from the bath and stirred an additional 30 min at rt. The reaction was allowed to stand at rt 20 min without stirring prior to addition such that a finely divided particulate suspension could settle to the bottom of the

flask. Only the solution above the solid material was employed in addition reactions to electrophiles.

General Procedure 2: Condensation with 2-methylpropane-2-sulfinamide

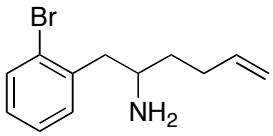
A flame-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with either an aldehyde or ketone (1.0 equiv), 2-methylpropane-2-sulfinamide (1.05 equiv), THF (0.5 M), and titanium ethoxide (2.0 equiv). The reaction stirred under a nitrogen atmosphere at rt (aldehyde) or reflux (ketone) until the starting material was consumed as judged by TLC analysis. The reaction was cooled, quenched with brine (0.5 M) and filtered through a plug of Celite. The plug was rinsed thoroughly with ethyl acetate. The filtrate was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography on silica gel.



***N*-Methoxy-*N*-methylpent-4-enamide (V-8).**[14]

An oven-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with 4-pentenoic acid (10.2 mL, 1.00 g, 100 mmol) and chloroform (400 mL, 0.25 M). *N,O*-dimethylhydroxyamine hydrochloride (14.63 g, 150 mmol), *N*-methylmorpholine (27.5 mL, 250 mmol), 1-hydroxybenzotriazole hydrate (14.86 g, 110 mmol), and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (21.09 g, 110 mmol) were added, and the reaction mixture was purged with N_2. The resulting mixture was stirred at rt overnight, then filtered through a fritted funnel. The solids were rinsed with 1:1 EtOAc/hexanes, and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 7.76 g (54%) of the title

compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93–5.81 (m, 1 H), 5.11–5.04 (m, 1 H), 5.02–4.98 (m, 1 H), 3.69 (s, 3 H), 3.19 (s, 3 H), 2.56–2.51 (m, 2 H), 2.41–2.36 (m, 2 H).



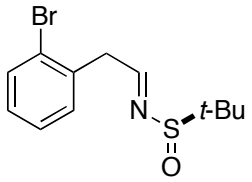
(±)-1-(2-bromophenyl)hex-5-en-2-amine (**V-1**)

2-bromobenzyl bromide (16.41 g, 66 mmol) in diethyl ether (300 mL) was converted the corresponding Grignard reagent according to General Procedure 1. The freshly made Grignard reagent was added dropwise to a 0 ºC solution of *N*-methoxy-*N*-methylpent-4-enamide (4.70 g, 33 mmol) in diethyl ether (30 mL) via cannula over 25 min. After the addition was complete, the reaction was removed from the ice bath and stirred at rt overnight. The reaction was placed in an ice bath and slowly quenched with saturated ammonium chloride. The reaction was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography on basic alumina to afford 1-(2-bromophenyl)hex-5-en-2-one (**V-9**) as a clear oil (6.15 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 1.0, 8.1 Hz, 1 H), 7.30–7.26 (m, 1 H), 7.21 (dd, J = 1.7, 7.6 Hz, 1 H), 7.16–7.12 (m, 1 H), 5.85–5.76 (m, 1 H), 5.05–4.96 (m, 2 H), 3.86 (s, 2 H), 2.60 (t, J = 7.3, 2 H), 2.38–2.33 (m, 2 H).

A portion of **V-9** (1.27 g, 5.0 mmol) was stirred with ammonium acetate (3.93 g, 5.1 mmol) and sodium cyanoborohydride (223 mg, 3.6 mmol) in anhydrous methanol (15

mL, 0.33 M) under nitrogen at rt for 4 d. The reaction was quenched with 1 M HCl and concentrated *in vacuo* to remove methanol. The pH was raised 14 with 3 M NaOH and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on basic alumina to afford the title compound as a pale yellow oil (642 mg, 51%).

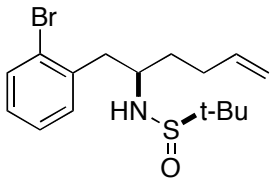
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.54 (m, 1 H), 7.27–7.22 (m, 2 H), 7.11–7.07 (m, 1 H), 5.89–5.80 (m, 1H), 5.07 (dd, J = 2.0, 3.4 Hz, 1 H), 5.04–4.95 (m, 1 H), 3.15–3.09 (m, 1 H), 2.97 (dd, J = 4.9, 13.7 Hz, 1 H), 2.60 (dd, J = 8.8, 13.7 Hz, 1 H), 2.29–2.19 (m, 1 H), 2.18–2.13 (m, 1 H), 1.66–1.58 (m, 1 H), 1.53–1.45 (m, 1 H), 1.22 (bs, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.5, 133.0, 131.6, 128.0, 127.3, 125.0, 114.7, 50.8, 44.8, 36.9, 30.5; IR (film) 3371, 3287, 2920, 1640 cm^{-1}. MS (ESI) 254.0554 (245.0544 calcd for $C_{12}H_{16}BrN$, M + H^+).



(–)-(*R*,*E*)-*N*-(2-(2-bromophenyl)ethylidene)-2-methylpropane-2-sulfinamide (V-14a). An oven-dried round bottom flask equipped with a magnetic stir bar was charged with 2-(2-bromophenyl)ethanol (1.00 g, 5.0 mmol) and purged with nitrogen. Methylene chloride (16 mL, 0.32 M) was added and the reaction was cooled to 0 ºC. Trichloroisocyanuric acid (1.16 g, 5.0 mmol) was added and the reaction stirred at 0 ºC for 5 min. 2,2,6,6-Tetramethyl-piperidin-1-oxyl (81 mg, 0.50 mmol) was added and the

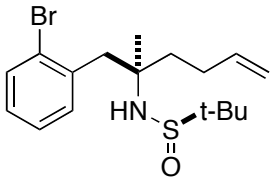
reaction was stirred an additional 10 min. The reaction mixture was filtered through Celite. The Celite was rinsed with fresh methylene chloride. The filtrate was washed with 10% Na_2CO_3 (3 x 50 mL), 1 M HCl (3 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford 2-(2-bromophenyl)acetaldehyde[15] as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.7 Hz 1 H), 7.62 (dd, *J* = 1.0, 8.1 Hz, 1 H), 7.34–7.30 (m, 1 H), 7.27–7.23 (m, 1 H), 7.21–7.17 (m, 1 H), 3.87 (d, *J* = 1.7 Hz, 2 H).

The crude 2-(2-bromophenyl)acetaldehyde was condensed with (*R*)-2-methylpropane-2-sulfinamide (641 mg, 5.30 mmol) according to General Procedure 2 to afford 619 mg (41%) of the title compound as a clear oil. $[\alpha]^{23}_D$ –201.6 (*c* 2.42, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (t, *J* = 4.6 Hz, 1 H), 7.58 (dd, *J* = 1.0, 8.1 Hz, 1 H), 7.31–7.23 (m, 2 H), 7.17–7.13 (m, 1 H), 3.99 (d, *J* = 4.6 Hz, 2 H), 1.18 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 135.0, 133.0, 131.2, 128.9, 127.7, 124.8, 57.0, 42.7, 22.4; IR 3059, 2959, 1619 cm^{-1}. MS (ESI) 302.0202 (302.0209 calcd for $C_{12}H_{16}BrNOS$, M + H^+).



(+)-(R_s,*R*)-*N*-(1-(2-bromophenyl)hex-5-en-2-yl)-2-methylpropane-2-sulfinamide (V-15). 4-bromo-1-butene (0.41 mL, 4.0 mmol) in diethyl ether (4 mL) was converted to the corresponding Grignard via General Procedure 1. The freshly made Grignard solution was added dropwise to a –55 ºC solution of **V-14a** (602 mg, 2.0 mmol) in methylene chloride (10 mL) over 5 min. The resulting mixture was slowly warmed from –55 ºC to –

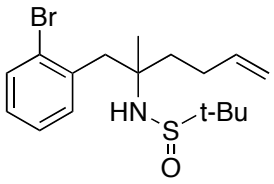
15 ºC over 4 h. TLC analysis indicated the reaction was not to full conversion. The reaction was cooled to –78 ºC and allowed to warm overnight (12 h) to +10 ºC. The reaction was quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with methylene chloride (4 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford 478 mg (67%) of the title compound as a 22:1 mixture of diastereomers as a clear oil which solidified to a white solid upon cooling. mp 69–75 ºC $[\alpha]^{23}_{D}$ +9.2 (*c* 2.48, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.51 (m, 1 H), 7.28–7.21 (m, 2 H), 7.09–7.04 (m, 1 H), 5.88–5.79 (m, 1 H), 5.12–5.06 (m, 1 H), 5.03–4.99 (m, 1H), 3.63–3.56 (m, 1 H), 3.17 (d, *J* = 7.6 Hz, 1 H), 2.99 (dd, *J* = 5.4, 11.7 Hz, 1 H), 2.95–2.90 (m, 1 H), 2.33–2.22 (m, 2 H), 1.93–1.85 (m, 1 H), 1.82–1.74 (m, 1 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 132.8, 132.0, 128.1, 127.3, 125.1, 115.3, 57.4, 55.8, 42.5, 35.5, 30.0, 22.4; IR (film) 3216, 3071, 2924, 1640. MS (ESI) 358.0835 (358.0835 calcd for $C_{16}H_{24}BrNOS$, M + H^+).



(–)-(*R*$_S$,*R*)-*N*-(1-(2-bromophenyl)-2-methylhex-5-en-2-yl)-2-methylpropane-2-sulfinamide (V-18). **V-9** (1.92 g, 7.57 mmol) was condensed with (*R*)-2-methylpropane-2-sulfinamide (963 mg, 7.94 mmol) according to General Procedure 2 to afford 1.88 g (70%) of (–)-(*R*)-*N*-(1-(2-bromophenyl)hex-5-en-2-ylidene)-2-methylpropane-2-sulfinamide (**V-17**) as a 1:1 mixture of diastereomers as judged by ^{1}H NMR. Data are for

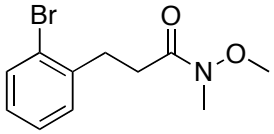
the mixture. $[\alpha]^{23}_{D}$ –85.0 (*c* 3.31, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.52 (m, 2 H), 7.32–7.23 (m, 4 H), 7.20–7.09 (m, 2 H), 5.93–5.82 (m, 1 H), 5.78–5.69 (m, 1 H), 5.12 (d, *J* = 17.6 Hz, 1 H), 5.05 (d, *J* = 10.4 Hz, 1 H), 4.99–4.91 (m, 2 H), 4.37 (d, *J* = 15.8 Hz, 1 H), 4.22 (d, *J* = 15.6 Hz, 1 H), 3.92–3.83 (m, 2 H), 2.99–2.91 (m, 1 H), 2.89–2.80 (m, 1 H), 2.51–2.44 (m, 2 H), 2.37–2.32 (m, 4 H), 1.31 (s, 9 H), 1.04 (s, 9 H).

A flame-dried flask cooled under a stream of nitrogen was charged with a portion of **(–)-V-17** (772 mg, 2.17 mmol). The reaction vessel was purged with nitrogen and charged with toluene (2.2 mL). The reaction was cooled to –78 ºC. Trimethyl aluminum (2.0 M in toluene, 1.2 mL, 2.4 mmol) was added. The mixture stirred at –78 ºC for 5 min, then was added via cannula over 10 min to a –78 ºC solution of methyl lithium (1.6 M in diethyl ether, 3.0 mL, 4.8 mmol) in toluene (6.6 mL). The reaction stirred at –78 ºC for 4 h. The reaction was placed in an ice bath and quenched with saturated ammonium chloride until bubbling stopped. The mixture was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified to afford 385 mg (50% recovery) of **(–)-V-17** and 285 mg (35%) of the title compound as a yellow oil which was a 12:1 mixture of diastereomers as determine by ^{1}H NMR. Data are for the major isomer. $[\alpha]^{23}_{D}$ –4.2 (*c* 2.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.50 (dd, *J* = 1.7, 7.6 Hz, 1 H), 7.29–7.24 (m, 1 H), 7.12–7.07 (m, 1 H), 5.86–5.75 (m, 1 H), 5.05–4.93 (m, 2 H), 3.33 (s, 1 H), 3.21 (d, *J* = 13.6 Hz, 1 H), 3.08 (d, *J* = 13.6 Hz, 1 H), 2.15–2.12 (m, 2 H), 1.83–1.75 (m, 1 H), 1.64–1.55 (m, 1 H), 1.43 (s, 3 H), 1.21 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 136.7, 133.3, 133.1, 128.3, 127.2, 126.4, 114.5, 58.9, 56.0, 47.1, 39.4, 27.9, 26.2, 22.8; IR (film) 3301, 3220, 3071, 2976, 1640 cm^{-1}. MS (ESI) 372.0992 (372.0991 calcd for $C_{17}H_{26}BrNOS$, $M + H^+$).



(±)-*N*-(1-(2-bromophenyl)-2-methylhex-5-en-2-yl)-2-methylpropane-2-sulfinamide (V-17). **V-9** (2.23 g, 8.8 mmol) was condensed with (±)-2-methylpropane-2-sulfinamide (1.12 g, 9.2 mmol) according to General Procedure 2 to afford 1.98 g (63%) of (±)-*N*-(1-(2-bromophenyl)hex-5-en-2-ylidene)-2-methylpropane-2-sulfinamide (**V-17**) as a 1:1 mixture of diastereomers as judged by ^{1}H NMR, which matched data listed above for **(–)-V-17**.

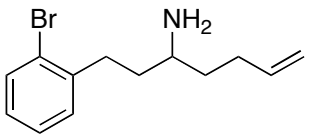
A flame-dried flask cooled under a stream of nitrogen was charged with **V-17** (1.98 g, 5.52 mmol). The reaction vessel was purged with nitrogen and charged with toluene (5.5 mL). The reaction was cooled to –78 ºC. Trimethyl aluminum (2.0 M in toluene, 3.0 mL, 6.0 mmol) was added. The mixture stirred at –78 ºC for 5 min, then was added via cannula over 10 min to a –78 ºC solution of methyl lithium (1.6 M in diethyl ether, 7.5 mL, 12.1 mmol) in toluene (18 mL). The reaction stirred at –78 ºC for 4 h. The reaction was placed in an ice bath and quenched with saturated ammonium chloride until bubbling stopped. The mixture was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified to afford 1.25 g (63% recovery) of **V-17** and 588 mg (29%) of the title compound as a yellow oil which was a 12:1 mixture of diastereomers as determine by ^{1}H NMR. ^{1}H NMR data were identical to that of (–)-**V-18**.



3-(2-bromophenyl)-*N*-methoxy-*N*-methylpropanamide (V-10a).

A round bottom flask equipped with a magnetic stir bar was charged with 3-(2-bromophenyl)propanoic acid (4.00 g, 17.5 mmol), *N,O*-dimethyl hydroxylamine hydrogen chloride (2.90 g, 29.7 mmol), THF (35 mL, 0.5 M), and water (35 mL, 0.5 M). 1 M NaOH (3 mL) added. A mixture of EDCI (8.39 g, 43.8 mmol) and 1 M NaOH (7 mL) in water (117 mL) was added dropwise over 20 min. After the addition was complete, 1 M NaOH (5.5 mL) was added to raise the pH of the reaction to 4.5. The reaction stirred at rt 8 h. The reaction was saturated with sodium chloride. The reaction mixture was extracted with ethyl acetate (5 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford the title compound as a clear oil (4.43 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.0, 8.0 Hz, 1 H), 7.30 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.24 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.07 (dt, *J* = 1.5, 7.5 Hz, 1 H), 3.63 (s, 3 H), 3.18 (s, 3 H), 3.10–3.06 (m, 2 H), 2.76 (t, *J* = 7.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 140.4, 132.7, 130.7, 127.8, 127.5, 124.3, 61.1, 31.9, 31.3, 31.1; IR (film) 3312, 2936, 1664 cm^{-1}. MS (ESI) 272.0274 (272.0281 calcd for $C_{11}H_{14}Br\ NO_2$, M + H^+).



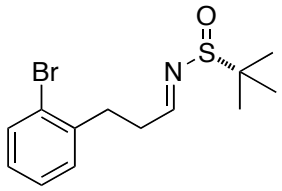
(±)-1-(2-bromophenyl)hept-6-en-3-amine (**V-12**).

4-bromo-1-butene (0.75 mL, 7.35 mmol) in diethyl ether (15 mL) was converted to the Grignard reagent according to General Procedure 1. The freshly made Grignard reagent was added dropwise to a 0 ºC solution of 3-(2-bromophenyl)-*N*-methoxy-*N*-methylpropanamide (1.00 g, 3.67 mmol) in diethyl ether (7 mL) via cannula over 25 min. After the addition was complete, the reaction was removed from the ice bath and stirred at rt 1.5 h. The reaction was placed in an ice bath and slowly quenched with saturated ammonium chloride. The reaction was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford 1-(2-bromophenyl)hept-6-en-3-one[16] (**V-11a**) as a clear oil (858 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.1 Hz, 1 H), 7.25–7.22 (m, 2 H), 7.09–7.04 (m, 1 H), 5.84–5.75 (m, 1 H), 5.04–4.96 (m, 2 H), 3.03–2.99 (m, 2 H), 2.77–2.73 (m, 2 H), 2.53–2.49 (m, 2 H), 2.36–2.30 (m, 2 H).

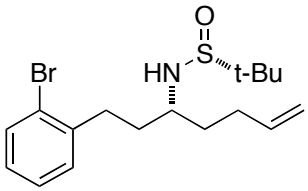
V-11a (858 g, 3.21 mmol) was stirred with ammonium acetate (2.54 g, 32.7 mmol) and sodium cyanoborohydride (202 mg, 3.21 mmol) in anhydrous methanol (10 mL, 0.33 M) under nitrogen at reflux 1 d. The reaction was quenched with 1 M HCl and concentrated *in vacuo* to remove methanol. The pH was raised to 14 with 3 M NaOH and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate. The crude product was purified by flash chromatography on basic alumina to afford the title compound as a clear oil (549 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1 H), 7.24–7.22 (m, 2 H), 7.08–7.02 (m, 1 H), 5.89–5.77 (m, 1 H), 5.07–5.00 (m, 1 H), 4.98–4.94 (m, 1 H), 2.90–2.71 (m, 3

H), 2.22–2.08 (m, 2 H), 1.80–1.70 (m, 1 H), 1.64–1.51 (m, 2 H), 1.47–1.37 (m, 1 H), 1.19 (bs, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 138.6, 132.8, 130.3, 127.52, 127.47, 124.4, 114.6, 50.6, 38.3, 37.2, 32.9, 30.5; IR (film) 3375, 3283, 3068, 2927, 1639 cm^{-1}. MS (ESI) 268.0696 (268.0701 calcd for $C_{13}H_{18}BrN$, M + H^+).

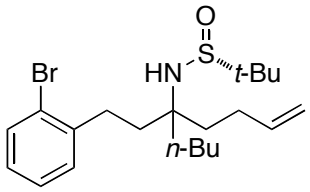


(–)-(*R*,*E*)-*N*-(3-(2-bromophenyl)propylidene)-2-methylpropane-2-sulfinamide (V-14b).[17] 3-(2-bromophenyl)propanal[12] (765 mg, 3.59 mmol) was condensed with (*R*)-2-methylpropane-2-sulfinamide (414 mg, 3.42 mmol) according to General Procedure 2 to afford 870 mg (77%) of the title compound as a clear oil, $[\alpha]^{23}_D$ –117.6 (*c* 0.92, $CHCl_3$) [lit.[17] $[\alpha]^{22}_D$ –156.2 (*c* 0.98, $CHCl_3$)].^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, *J* = 4.1 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.25–7.23 (m, 2 H), 7.11–7.06 (m, 1 H), 3.12–3.07 (m, 2 H), 2.90–2.84 (m, 2 H), 1.17 (s, 9 H).



(–)-(*R*$_s$,*R*)-*N*-(1-(2-bromophenyl)hept-6-en-3-yl)-2-methylpropane-2-sulfinamide (V-16). 4-bromo-1-butene (0.41 mL, 4.0 mmol) in diethyl ether (4 mL) was converted to the corresponding Grignard reagent according to General Procedure 1. The freshly made Grignard solution was added dropwise to a –55 ºC solution of **V-14b** (602 mg, 2.0 mmol)

in methylene chloride (10 mL) over 5 min. Reaction warmed from –55 ºC to –10 ºC over 3.5 h at a rate of approximately 13 °C/hr. The reaction was quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford 596 mg (62%) of the title compound as a 10:1 mixture of diastereomers as a yellow oil. Data are for the major diastereomer. $[\alpha]^{23}_{D}$ –30.4 (*c* 1.19, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.51 (m, 1 H), 7.26–7.20 (m, 2 H), 7.08–7.04 (m, 1 H), 5.86–5.80 (m, 1 H), 5.09–5.03 (m, 1 H), 4.99 (dd, *J* = 1.7, 10.3 Hz, 1 H), 3.36–3.31 (m, 1 H), 3.15 (d, *J* = 6.8 Hz, 1 H), 2.94–2.87 (m, 1 H), 2.74–2.67 (m, 1 H), 2.18 (dd, *J* = 7.6, 14.4 Hz, 2 H), 1.90–1.69 (m, 4 H), 1.24 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 137.9, 132.8, 130.3, 127.7, 127.6, 124.3, 115.3, 56.3, 55.9, 35.9, 35.5, 32.4, 30.0, 22.8; IR (film) 3222, 3071, 2925, 1690, 1640 cm^{-1}. MS (ESI) 372.0990 (372.0991 calcd for $C_{17}H_{26}BrNOS$, M + H$^+$).

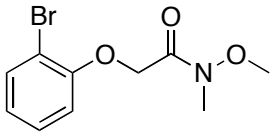


(–)-(R)-N-(5-(2-bromophenethyl)non-1-en-5-yl)-2-methylpropane-2-sulfinamide (V-21). **V-11a** (1.50 g, 5.60 mmol) was condensed with (*R*)-2-methylpropane-2-sulfinamide (715 mg, 5.90 mmol) according to General Procedure 2 to afford 1.62 g (78%) of (*R*)-*N*-(1-(2-bromophenyl)hept-6-en-3-ylidene)-2-methylpropane-2-sulfinamide (**V-20**) as a 1:1 mixture of diastereomers, as determined by ^{1}H and ^{13}C NMR. Data is

reported for the mixture. $[\alpha]^{23}_{D}$ –125.2 (*c* 2.41, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2 H), 7.34 (d, *J* = 7.3 Hz, 1 H), 7.26–7.21 (m, 3 H), 7.10–7.05 (m, 2 H), 5.87–5.78 (m, 2 H), 5.10–4.98 (m, 4 H), 3.09–2.98 (m, 5 H), 2.94–2.86 (m, 2 H), 2.82–2.71 (m, 3 H), 2.61–2.48 (m, 2 H), 2.42–2.35 (m, 4 H), 1.30 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 185.7, 140.3, 139.5, 137.3, 136.4, 132.8, 132.7, 130.8, 130.2, 128.2, 127.9, 127.8, 127.5, 124.3, 124.0, 115.9, 115.3, 56.6, 56.5, 40.7, 40.5, 36.7, 35.7, 33.9, 32.1, 31.4, 29.3, 22.3 (one signal missing due to incidental equivalence).

A flame-dried flask cooled under a stream of nitrogen was charged with a portion of **V-20** (1.44 mg, 3.88 mmol). The reaction vessel was purged with nitrogen and charged with toluene (4 mL). The reaction was cooled to –78 ºC. Trimethyl aluminum (2.0 M in toluene, 2.1 mL, 4.2 mmol) was added. The mixture stirred at -78 ºC for 5 min, then was added via cannula over 10 min to a –78 ºC solution of *n*-butyl lithium (2.0 M in diethyl ether, 4.3 mL, 8.6 mmol) in toluene (13 mL). The reaction stirred at –78 ºC for 7 h. The reaction was placed in an ice bath and quenched with saturated ammonium chloride until bubbling stopped. The mixture was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford 1.39 g (83%) of the title compound as a white solid, mp 51–56 ºC which was circa 1:1 mixture of diastereomers as determined by ^{1}H and ^{13}C NMR. Data is for mixture. $[\alpha]^{23}_{D}$ –48.1 (*c* 3.34, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2 H), 7.34–7.29 (m, 2 H), 7.25–7.21 (m, 2 H), 7.07–7.01 (m, 2 H), 5.89–5.79 (m, 2 H), 5.10–5.02 (m, 2 H), 5.00–4.94 (m, 2 H), 3.24 (s, 2 H), 2.83–2.72 (m, 4 H), 2.19–2.12 (m, 4 H), 1.85–1.78 (m, 4 H), 1.76–1.57 (m, 8 H), 1.38–1.32 (m, 8 H), 1.25 (s, 18 H), 0.97–0.91 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.47, 141.45, 138.4, 138.3, 132.61, 132.59, 130.7, 130.6, 127.7,

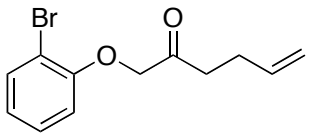
127.6, 124.1, 114.7, 114.6, 60.1, 55.9, 39.01, 38.96, 37.7, 37.3, 37.0, 29.9, 27.5, 27.4, 25.1, 25.0, 23.1, 23.0, 22.8, 14.0 (nine signals missing due to incidental equivalence); IR (film) 3307, 3236, 3070, 2953, 1640 cm^{-1}. MS (ESI) 428.1607 (428.1617 calcd for $C_{21}H_{34}BrNOS$, $M + H^+$).



2-(2-bromophenoxy)-*N*-methoxy-*N*-methylacetamide (V-10b)

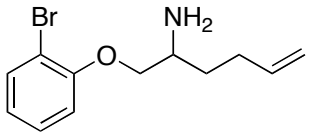
A round bottom flask equipped with a magnetic stir bar was charged with 2-(2-bromophenoxy)acetic acid[13] (1.11 g, 4.80 mmol) and purged with nitrogen. Methylene chloride (9.6 mL) was added and the reaction was cooled to 0 ºC. 1,1′-carbonyldiimidazole (1.01 g, 6.24 mmol) was added and the reaction was purged with nitrogen. The reaction stirred at rt 30 min. Triethylamine (0.94 mL, 0.68 g, 6.7 mmol) was added and the reaction was cooled to 0 ºC. *N,O*-dimethyl hydroxylamine hydrogen chloride was added in one portion. The reaction was purged with nitrogen and stirred at rt 14 h. The reaction was quenched with 1 M HCl (15 mL). The layers were separated. The aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford 1.233 g (94%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.53 (m, 1 H), 7.26–7.22 (m, 1 H), 6.91–6.85 (m, 2 H), 4.90 (s, 2 H), 3.77 (s, 3 H), 3.24 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 154.8, 133.5, 128.4, 122.7, 114.0, 112.3, 66.8, 61.8, 32.3; IR

(film) 2941, 1686, 1479 cm^{-1}. MS (ESI) 274.0072 (274.0073 calcd for $C_{10}H_{12}BrNO_3$, M + H^+).



1-(2-bromophenoxy)hex-5-en-2-one (V-11b)

4-bromo-1-butene (0.89 mL, 8.8 mmol) in diethyl ether (12 mL) was converted to the corresponding Grignard reagent according to General Procedure 1. The freshly made Grignard reagent was added dropwise to a 0 ºC solution of **V-10b** (1.20 g, 4.4 mmol) in diethyl ether (5 mL) via cannula over 15 min. After the addition was complete, the reaction was removed from the ice bath and stirred at rt 1 h. The reaction was placed in an ice bath and slowly quenched with saturated ammonium chloride. The reaction was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford 871 mg (74%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 1.5, 6.4 Hz, 1 H), 7.28–7.23 (m, 1 H), 6.91–6.87 (m, 1 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 5.89–5.81 (m, 1 H), 5.10–5.05 (m, 1 H), 5.00 (dd, *J* = 1.0, 9.3 Hz), 4.56 (s, 2 H), 2.84 (t, *J* = 7.3 Hz, 2 H), 2.43–2.38 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 154.2, 136.7, 133.7, 128.6, 122.9, 115.5, 113.1, 112.2, 73.5, 38.4, 27.0; IR (film) 2917, 1723 1480 cm^{-1}. MS (ESI) 290.9991 (290.9991 calcd for $C_{12}H_{13}BrO_2$, M + Na^+).



(±)-1-(2-bromophenoxy)hex-5-en-2-amine (V-13)

V-11b (1.405 g, 5.22 mmol) was stirred with ammonium acetate (4.10 g, 53.2 mmol) and sodium cyanoborohydride (328 mg, 5.22 mmol) in anhydrous methanol (16 mL, 0.33 M) under nitrogen at reflux 1 d. The reaction was quenched with 1 M HCl and concentrated *in vacuo* to remove methanol. The pH was raised to 14 with 3 M NaOH and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate. The crude product was purified by flash chromatography on basic alumina to afford the title compound as a clear oil (630 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 1.7, 6.1 Hz, 1 H), 7.27–7.22 (m, 1 H), 6.89–6.81 (m, 2 H), 5.89–5.80 (m, 1 H), 5.10–4.98 (m, 2 H), 4.01–3.98 (m, 1 H), 3.80–3.75 (m, 1 H), 3.26–3.21 (m, 1 H), 2.30–2.15 (m, 2 H), 1.72–1.64 (m, 1 H), 1.58–1.49 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 138.1, 133.2, 128.4, 121.9, 115.0, 113.3, 112.3, 74.2, 50.1, 33.1, 30.3; IR (film) 3375, 3282, 3073, 2925 cm^{-1}. MS (ESI) 270.0491 (270.0488 calcd for $C_{12}H_{16}BrNO$, M + H^+).

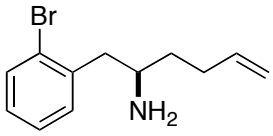
General Procedure 3: Deprotection of Sulfinamides.

A flame-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with sulfinamide (1 equiv) and anhydrous methanol (1 M) under nitrogen. A 4 M solution of hydrogen chloride in 1,4-dioxane (4 equiv) was added via syringe. The reaction stirred at rt for 15 min. The solvent was removed via a nitrogen purge. The crude reaction mixture was diluted with methylene chloride and the pH was

raised to 14 with aqueous sodium hydroxide. The layers were separated, the aqueous layer was extracted with methylene chloride (4 x), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on basic alumina.

General Procedure 4 - Mosher Amide Analysis

In order to assess enantiomeric purity of the amine substrates, the Mosher amides were generated using the following procedure. A flame-dried vial equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with amine (1.0 equiv), methylene chloride (10 mL solvent/mmol amine), (S)-α-methoxy-α-trifluoromethylphenylacetic acid (1.2 equiv), *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.2 equiv), and triethylamine (1.2 equiv). The vial was purged with nitrogen and stirred at rt 36 h. The reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel. Enantiomeric purity was determined by ^{19}F NMR analysis.



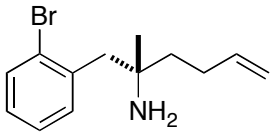
(+)-(R)-1-(2-bromophenyl)hex-5-en-2-amine (V-1)

The reaction of **V-15** (475 mg, 1.30 mmol) was conducted according to General Procedure 3 to afford 264 mg (80%) of the title compound as a pale yellow oil. $[\alpha]^{23}_{D}$ +13.4 (*c* 2.60, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for (±)-**V-1**. The enantiomeric purity of the title compound was determined by conversion of 64 mg

(0.25 mmol) of **V-1** to the corresponding Mosher amide using General Procedure 4. This procedure afforded 13 mg (11%) of **V-39**. The enantiopurity was determined to be 92% ee by ^{19}F NMR analysis. The absolute stereochemistry of **(+)-V-1** was assigned based on models established by Ellman.[4]

(2*S*,1'*R*)-*N*-[1-(2-bromophenyl)hex-5-en-2-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (V-39)

^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.49 (m, 3 H), 7.41–7.37 (m, 3 H), 7.26–7.20 (m, 2 H), 7.11–7.05 (m, 1 H), 6.61 (d, *J* = 8.6 Hz, 1 H), 5.80–5.68 (m, 1 H), 5.00–4.93 (m, 2 H), 4.37–4.26 (m, 1 H), 3.27–3.26 (m, 3 H), 3.01–2.97 (m, 2 H), 2.11–1.99 (m, 2 H), 1.74–1.61 (m, 2 H); ^{19}F (376 MHz, $CDCl_3$) δ -68.71 (s, 3 F); IR 3400, 3339, 2925, 1695, 1686 cm^{-1}. MS (ESI) 470.0940 (470.0937 calcd for $C_{22}H_{23}BrF_3NO_2$, $M + H^+$).



(–)-(S)-1-(2-bromophenyl)-2-methylhex-5-en-2-amine (V-19)

The reaction of **(–)-V-18** (415 mg, 1.11 mmol) was conducted according to General Procedure 3 to afford 240 mg (81%) of the title compound as a clear oil. $[\alpha]^{23}_D$ –14.6 (*c* 2.60, CH_2Cl_2). ^1H HMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 1.2, 6.8 Hz, 1 H), 7.30–7.23 (m, 2 H), 7.10–7.07 (m, 1 H), 5.91–5.83 (m, 1 H), 5.09–5.04 (m, 1 H), 4.99–4.95 (m, 1 H), 2.91 (s, 2 H), 2.24–2.17 (m, 2 H), 1.64–1.51 (m, 2 H), 1.29 (bs, 2 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 137.9, 133.1, 132.4, 127.9, 126.9, 126.3, 114.3, 53.4, 47.6, 42.6, 28.5, 27.3; IR (film) 3367, 3298, 3071, 2921, 1640 cm^{-1}. MS (ESI) 268.0696 (268.0695 calcd for $C_{13}H_{18}BrN$, $M + H^+$).

The enantiomeric purity of the title compound was determined by conversion of 76 mg (0.28 mmol) of **V-19** using General Procedure 4. This procedure afforded 12 mg (8%) of **V-40**. The enantiopurity was determined to be 87% ee by ^{19}F NMR analysis.

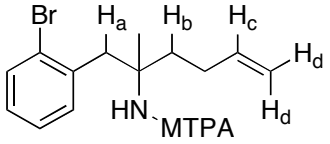
(2*S*,1'*S*)-*N*-[1-(2-bromophenyl)-2-methylhex-5-en-2-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (V-40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.49 (m, 3 H), 7.40–7.37 (m, 3 H), 7.22–7.17 (m, 2 H), 7.11–7.06 (m, 1 H), 6.71 (s, 1 H), 5.81–5.72 (m, 1 H), 5.00–4.92 (m, 2 H), 3.47 (d, *J* = 11.2 Hz, 1 H), 3.38–3.37 (m, 3 H), 3.12 (d, *J* = 11.1 Hz, 1 H), 2.13–1.94 (m, 3 H), 1.87–1.79 (m, 1 H), 1.34 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.92 (s, 3 F); IR (film) 3404, 3377, 2923, 1697 cm^{-1}. MS (ESI) 484.1093 (484.1094 calcd for $C_{23}H_{25}BrF_3NO_2$, M + H^+).

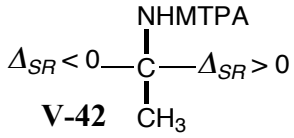
To determine the absolute stereochemistry of the title compound, 55 mg (0.21 mmol) was reacted with (R)-α-methoxy-α-trifluoromethylphenylacetic acid in an analogous to General Procedure 4 to afford 13 mg (12%) of **V-41**. Modified Mosher amide analysis was conducted as described below.

(2*R*,1'*S*)-*N*-[1-(2-bromophenyl)-2-methylhex-5-en-2-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (V-41). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (m, 3 H), 7.47–7.43 (m, 3 H), 7.13–7.05 (m, 2 H), 7.00–6.97 (m, 1 H), 6.68 (s, 1 H), 5.86–5.75 (m, 1 H), 5.05–4.94 (m, 2 H), 3.40–3.34 (m, 4 H), 3.08 (d, *J* = 13.8 Hz, 1 H), 2.19–2.03 (m, 3 H), 1.90–1.82 (m, 1 H), 1.34 (s, 3 H); ^{19}F (376 MHz, $CDCl_3$) δ -68.05 (s, 3 F); IR (film) 3396, 2929, 1699 cm^{-1}. MS 484.1096 (484.1094 calcd for $C_{23}H_{25}BrF_3NO_2$, M + H^+).

The absolute stereochemistry of (–)-**V-19** tentatively assigned based on a modified Mosher amide analysis, using Δ_{SR}.[18] The methyl signal does not shift between **V-40** and **V-41**, thus the methyl group was assigned the place of the hydrogen in the model (**V-42**)

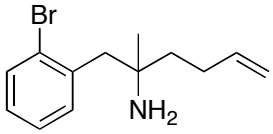
reported by Kusumi and coworkers.[18] Signals reported in this table are centers for multiplets or the peak if a defined splitting pattern.





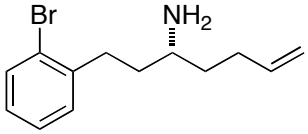
V-42

Proton	*S*-MTPA (ppm) **V-40**	*R*-MTPA (ppm) **V-41**	Δ_{SR} (Hz)
H_a	3.12	3.08	16
CH_3	1.34	1.34	0
H_b	2.04	2.11	-30
H_c	5.77	5.81	-16
H_d	4.96	5.00	-14



(±)-1-(2-bromophenyl)-2-methylhex-5-en-2-amine (V-19)

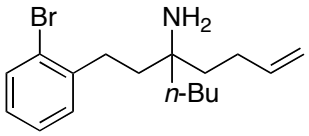
The reaction of **(±)-V-18** (588 mg, 1.6 mmol) was conducted according to General Procedure 3 to afford 376 mg (88%) of the title compound as a clear oil. ^{1}H NMR data matched that reported above for **(–)-V-19**.



(+)-(R)-1-(2-bromophenyl)hept-6-en-3-amine (V-12)

The reaction of **V-16** (550 mg, 1.48 mmol) was conducted according to General Procedure 3 to afford 317 mg (80%) of the title compound as a clear oil. In order to increase the level of enantiopurity, the amine was stirred with (L)-tartaric acid (176 mg, 1.17 mmol, 1 equiv) in a mixture of methanol (1.2 mL) and water (2 mL). After 1 min, the reaction solidified. The white solid was recrystallized from an ethanol/ethyl acetate/water mixture. The recrystallized salt was suspended in EtOAc and the pH was raised to 14 with NaOH (aq). The layers were separated and the aqueous layer was extracted with methylene chloride (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered through alumina. The filtrate was concentrated *in vacuo* to afford 152 mg (48% recovery) of the title compound as a clear oil. $[\alpha]^{23}_{D}$ +10.5 (*c* 2.73, CH_2Cl_2). ^{1}H NMR data were identical to those reported above for **(±)-12**. The enantiomeric purity of the title compound was determined by conversion of 67 mg (0.25 mmol) of **(+)-V-12** to the corresponding Mosher amide using General Procedure 4. This procedure afforded 17 mg (14%) of **V-43**. The enantiopurity was determined to be 88% ee by ^{19}F NMR analysis. The absolute stereochemistry of **(+)-V-12** was assigned based on models established by Ellman.[4]

(2*S*,1'*R*)-*N*-[1-(2-bromophenyl)hept-6-en-3-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (V-43). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.49 (m, 3 H), 7.45–7.40 (m, 3 H), 7.26–7.19 (m, 2 H), 7.10–7.03 (m, 1 H), 6.67 (d, *J* = 9.1 Hz, 1 H), 5.79–5.70 (m, 1 H), 5.00–4.92 (m, 2 H), 4.12–4.02 (m, 1 H), 3.46 (s, 3 H), 2.89–2.80 (m, 1 H), 2.76–2.67 (m, 1 H), 2.05–1.99 (m, 2 H), 1.93–1.83 (m, 1 H), 1.78–1.52 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.60 (s, 3 F); IR (film) 3408, 3339, 2925, 1686 cm^{-1}. MS (ESI) 484.1094 (484.1094 calcd for $C_{23}H_{25}BrF_3NO_2$, M + H$^+$).



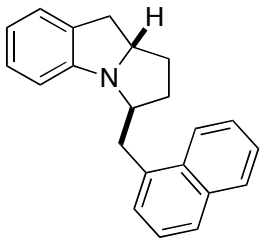
(±)-5-(2-bromophenethyl)non-1-en-5-amine (V-21)

The reaction of **V-20** (1.312 g, 3.06 mmol) was conducted according to General Procedure 3 to afford 907 mg (91%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1 H), 7.24–7.21 (m, 2 H), 7.07–7.02 (m, 1 H), 5.91–5.80 (m, 1 H) 5.05 (dd, *J* = 1.7, 17.1 Hz, 1 H), 4.96 (d, *J* = 10.1 Hz, 1 H), 2.75–2.70 (m, 2 H), 2.15–2.08 (m, 2 H), 1.62–1.47 (m, 2 H), 1.44–1.39 (m, 2 H), 1.37–1.30 (m, 6 H), 1.10 (bs, 2 H), 0.95–0.91 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 139.1, 132.8, 130.3, 127.5, 127.4, 124.2, 114.2, 53.3, 40.7, 39.7, 39.2, 30.7, 28.0, 25.6, 23.4, 14.1; IR (film) 3371, 3310, 3071, 2930 cm^{-1}. MS (ESI) 324.1321 (324.1321 calcd for $C_{17}H_{26}BrN$, M + H^+).

5.6.2 Preparation and Characterization of Products

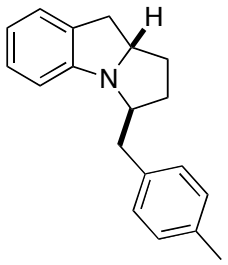
General Procedure 5 - Palladium Catalyzed Tandem *N*-Arylation/Carboamination. An oven-dried Schlenk tube equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol% complex, 4 mol% Pd) or $Pd(OAc)_2$ (4 mol%), $PCy_3{\cdot}HBF_4$ (4 or 8 mol%) or Cy_4DPE-Phos (4 mol%), sodium *tert*-butoxide (2.4 equiv), and the aryl chloride if solid (1.2 equiv). The Schlenk tube was evacuated and refilled with nitrogen three times. The primary amine substrate (1.0 equiv) was added as a solution in toluene (4 mL/mmol substrate), along with the aryl chloride if liquid. The resulting mixture was heated to 100 °C until the intermediate was consumed as judged by GC analysis. The reaction mixture was cooled to rt and treated with saturated aqueous

ammonium chloride (2 mL) and ethyl acetate (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

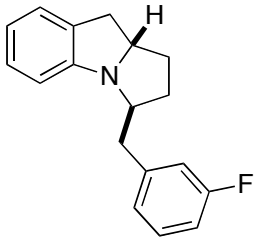


(±)-(3*S,9a*S**)-3-(Naphthalen-1-ylmethyl)-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V-28).** The reaction of **V-1** (64 mg, 0.25 mmol) with 1-chloronapthalene (41 mg, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 59 mg (79%) of the title compound as a tan solid, mp 65–78 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 5:1 mixture of diastereomers. The product was isolated as an 8:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 1 H), 7.88–7.85 (m, 1 H), 7.80–7.72 (m, 1 H), 7.55–7.36 (m, 4 H), 7.00–6.98 (m, 1 H), 6.83 (t, *J* = 7.8 Hz, 1 H), 6.63 (dt, *J* = 1.2, 7.4 Hz, 1 H), 5.83 (d, *J* = 7.8 Hz, 1 H), 4.09–4.02 (m, 1 H), 3.76–3.68 (m, 1 H), 3.42 (dd, *J* = 7.1, 13.7 Hz, 1H), 3.31 (dd, *J* = 6.7, 13.7 Hz, 1 H), 3.14 (dd, *J* = 9.4, 16.1 Hz, 1 H), 2.92 (d, *J* = 2.3 Hz, 1 H), 2.03–1.95 (m, 1 H), 1.90–1.82 (m, 1 H), 1.74–1.63 (m, 1 H), 1.38–1.27 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 136.1, 133.9, 132,2, 129.1, 128.8, 127.6, 127.4, 126.9, 125.8, 125.6, 125.4, 124.8, 124.0,

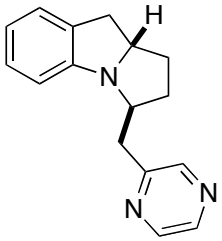
119.0, 110.0, 66.3, 64.9, 41.2, 33.5, 33.1, 32.0; IR (film) 3045, 2927, 1603 cm^{-1}. MS (ESI) 300.1753 (300.1752 calcd for $C_{22}H_{21}N$, M + H^+).



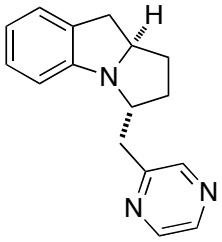
(±)-(3*S,9a*S**)-3-(4-Methylbenzyl)-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V-27).** The reaction of **V-1** (64 mg, 0.25 mmol) with 4-chlorotoluene (36 µL, 38 mg, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 51 mg (77%) of the title compound as an off-white solid, mp 42–45 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 20:1 mixture of diastereomers. The product was isolated as a >20:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.8, 2 H), 7.11 (d, *J* = 7.8 Hz, 2 H), 7.03 (d, *J* = 6.8 Hz, 1 H), 6.98–6.94 (m, 1 H), 6.68 (dt, *J* = 1.0, 7.3 Hz, 1 H), 6.13 (d, *J* = 7.8 Hz, 1 H), 4.00–3.94 (m, 1 H), 3.51–3.47 (m, 1 H), 3.15 (dd, *J* = 9.3, 15.6 Hz, 1 H), 2.96 (dd, *J* = 6.8, 13.2 Hz, 1 H), 2.91 (dd, *J* = 2.0, 16.1 Hz, 1 H), 2.79 (dd, *J* = 6.3, 13.2 Hz, 1 H), 2.33 (s, 3 H), 2.01 (dtd, *J* = 1.5, 7.3, 12.3 Hz, 1 H), 1.85–1.81 (m, 1 H), 1.64–1.55 (m, 2 H), 1.38–1.28 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 136.8, 135.5, 129.4, 129.1, 129.0, 127.4, 124.8, 118.9, 110.0, 67.4, 64.9, 43.8, 33.4, 32.9, 31.9, 21.0; IR (film) 3021, 2923, 1603 cm^{-1}. MS (ESI) 264.1752 (264.1752 calcd for $C_{19}H_{21}N$, M + H^+).



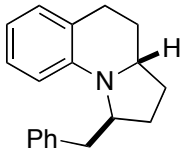
(±)-(3*S,9a*S**)-3-(3-Fluorobenzyl)-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V-29).** The reaction of **V-1** (64 mg, 0.25 mmol) with 1-chloro-3-fluorobenzene (32 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (7.4 mg, 0.020 mmol) to afford 28 mg (42%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 5:1 mixture of diastereomers. The product was isolated as a >20:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.24 (m, 1 H), 7.09 (d, *J* = 7.8 Hz, 1 H), 7.05–7.01 (m, 2 H), 6.97–6.90 (m, 2 H), 6.69 (dt, *J* = 1.0, 7.3 Hz, 1 H0, 6.04 (d, *J* = 7.8 Hz, 1 H), 4.00–3.93 (m, 1 H), 3.53–3.46 (m, 1 H), 3.15 (dd, *J* = 9.4, 16.0 Hz, 1 H), 2.98–2.90 (m, 2 H), 2.86–2.82 (m, 1 H), 2.08–2.01 (m, 1 H), 1.88–1.82 (m, 1 H), 1.64–1.55 (m, 1 H), 1.39–1.29 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (d, *J* = 243.6 Hz), 154.5, 142.6 (d, *J* = 7.3 Hz), 129.7 (d, *J* = 8.3 Hz), 129.1, 127.5, 125.2 (d, *J* = 2.9 Hz), 124.9, 119.1, 116.4 (d, *J* = 20.4 Hz), 113.0 (d, *J* = 20.9 Hz), 109.9, 67.1, 64.9, 43.9 (d, *J* = 1.5 Hz), 33.4, 32.9, 31.9; IR (film) 3043, 2927 cm^{-1}. MS (ESI) 268.1499 (268.1496 calcd for $C_{18}H_{18}FN$, M + H$^+$).



(±)-(3*S,9a*S**)-3-(Pyrazin-2-ylmethyl)-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V-30).** The reaction of **V-1** (64 mg, 0.25 mmol) with 2-chloropyrazine (27 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (3.7 mg, 0.010 mmol) to afford 37 mg (59%) of the title compound as a brown solid, mp 83–87 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 7:1 mixture of diastereomers. The product was isolated as an 8:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 2 H), 8.46–8.44 (m, 1 H), 7.05–7.01 (m, 1 H), 6.96–6.92 (m, 1 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 6.02 (d, *J* = 7.8 Hz, 1 H), 4.00–3.93 (m, 1 H), 3.83–3.77 (m, 1 H), 3.17–3.05 (m, 3 H), 2.92 (d, *J* = 15.6 Hz, 1 H), 2.16–2.09 (m, 1 H), 1.91–1.85 (m, 1 H), 1.71–1.62 (m, 1 H), 1.44–1.33 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 154.1, 145.8, 144.0, 142.4, 128.9, 127.4, 124.9, 119.2, 109.8, 65.2, 64.7, 43.4, 33.4, 32.8, 31.7; IR (film) 3043, 2925, 1603. MS (ESI) 252.1497 (252.1495 calcd for $C_{16}H_{17}N_3$, M + H^+).

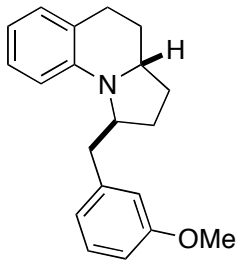


(–)-(3*R*,9a*R*)-3-(pyrazin-2-ylmethyl)-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (#). The reaction of **(+)-V-1** (64 mg, 0.25 mmol) with 2-chloropyrazine (27 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (3.7 mg, 0.010 mmol) to afford 33 mg (53%) of the title compound as a brown solid, mp 60–64 ºC, $[\alpha]^{23}_D$ –133.3 (*c* 1.13, CH_2Cl_2). The product was determined to be 86% ee by chiral HPLC analysis [Chiralcel OD-H, 0.46 cm x 15 cm, 8% isopropanol/hexanes, 1.0 mL/min, RT = 5.6 and 6.6 min]. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 7:1 mixture of diastereomers. The product was isolated as an 8:1 mixture of diastereomers. ^{1}H NMR data were identical to those reported above for **(±)-V-30**.



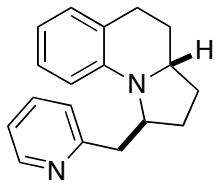
(±)-(1*S,3a*S**)-1-Benzyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (V-23).** The reaction of **V-12** (67 mg, 0.25 mmol) with chlorobenzene (31 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 45 mg (68%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 12:1 mixture of diastereomers. The product was isolated as a 25:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.28 (m, 2 H), 7.24–7.20 (m, 3 H), 7.14–7.10 (m, 1 H), 7.05–6.99 (m, 1 H), 6.62 (d, *J* = 8.3 Hz, 1 H), 6.58–6.54 (m, 1 H), 4.02–3.96 (m, 1 H), 3.48–3.42 (m, 1 H), 3.17 (dd, *J* = 3.4, 13.7 Hz, 1 H), 2.84–2.77 (m, 1 H), 2.73–2.68 (m, 1 H),

2.62 (dd, J = 9.3, 13.2 Hz, 1 H), 2.09–1.96 (m, 3 H), 1.77–1.69 (m, 1 H), 1.44–1.34 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 139.2, 129.5, 128.6, 128.3, 127.2, 126.1, 122.0, 114.6, 109.6, 59.8, 58.1, 38.9, 31.8, 29.5, 28.4, 27.4; IR (film) 3024, 2934 cm^{-1}. MS (ESI) 264.1740 (264.1752 calcd for $C_{19}H_{21}N$, M + H^+).

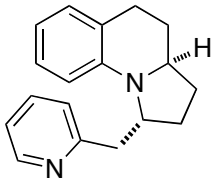


(±)-(1*S,3a*S**)-1-(3-Methoxybenzyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (V-33).** The reaction of **V-12** (67 mg, 0.25 mmol) with 3-chloroanisole (37 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 49 mg (67%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as an 8:1 mixture of diastereomers. The product was isolated as a 22:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.19 (m, 1 H), 7.13–7.09 (m, 1 H), 6.99 (d, J = 7.3 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.78–6.75 (m, 2 H), 6.61 (d, J = 8.3 Hz, 1 H), 6.55 (dt, J = 1.0 Hz, 7.3 Hz, 1 H), 4.02–3.96 (m, 1 H), 3.78 (s, 3 H), 3.48–3.42 (m, 1 H), 3.15 (dd, J = 3.0, 13.3 Hz, 1 H), 2.84–2.76 (m, 1 H), 2.73–2.67 (m, 1 H), 2.60 (dd, J = 9.3, 13.2 Hz, 1 H), 2.09–1.97 (m, 3 H), 1.77–1.69 (m, 1 H), 1.43–1.30 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 143.6, 140.8, 129.2, 128.6, 127.2, 122.0, 115.4, 114.6, 111.3, 109.6, 59.6, 58.1, 55.1, 38.9, 31.8, 29.6, 28.4, 27.4 (one carbon missing due

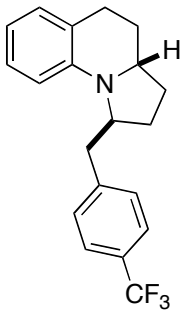
to incidental equivalence); IR (film) 2934, 2838 cm^{-1}. MS (ESI) 294.1859 (294.1852 calcd for $C_{20}H_{23}NO$, $M + H^+$).



(±)-(1*S,3a*S**)-1-(Pyridin-2-ylmethyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (V-35).** The reaction of **V-12** (67 mg, 0.25 mmol) with 3-chloropyridine (29 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (3.7 mg, 0.010 mmol) to afford 38 mg (57%) of the title compound as a yellow oil. ^1H NMR analysis of the crude reaction mixture indicated the product was formed as a 10:1 mixture of diastereomers. The product was isolated as a >20:1 mixture of diastereomers; data are for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$) δ 8.59–8.57 (m, 1 H), 7.60–7.55 (m, 1 H), 7.16–7.08 (m, 3 H), 6.99 (d, J = 7.2 Hz, 1 H), 6.66 (dd, J = 2.8, 5.2 Hz, 1 H), 6.58–6.53 (m, 1 H), 4.24–4.16 (m, 1 H), 3.52–41 (m, 1 H), 3.41–3.36 (m, 1 H), 2.85–2.68 (m, 3 H), 2.10–1.95 (m, 3 H), 1.85–1.75 (m, 1 H), 1.49–1.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 149.3, 143.6, 136.1, 128.5, 127.3, 124.0, 121.8, 121.2. 114.7, 109.9, 58.9, 57.9, 41.3, 31.7, 29.4, 28.4, 27.5; IR (film) 3062, 2932 cm^{-1}. MS (EI) 264.1632 (264.1626 calcd for $C_{18}H_{20}N_2$, M^+).

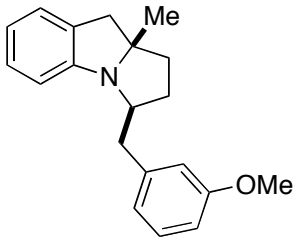


(+)-(1*R*,3a*R*)-1-(pyridin-2-ylmethyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (V-35). The reaction of **(+)-V-12** (67 mg, 0.25 mmol) with 3-chloropyridine (29 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (3.7 mg, 0.010 mmol) to afford 43 mg (65%) of the title compound as a yellow oil, $[\alpha]^{23}_D$ +19.4 (*c* 0.34, CH_2Cl_2). The product was determined to be 92% ee by chiral HPLC analysis [Chiralcel OD-H, 0.46 cm x 15 cm, 0.5% isopropanol/hexanes, 2.0 mL/min, RT = 4.8 and 11.2 min]. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 10:1 mixture of diastereomers. The product was isolated as a 20:1 mixture of diastereomers. ^{1}H NMR data were identical to those reported above for **(±)-V-35**.



(±)-(1*S,3a*S**)-1-[4-(Trifluoromethyl)benzyl]-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (V-34).** The reaction of **V-12** (64 mg, 0.25 mmol) with 4-chlorobenzotrifluoride (40 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (7.4 mg, 0.020 mmol) to afford 48 mg (58%) of the title compound as a pale

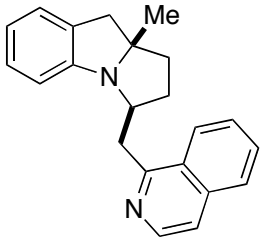
yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 3:1 mixture of diastereomers. The product was isolated as a 7:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 2 H) 7.31 (d, *J* = 7.9 Hz, 2 H), 7.14–7.09 (m, 1 H), 7.01 (d, *J* = 7.1 Hz, 1 H), 6.60–6.56 (m, 2 H), 4.04–3.99 (m, 1 H), 3.42–3.36 (m, 1 H), 3.18 (dd, *J* = 2.9, 13.4 Hz, 1 H), 2.83–2.67 (m, 3 H), 2.09–1.97 (m, 3 H), 1.71–1.64 (m, 1 H), 1.42–1.29 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 143.2, 129.9, 128.7, 128.0, 127.2, 125.1 (q, *J* = 3.5 Hz), 124.3 (q, *J* = 270 Hz), 122.1, 114.9, 109.5, 59.4, 58.3, 38.7, 31.7, 29.5, 28.4, 27.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ 62.3 (s, 3 F). IR (film) 2934, 1602 cm^{-1}. MS (EI) 331.1548 (331.1548 calcd for $C_{20}H_{20}F_3N$, M^+).



(+)-(3*S*,9a*S*)-3-(3-Methoxybenzyl)-9a-methyl-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V-32). The reaction of **(–)-V-19** (67 mg, 0.25 mmol) with 3-chloroanisole (37 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 55 mg (75%) of the title compound as a pale yellow oil, $[\alpha]^{23}_D$ +97.5 (*c* 1.95, CH_2Cl_2). The product was determined to be 91% ee by chiral HPLC analysis [Chiralcel OJ-H, 0.46 cm x 25 cm, 0.1% isopropanol/hexanes, 0.8 mL/min, RT = 9.3 and 12.7 min]. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed a 10:1 mixture of diastereomers. The product was isolated as a >20:1 mixture of diastereomers;

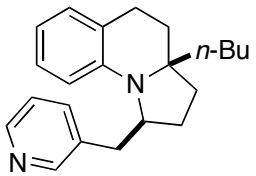
data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.19 (m, 1 H), 6.99–6.89 (m, 3 H), 6.84 (s, 1 H), 6.79–6.75 (m, 1 H), 6.69–6.65 (m, 1 H), 6.03 (d, *J* = 7.9 Hz, 1 H), 3.79 (s, 3 H), 3.49–3.41 (m, 1 H), 3.10 (d, *J* = 16.1 Hz, 1 H), 3.00 (dd, *J* = 7.4, 13.0 Hz, 1 H), 2.87–2.79 (m, 2 H), 2.08–2.01 (m, 1 H), 1.86–1.70 (m, 2 H), 1.62–1.54 (m, 1 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 155.2, 141.6, 129.2, 129.1, 127.5, 124.4, 122.1, 119.0, 115.4, 111.3, 110.3, 72.1, 68.1, 55.2, 45.7, 42.6, 37.1, 31.9, 28.4; IR (film) 2957, 1602 cm^{-1}. MS (ESI) 294.1857 (294.1852 calcd for calcd for $C_{20}H_{23}NO$, M + H^+).

(±)-(3*S,9a*S**)-3-(3-Methoxybenzyl)-9a-methyl-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V-32).** The reaction of **(±)-V-19** (67 mg, 0.25 mmol) with 3-chloroanisole (37 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 55 mg (75%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 10:1 mixture of diastereomers. The product was isolated as a >20:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR data were identical to those reported above for (+)-**V-32**.



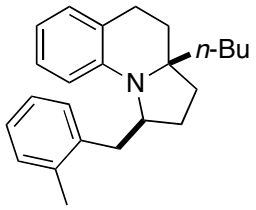
(±)-(3*S,9a*S**)-3-(Isoquinolin-1-ylmethyl)-9a-methyl-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (V-31).** The reaction of **V-19** (67 mg, 0.25 mmol) with 1-

chloroisoquinoline (49 mg, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (3.7 mg, 0.010 mmol) to afford 38 mg (47%) of the title compound as a bright yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 5:1 mixture of diastereomers. The product was isolated as a 14:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1 H), 8.05–8.02 (m, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.74–7.70 (m, 1 H), 7.53–7.51 (m, 1 H), 7.47 (dd, *J* = 2.0, 13.2 Hz, 1 H), 6.97 (d, *J* = 7.1 Hz, 1 H), 6.81–6.78 (m, 1 H), 6.65–6.61 (m, 1 H), 5.84 (d, *J* = 7.8 Hz, 1 H), 3.85– 3.80 (m, 1 H), 3.29 (dd, *J* = 1.7, 6.8 Hz, 2 H)), 3.11 (d, *J* = 15.9 Hz, 1 H), 2.86 (d, *J* = 15.9 Hz, 1 H), 2.23–2.16 (m, 1 H), 2.00–1.91 (m, 1 H), 1.78–1.74 (m, 1 H), 1.66–1.59 (m, 2 H), 1.39 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 155.0, 147.9, 136.0, 129.2, 128.95, 128.93, 127.6, 127.4, 126.9, 125.8, 124.4, 123.2, 119.0, 110.3, 72.3, 66.7, 48.4, 42.5, 37.0, 32.0, 28.2; IR (film) 2957, 1600 cm^{-1}. MS (ESI) 315.1859 (315.1856 calcd for $C_{22}H_{22}N_2$, M + H^+).



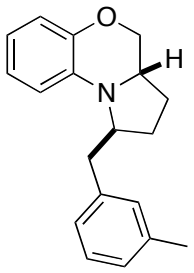
(±)-(1*S,3a*S**)-3a-Butyl-1-(pyridin-3-ylmethyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (V-37).** The reaction of **V-22** (81 mg, 0.25 mmol) with 3-chloropyridine (29 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol) and $PCy_3{\cdot}HBF_4$ (3.7 mg, 0.010 mmol) to afford 38 mg (47%) of the title compound as a red solid, mp 76–85 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 7:1 mixture of

diastereomers. The product was isolated as a 10:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56–8.53 (m, 1 H), 8.49 (dd, *J* = 1.5, 6.3 Hz, 1 H), 7.58 (dt, *J* = 7.7, 9.5 Hz, 1 H), 7.26–7.22 (m, 1 H), 7.11–7.07 (m, 1 H), 7.04–7.02 (m, 1 H), 6.63–6.57 (m, 2 H), 3.89–2.83 (m, 1 H), 3.25 (dd, *J* = 3.9, 11.8 Hz, 1 H), 2.83–2.75 (m, 1 H), 2.72–2.66 (m, 1 H), 2.64–2.59 (m, 1 H), 2.12–1.92 (m, 3 H), 1.80–1.72 (m, 1 H), 1.69–1.54 (m, 2 H), 1.34–1.14 (m, 6 H), 0.92–0.88 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 147.8, 144.0, 136.7, 134.8, 129.1, 127.0, 123.4, 121.3, 115.3, 111.5; IR (film) 2928 cm^{-1}. MS (ESI) 321.2326 (321.2325 calcd for $C_{22}H_{28}N_2$, M + H^+).



(±)-(1*S,3a*S**)-3a-Butyl-1-(2-methylbenzyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (V-38).** The reaction of **V-22** (81 mg, 0.25 mmol) with 2-chlorotoluene (35 μL, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 66 mg (79%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 12:1 mixture of diastereomers. The product was isolated as an 11:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.24 (m, 1 H), 7.21–7.15 (m, 3 H), 7.11–7.01 (m, 2 H), 6.64–6.58 (m, 2 H), 4.00–3.94 (m, 1 H), 2.26 (dd, *J* = 4.0, 14.5 Hz, 1 H), 2.85–2.77 (m), 2.72 (dd, *J* = 10.0, 14.0 Hz, 1 H), 2.65–2.59 (m, 1 H), 2.44 (s, 3

H), 2.15–2.07 (m, 1 H), 2.00–1.95 (m, 1 H), 1.94–1.86 (m, 1 H), 1.80–1.71 (m, 2 H), 1.68–1.61 (m, 1 H), 1.38–1.19 (m, 7 H), 0.94–0.90 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 138.0, 136.4, 130.3, 129.9, 129.1, 126.9, 126.2, 125.9, 121.0, 115.1, 112.3, 63.1, 63.0, 39.3, 38.8, 36.3, 28.1, 27.9, 26.7, 24.6, 23.4, 20.3, 14.2; IR (film) 2927 cm^{-1}. MS (EI) 333.2459 (333.2457 calcd for $C_{24}H_{31}N$, M^+).

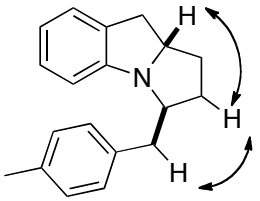


(±)-(1*S,3a*S**)-1-(3-Methylbenzyl)-2,3,3a,4-tetrahydro-1*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]oxazine (V-38).** The reaction of **V-13** (68 mg, 0.25 mmol) with 3-chlorotoluene (36 μL, 38 mg, 0.30 mmol) was conducted according to General Procedure 5 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and Cy_4DPE-Phos (5.6 mg, 0.010 mmol) to afford 24 mg (35%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed a 5:1 mixture of diastereomers. The product was isolated as a 15:1 mixture of diastereomers; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.17 (m, 1 H), 7.08–7.02 (m, 3 H), 6.90–6.85 (m, 2 H), 6.70 (dd, *J* = 1.5, 7.9 Hz, 1 H), 6.63–6.58 (m, 1 H), 4.27 (dd, *J* = 3.9, 10.3, 1 H), 4.05–3.90 (m, 1 H), 3.65–3.58 (m, 1 H), 3.35 (t, *J* = 10.0 Hz, 1 H), 3.11 (dd, *J* = 4.0, 13.6 Hz, 1 H), 2.66 (dd, *J* = 8.8, 13.3 Hz, 1 H), 2.33 (s, 3 H), 2.04–1.96 (m, 1 H), 1.95–1.87 (m, 1 H), 1.80–1.73 (m, 1 H), 1.50–1.43 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 138.8, 138.0, 134.4, 130.3, 128.3, 127.0, 126.5, 122.0, 116.3, 112.2,

67.5, 62.8, 55.2, 40.4, 28.4, 26.7, 21.4 (one signal missing due to incidental equivalence); IR (film) 2920, 1500 cm^{-1}. MS (EI) 279.1616 (279.1623 calcd for $C_{19}H_{21}NO$, M^+).

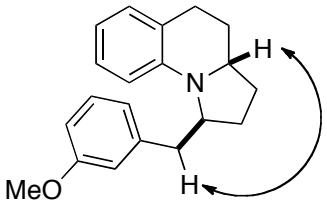
5.6.3 Assignment of Stereochemistry

The relative stereochemistry of **V-27** was determined based on the nOe signals depicted below.



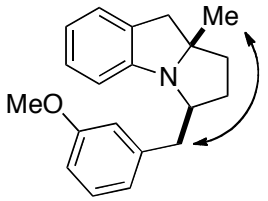
The stereochemistry of **V-28–30** were assigned based on analogy to the above molecule.

The relative stereochemistry of **V-33** was determined based on the nOe signals depicted below.



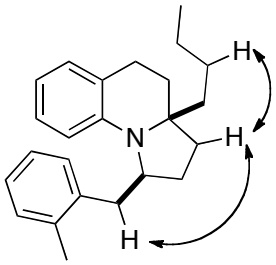
The stereochemistry of **V-23**, **V-34**, and **V-35** were assigned based on analogy to the above molecule.

The relative stereochemistry of **V-32** was determined based on the nOe signals depicted below.



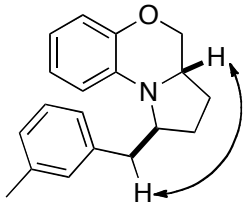
The stereochemistry of **V-31** was assigned based on analogy to the above molecule.

The relative stereochemistry of **V-36** was determined based on the nOe signals depicted below.



The stereochemistry of **V-37** was assigned based on analogy to the above molecule.

The relative stereochemistry of **V-38** was determined based on the nOe signals depicted below.



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[1] Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206.

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[3] (a) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906–13907. (b) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575–2578.

[4] Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron*, **1999**, *55*, 8883–8904.

[5] See Experimental Section for details of Mosher amide analysis.

[6] BINAP = (1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine); dppf = 1,1′-Bis(diphenylphosphino)ferrocene; DPE-Phos = Bis[(2-diphenylphosphino)phenyl] ether

[7] (a) Shekhar, S. Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584–3591 and references cited therein. (b) Hartwig, J. F. *Synlett* **1997**, 329–340.

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[10] Small differences in enantiopurity between substrates and products are attributed to use of Mosher amide NMR analysis for substrates and HPLC analysis for products.

[11] 2-chlorothiophene and 3-chlorothiophene were not viable coupling partners under these reaction conditions.

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Chapter 6

Importance of Isoxazolidines and Methods for Their Synthesis

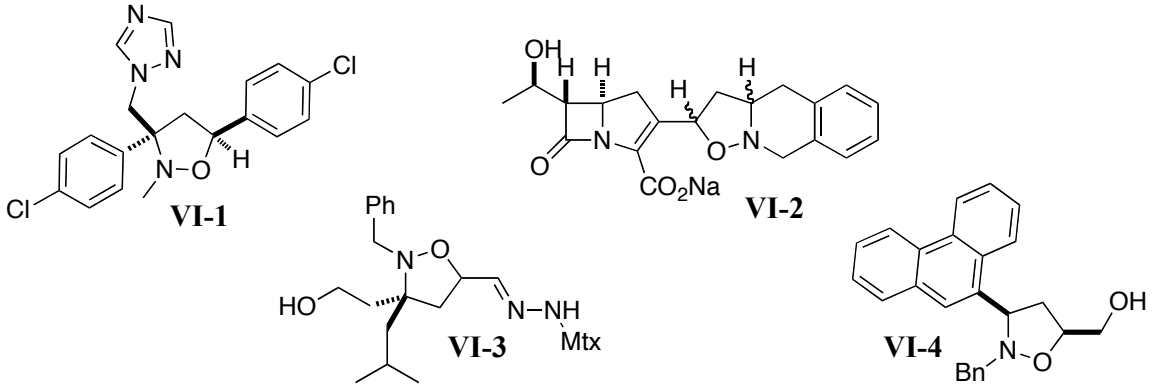
6.1 Importance of Isoxazolidines

Isoxazolidines are important molecules for a couple reasons. First, many molecules in this family display biological activity. Second, isoxazolidines are useful synthetic intermediates towards the synthesis of 1,3-amino alcohols, as well as a variety of bicyclic heterocycles.

6.1.1 Biological Activity of Isoxazolidines

Isoxazolidines exhibit a broad range of biological activity, such as antiviral (**VI-1**) and antibacterial (**VI-2**) (Figure 6-1).[1,2] The first small molecule transcription activator also is an isoxazolidine (**VI-3**).[3] In addition **VI-4** has been shown to cause cell death in MOLT-3 leukemia cells.[4] As these representative examples demonstrate, isoxazolidines have an influence on a wide scope of biological processes.

Figure 6-1: Biologically Active Isoxazolidines

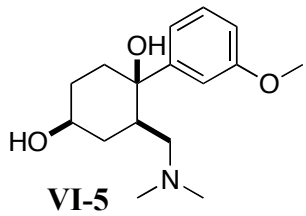


6.1.2 Synthetic Uses of Isoxazolidines

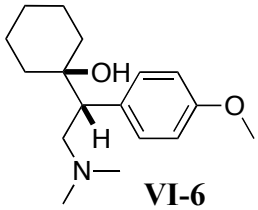
Along with having important biological properties, isoxazolidines are also important synthetic intermediates. The N-O bond can be cleaved to afford a 1,3-amino-alcohol.[5] Additionally, these molecules have been used as synthetic intermediates in the synthesis of a variety of naturally occurring alkaloids.[6]

1,3-amino alcohols are interesting for a few reasons, including their biological activity; they are also used as chiral ligands. For example, **VI-5** has been shown to have analgesic properties (Figure 6-2).[7] The antidepressant venlafaxine, **VI-6**, is also a 1,3-amino alcohol.[8] The borane complex **VI-7** with a chiral 1,3-amino alcohol ligand is used for the enantioselective reduction of ketones (eq 1).[9]

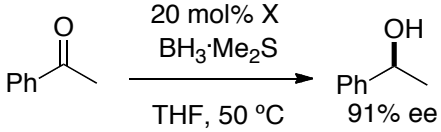
Figure 6-2: Biologically Active 1,3-Amino Alcohols

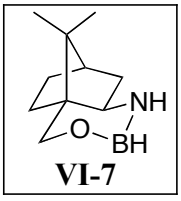


VI-5



VI-6





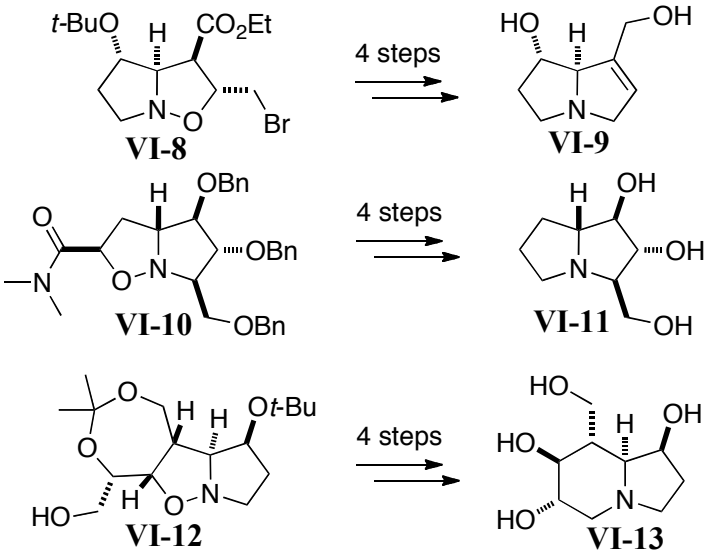
VI-7

(1)

Isoxazolidines have been used as key synthetic intermediates in the synthesis of pyrrolizidine and indolizidine alkaloids (Scheme 6-1). Various polyhydroxylated pyrrolizidine and indolizidine alkaloids inhibit glycosidases and have thus been studied as antitumor, antibacterial, antiviral, and anti-inflammatory agents.[6] Many of these alkaloids and their unnatural epimers have been synthesized for these studies. For example, (+)-heliotridine (**VI-9**) was synthesized in four steps from (**VI-8**).[10]

Hyacinthacine A_2 (**VI-11**) can be synthesized from isoxazolidine **VI-10** in four steps.[11] Additionally, the indolizidine 8-homocastanospermine (**VI-13**) can be synthesized from isoxazolidine **VI-12**.[12]

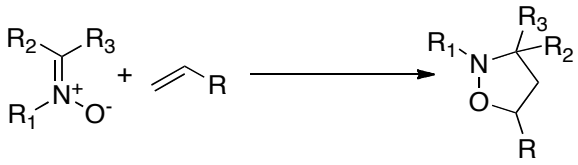
Scheme 6-1: Synthesis of Bis-Fused Alkaloids from Isoxazolidine Intermediates



6.2 Methods for the Synthesis of Isoxazolidines

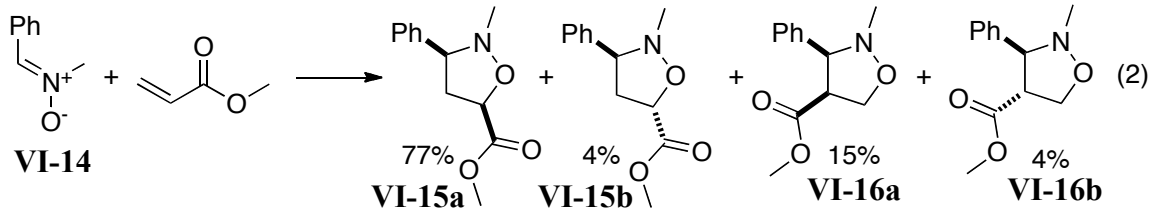
The most common method for the synthesis of isoxazolidines is 1,3-dipolar cycloaddition of nitrones with alkenes (Scheme 6-2).[13] However, other methods have also been developed as the dipolar cycloaddition unfortunately suffers from several limitations. These methods include radical cyclization, as well as palladium catalyzed methods. In addition, isoxazolines can be derivatized or reduced to form isoxazolidines.

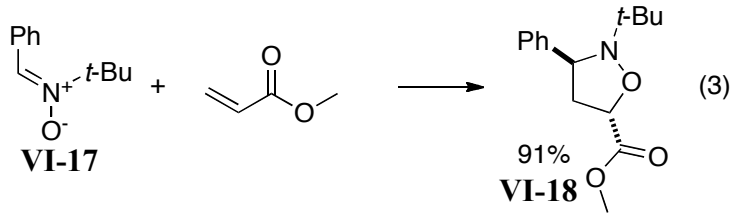
Scheme 6-2: 1,3-Dipolar Cycloaddition to Generate Isoxazolidines



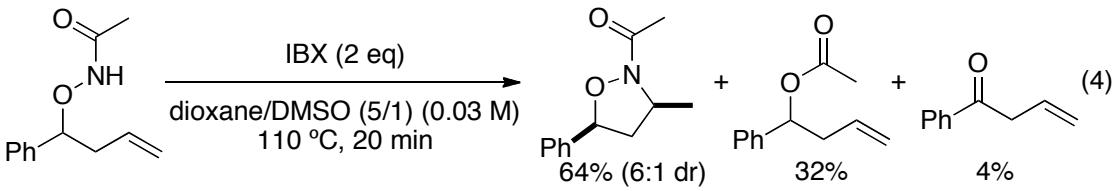
The 1,3-dipolar cycloaddition of nitrones with alkenes to generate isoxazolidines was first reported circa 1960 by several groups.[14] Since this time, this reaction has been

well developed to include Lewis acid mediated reactions, as well as enantioselective variations of this reaction. However, olefin electronics and the steric bulk of both reaction components can lead to mixtures of regioisomers.[13] In addition, as a result of *E,Z* isomerization of the nitrone, the diastereoselectivity of the 1,3-dipolar cycloaddition is not always high.[13] For example, the reaction of methyl acrylate with **VI-14** leads to a mixture 4:1 mixture of regioisomers (**VI-15** and **V-16**), along with a mixture of diastereomers (eq 2).[15] In contrast, nitrone **VI-17** which has a sterically encumbered *N*-*t*-butyl substituent instead of *N*-methyl leads to one product, **VI-18**, cleanly (eq 3).[15] As this example demonstrates, this method of isoxazolidine generation is not without limitations.

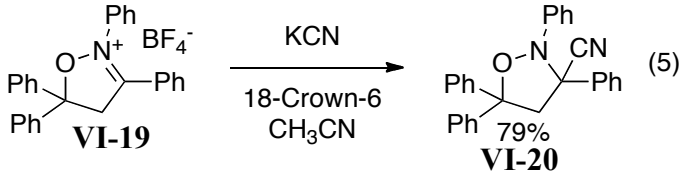


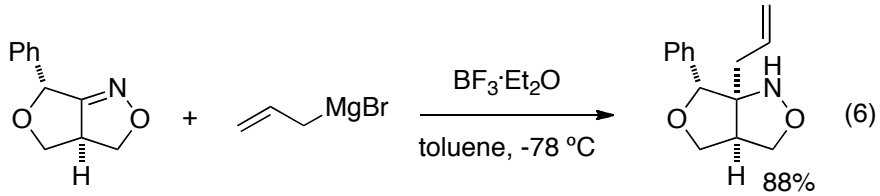


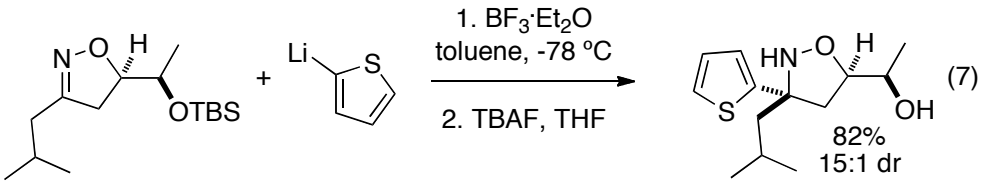
In order to overcome the limitations of regio- and diastereoselectivity in the 1,3-dipolar cycloaddition reaction, other methods of synthesizing isoxazolidines have been developed. One such method is the use of IBX as a radical initiator (eq 4).[16] This method also leads to a variety of side products as well, and must be run at high dilution to minimize these side reactions.

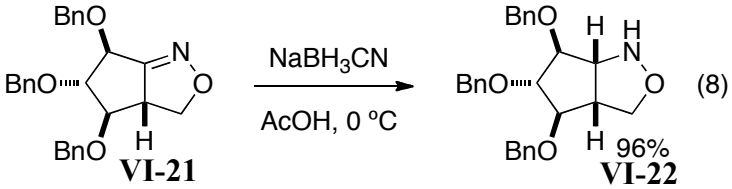


Another method for the synthesis of isoxazolidines is to functionalize Δ^2-isoxazolines. Addition of cyanide into an activated isoxazolium salt **VI-19** afforded nitrile substituted isoxazolidine **VI-20** (eq 5).[17] Activation of Δ^2-isoxazolines with $BF_3{\cdot}Et_2O$ allows for the addition of Grignard and organolithium reagents in good yield (eqs 6–7).[18,19] These methods allow for the buildup of molecular complexity. Hydride addition into Δ^2-isoxazolines leads to the reduction to the isoxazolidine, such as the sodium cyanoborohydride reduction of **VI-21** to **VI-22** (eq 8).[20]

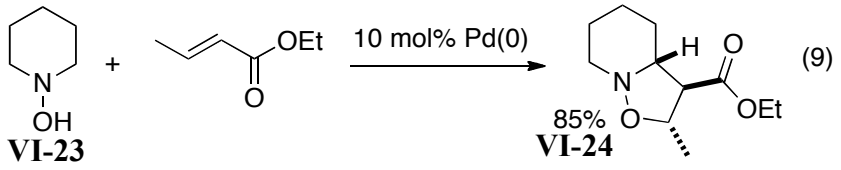








A few palladium catalyzed reactions have been developed for the synthesis of isoxazolidines, some of which have been previously discussed in Chapter 1. One non-carboamination palladium catalyzed process is related to the [3+2] cycloaddition of nitrones with alkenes. A palladium catalyst oxidizes cyclic hydroxylamines such as **VI-23** to the nitrone.[21] With an external olefin present, the cycloaddition reaction occurs to afford the isoxazolidine product, **VI-24**, in moderate to good yield (eq 9).



(9)

Lastly, a carboetherification reaction has been developed which allows for the generation of isoxazolidines from *N*-butenyl hydroxylamines. Two reports of this reaction suggest that the choice of reaction conditions has an impact on the diastereoselectivity of these reactions.[22] This reaction will be further discussed in Chapter 7.

6.3 Conclusion

Isoxazolidines are important for both their biological activity as well as their synthetic utility. Thus, many methods have been developed for their synthesis. However, a method that allows for the rapid functionalization of the side-chain is valuable for synthesizing a library of molecules. Our efforts towards this goal are discussed in Chapter 7.

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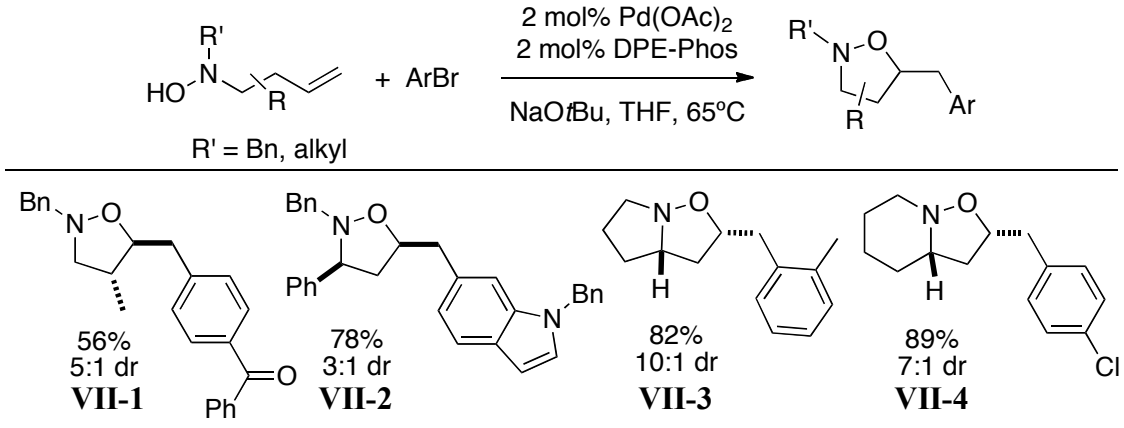
Chapter 7

Pd-Catalyzed Carboamination and Carboetherification Reactions for the Synthesis of Isoxazolidines[1]

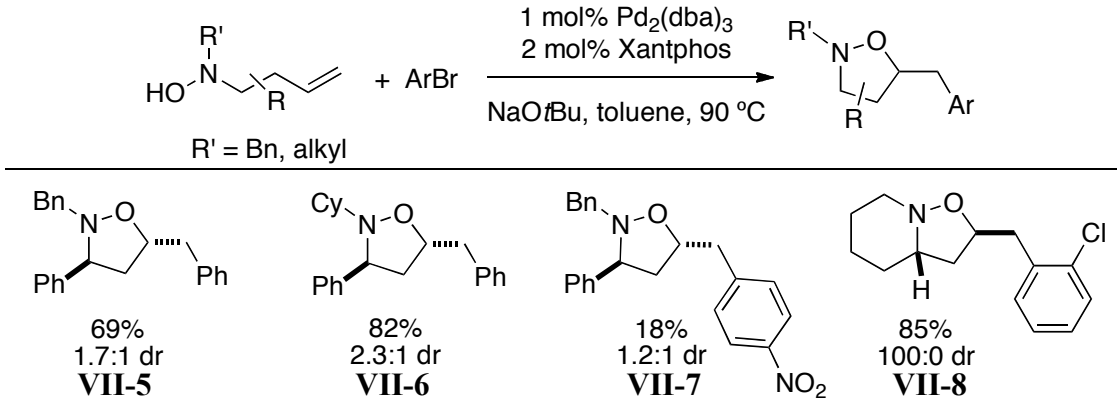
7.1 Introduction

Previously in our group, we have demonstrated that isoxazolidines can be synthesized in moderate to good stereoselectivity and yield via a carboetherification reaction.[2] This reaction coupled a *N*-butenyl hydroxylamine with an aryl bromide coupling partner to afford 3,5-*cis* or 4,5-*trans* isoxazolidines (Scheme 7-1). Shortly after this was reported in the literature, Chen and coworkers reported a related set of reactions which yield 3,5-*trans* isoxazolidines as the major stereoisomer (Scheme 7-2).[3]

Scheme 7-1: Previous Carboetherification Synthesis of Isoxazolidines with Representative Examples

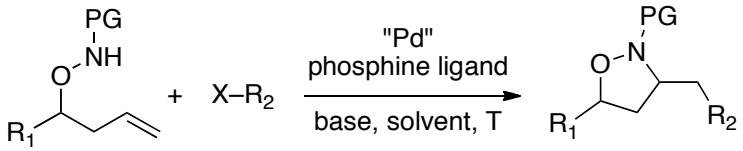


Scheme 7-2: Representative Example of Results from Chen and Coworkers



With these initial studies in hand, we sought to extend the scope of the palladium catalyzed synthesis of isoxazolidines. One extension we envisioned of this methodology was to use alkenyl bromides as coupling partners. In addition, we sought to develop a carboamination route to isoxazolidines (Scheme 7-3).

Scheme 7-3: General Carboamination Route to Isoxazolidines



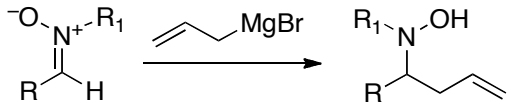
7.2 Extension of Carboetherification Methodology

The use of alkenyl halides as coupling partners would greatly expand the utility of isoxazolidine forming carboetherification reactions, as this allows for the installation of a side chain which can be further functionalized. Additionally, the alkenyl group can be hydrogenated to generate an aliphatic side chain. Thus, we sought to find conditions which allowed for alkenyl halide use in the generation of isoxazolidines from *N*-butenyl hydroxylamines.

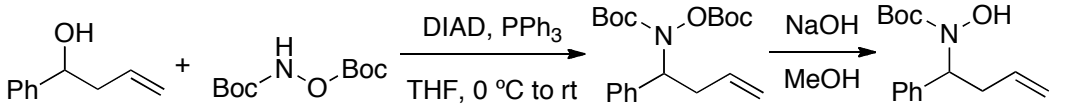
Substrates for the for the carboetherification reaction were generated in a straightforward manner. *N*-Alkyl and *N*-phenyl substrates were synthesized by addition

of allyl magnesium bromide into the corresponding nitrone (Scheme 7-4). The *N*-Boc substrate **VII-12** was synthesized via a Mitsunobu reaction with **VII-9** and **VII-10**, followed by cleavage of the *O*-Boc substituent **VII-11** with aqueous sodium hydroxide (Scheme 7-5).

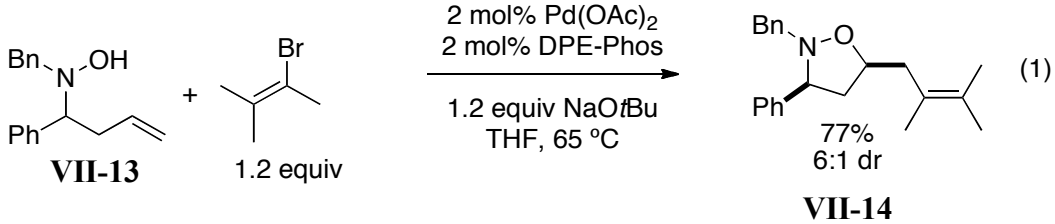
Scheme 7-4: Synthesis of *N*-butenyl Hydroxylamines

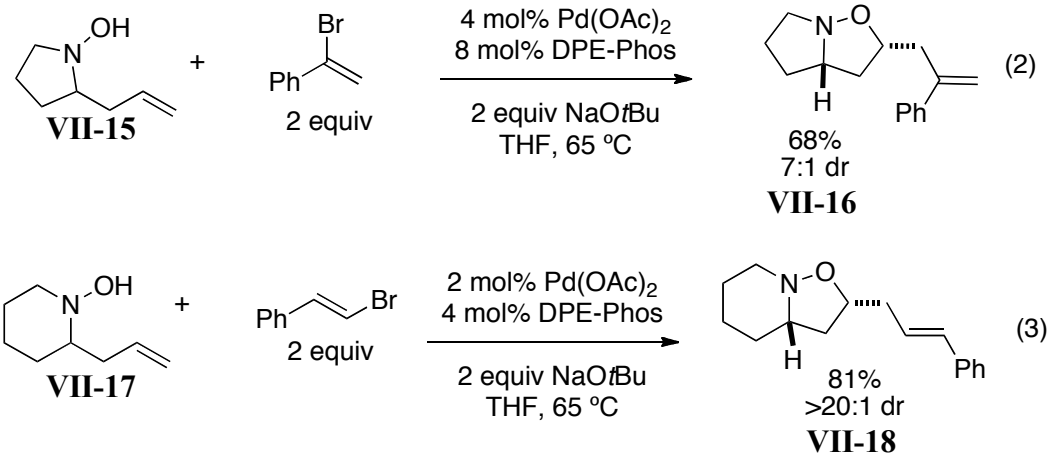


Scheme 7-5: Synthesis of VII-12



Conditions previously developed for use with aryl bromides (Scheme 1) needed to be optimized for successful use of alkenyl halides as coupling partners. As shown in eqs. 1–3, the phosphine ligand DPE-Phos was used with palladium acetate to generate the active catalyst. With 2-bromo-3-methyl-2-butene, no further optimization from the standard conditions was required to generate **VII-14** (eq 1). However, the palladium/ligand ratio had to be raised from 1:1 to 1:2 for both α- and β-bromostyrene (eq 2 and 3). Additionally, the catalyst loading had to increased for the reaction of **VII-15** α-bromostyrene to achieve full conversion (eq 2). All of the reactions did afford the desired products in good yield and moderate to good diastereoselectivity.

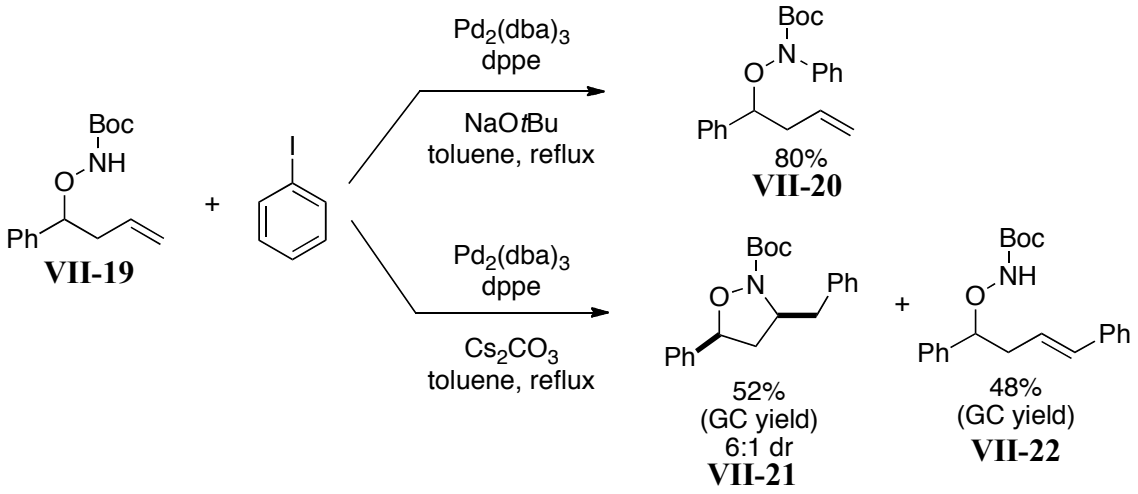




7.3 Development of a Carboamination Route to Isoxazolidines

We envisioned developing a complementary route to isoxazolidines via a carboamination of *O*-butenyl hydroxylamines where the nitrogen would be the cyclizing atom (Scheme 7-3). As we considered this approach, we noted a paper by Dongol and coworkers which described the transformation we had envisioned.[4] Dongol and coworkers reported a difference in chemoselectivity when NaO*t*-Bu or Cs_2CO_3 were employed as the base (Scheme 7-6). We were surprised by this report, as our proposed catalytic cycle predicts that the base should not influence the chemoselectivity of the reaction (see Chapter 1). Thus, we sought to reproduce their results. However, our attempts were unsuccessful (see below, Scheme 7-8). Thus, we sought to further develop this reaction.

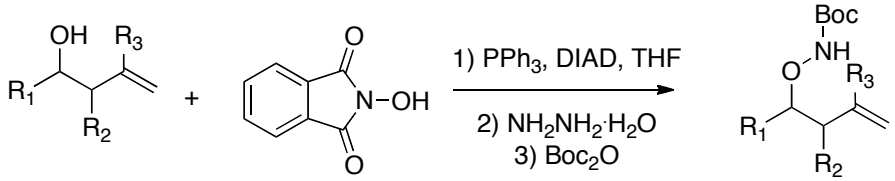
Scheme 7-6: Chemoselectivity Reported by Dongol in Reference 4



7.3.1 Substrate Synthesis

The required Boc protected hydroxylamine substrates were synthesized in three steps from the corresponding homoallylic alcohols. A Mitsunobu reaction followed by a protecting group exchange generated the desired substrates efficiently in good yield (Scheme 7-7). The material was carried crude through the first two steps, with only one chromatographic purification required after the last step to afford pure substrates.

Scheme 7-7: Synthesis of *N*-Boc-*O*-butenyl Hydroxylamines

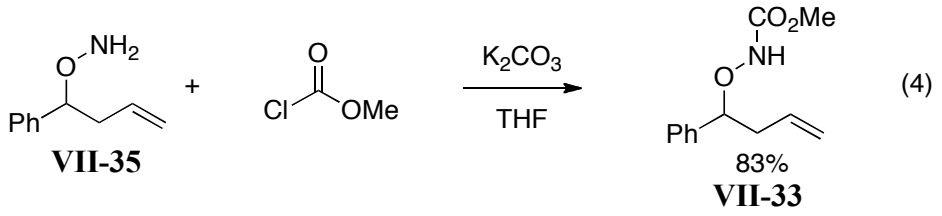


VII-9: R_1=Ph, R_2=H, R_3=H
VII-23: R_1=Me, R_2=H, R_3=H
VII-23: R_1=*p*-MeOPh, R_2=H, R_3=H
VII-24: R_1=CH_2OBn, R_2=H, R_3=H
VII-26: R_1=H, R_2=Ph, R_3=H
VII-27: R_1=Ph, R_2=H, R_3=Me

VII-19: 54%, R_1=Ph, R_2=H, R_3=H
VII-28: 83%, R_1=Me, R_2=H, R_3=H
VII-29: 45%, R_1=*p*-MeOPh, R_2=H, R_3=H
VII-30: 77%, R_1=CH_2OBn, R_2=H, R_3=H
VII-31: 81%, R_1=H, R_2=Ph, R_3=H
VII-32: 85%, R_1=Ph, R_2=H, R_3=Me

Substrates with substituents other than Boc on the cyclizing nitrogen were also synthesized. The methyl carbamate (**VII-33**, eq 4) and benzyl (**VII-34**, eq 5) protected

substrates were synthesized from the free hydroxylamine (**VII-35**). The *N*-phenyl substrate (**VII-36**) was synthesized via a Mitsunobu reaction of the corresponding homoallylic alcohol and *N*-Boc-*N*-phenyl hydroxylamine. The Boc group was then cleaved using trifluoroacetic acid to afford **VII-36** (eq 6).



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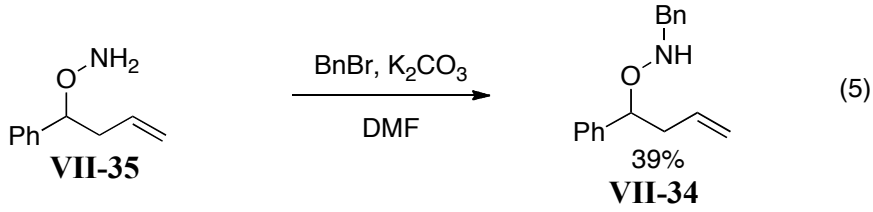

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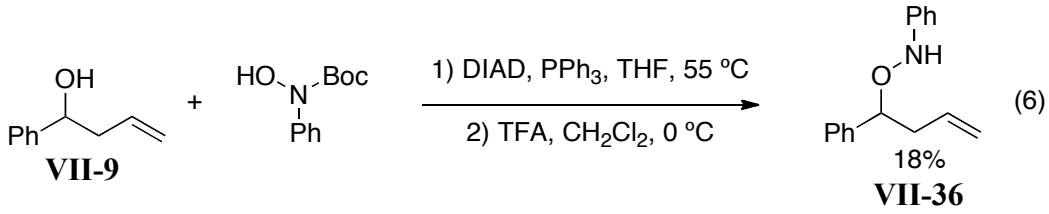
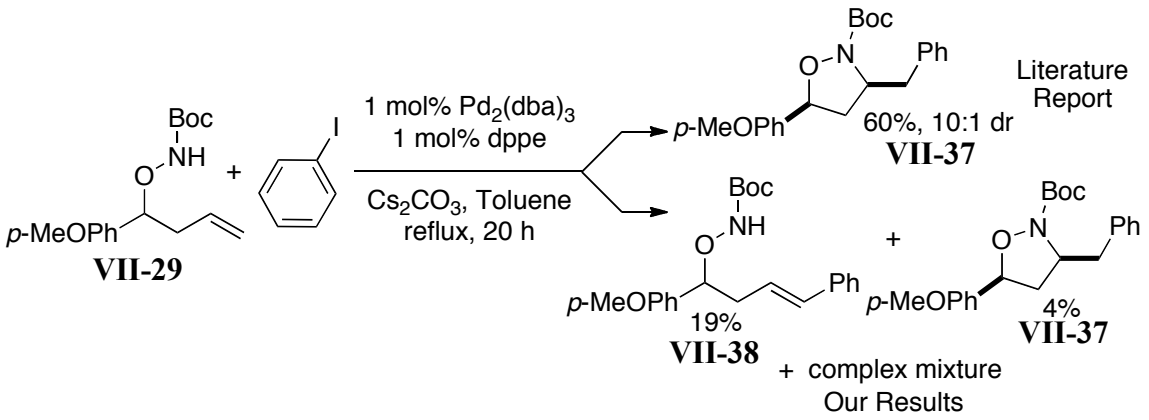


(6)

7.3.2 Attempts to Reproduce of Literature Results

To begin our investigation, we sought to reproduce the results of Dongol and coworkers (Scheme 7-8).[4] As only one reaction was reported with a yield, we opted to look at this example from their report. In our hands, we were unable to obtain a significant amount of the isoxazolidine product, but instead obtained Heck product **VII-38** as the major product. These attempts at reproducing the literature results were conducted by both myself and Natalie Giampietro.

Scheme 7-8: Our Attempt to Reproduce of Dongol's Results



7.3.3 Ligand Effects

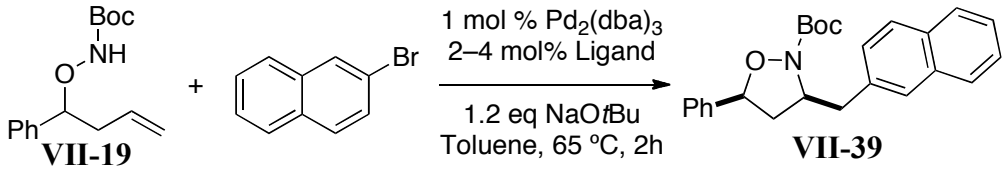
Being unable to reproduce the literature conditions, we sought to develop a carboamination reaction which would be efficient for the synthesis of isoxazolidines. To begin this effort, a variety of phosphine ligands were screened. Interestingly, ligand choice had an observable impact on the diastereomeric ratio of the isoxazolidine products (Table 7-1). This result was unprecedented in palladium-catalyzed carboamination reactions.

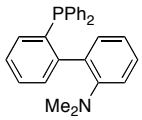
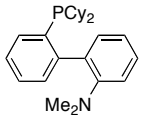
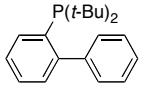
The influence on the diastereoselectivity of the reaction relative to the ratio of phosphine to palladium as well as reaction progress were investigated with three ligands (PCy_3, P*t*Bu_3, and P(*o*-tol)$_3$). A ratio of 1:1, 2:1, and 3:1 phosphine to palladium had no effect on the diastereoselectivity of the reaction. Additionally, the diastereoselectivity did not change relative to reaction progress, as determined by ^{1}H NMR.

Both the steric and electronic properties of the ligands had an effect on the diastereoselectivity and reactivity of the carboamination reaction. Bidentate ligands with a small bite angle ($\leq 93^\circ$) were unreactive at 65 ºC and required heating at 110 ºC in order to determine diastereocontrol (Table 7-1, entries 1 and 2).[5] As seen in entries 1–6, increased bite angle of bidentate ligands lead to increased diastereoselectivity (Table 7-

1). Relatively electron poor monodentate ligands lead to poor stereocontrol (Table 7-1, entries 7 and 8). With electron rich monodentate ligands, increased cone angle led to increased stereocontrol (Table 7-1, entries 9–12). Buchwald's hemilabile *o*-biphenyl derived ligands also followed the tread of increased steric bulk and electron density resulting in increased diastereoselectivity (Table 7-1, entries 13–15).

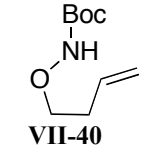
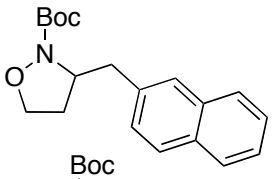
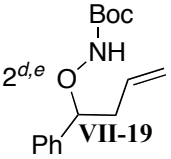
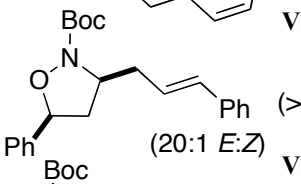
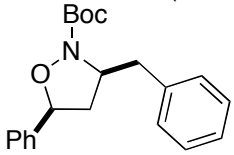
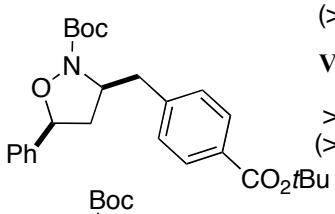
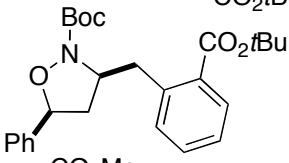
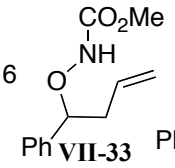
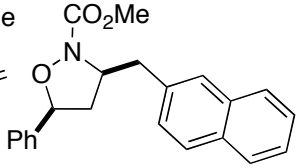
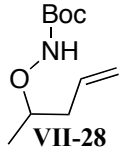
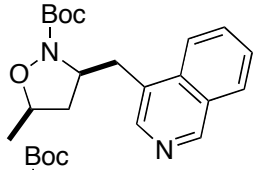
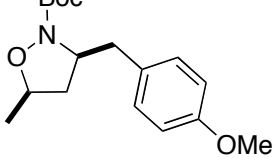
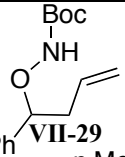
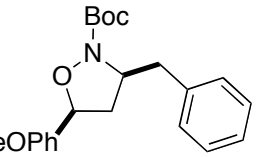
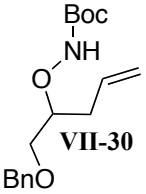
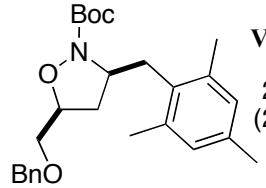
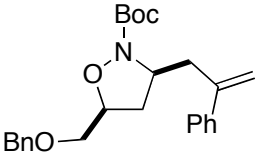
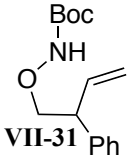
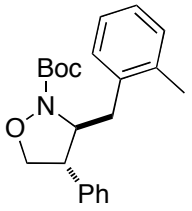
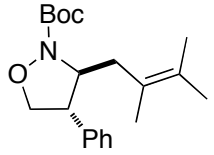
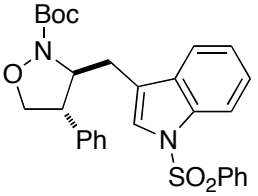
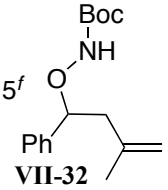
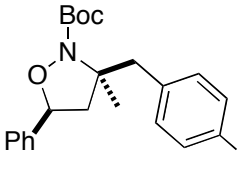
Table 7-1: Ligand Effect on Diastereomeric Ratio[a]



entry	ligand	**VII-19** (%)[b]	**VII-39** (%)[b]	dr	Bite/Cone angle[h]
1	dppe	0	22[d]	2:1[c]	86
2	(±)-BINAP	0	36[d]	3:1[c]	93
3	dppf	34	57	9:1	99
4	Dppf-*i*Pr	8	77[d]	8:1	103
5	DPE-Phos	9	84	13:1	104
6	Xantphos	41	57	12:1	108
7	PPh_3	43	5[d]	2:1	145
8	P(*o*-tol)$_3$	65	22[d]	2:1	194
9	PCy_3•HBF_4	0	32[d]	2:1[e]	170
10	PCy_2(*t*Bu)	18	73	2:1	174
11	PCy(*t*Bu)$_2$	14	82	7:1	178
12	P*t*Bu$_3$•HBF_4	3	88[d] (87)[f]	28:1	182
13		7	87[d]	7:1	
14		0	84	11:1	
15		45	28[g]	13:1	

[a] Conditions: 1.0 equiv **VII-18**, 1.2 equiv 2-bromonaphthalene, 1.2 equiv NaO*t*Bu, 1 mol% $Pd_2(dba)_3$, 2 mol% ligand (chelating bis-phosphines) or 4 mol% ligand (monodentate phosphines), toluene (0.25 M), 65 °C, 2 h. [b] ^{1}H NMR yield against an internal standard (average of two experiments). Incomplete mass balance is attributed to small errors in NMR integration unless otherwise noted. [c] The reaction was conducted at 110 °C. [d] A product resulting from Heck arylation of the substrate was also formed. [e] The reaction was conducted for ca. 45 h, as very low conversion (< 10%) was observed after 2 h. [f] Isolated yield (average of two experiments). [g] An unidentified side product was also formed in ca. 13% yield (NMR). [h] Bidentate ligands have bite angles reported; monodentate ligands have cone angles listed.

Table 7-2: Scope of Carboamination[a]

entry	substrate	product	yield (%)[b] dr[c]
1	 **VII-40**		**VII-41** 59 –
2[d,e]	 **VII-19**	 (20:1 *E*:*Z*)	**VII-42** 54 35:1 (>20:1)
3	**VII-19**		**VII-21** X = I: 61 >20:1 (>20:1) X = Br: 68 >20:1 (>20:1)
4	**VII-19**		**VII-43** 78 >20:1 (>20:1)
5	**VII-19**		**VII-44** 44 8:1 (6:1)
6	 **VII-33**		**VII-45** 84 >20:1 (>20:1)
7	 **VII-28**		**VII-46** 68 20:1 (17:1)
8	**VII-28**		**VII-47** 68 >20:1 (>20:1)
9	 *p*-MeOPh **VII-29**	 *p*-MeOPh	**VII-37** 75 >20:1 (>20:1)
10	 BnO **VII-30**	 BnO	**VII-48** 74 20:1 (20:1)
11	**VII-30**	 BnO Ph	**VII-49** 55 >20:1 (17:1)
12	 **VII-31** Ph	 Ph	**VII-50** 71 14:1 (13:1)
13	**VII-31**	 Ph	**VII-51** 62 >20:1 (>20:1)
14[d]	**VII-31**	 Ph SO_2Ph	**VII-52** 67 5:1 (5:1)
15[f]	 Ph **VII-32**	 Ph Ph	**VII-53** 58 >20:1 (4:1)

[a] Conditions: 1.0 equiv substrate, 1.2 equiv R–Br, 1.2 equiv NaO*t*-Bu, 1 mol% $Pd_2(dba)_3$, 4 mol% $PtBu_3$•HBF4, toluene (0.25 M), 65 °C. [b] Average isolated yields obtained from two or more experiments. [c] Diastereomeric ratio of the isolated material. Numbers in parentheses represent diastereomeric ratios observed in crude reaction mixtures. [d] The reaction was conducted using 1.5 mol% $Pd_2(dba)_3$ and 9 mol% P*t*Bu_3•HBF_4 at 90 °C. [e] The reaction was conducted using 2.0 equiv of β-bromostyrene and NaO*t*-Bu. [f] This reaction conducted by Mike Hay.

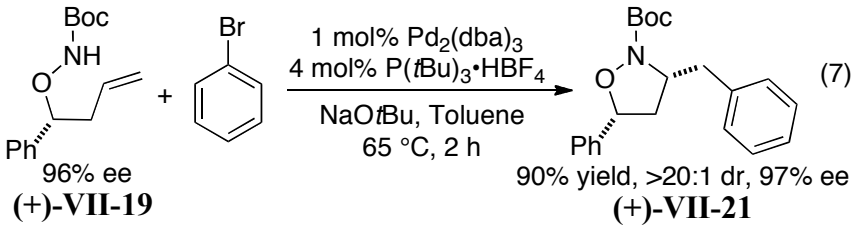
7.3.4 Scope of Isoxazolidine Synthesis via Carboamination

The reaction scope with respect to coupling partner and substrate was examined for the generation of isoxazolidines via a carboamination reaction (Table 7-2). Electron-rich, electron-neutral, electron-poor, sterically hindered and heterocyclic aryl bromides were suitable coupling partners. Alkenyl bromides were also effective coupling partners. Additionally, little difference was observed between the use of iodo- or bromobenzene as the coupling partner (Table 7-2, entry 3). Substrates protected as either methyl or *tert*-butyl carbamates afford 3,5-*cis* isoxazolidines in good yield and stereocontrol.

This method generates 3,5-*cis* and 4,5-*trans* isoxazolidines in good diastereoselectivity, with a few notable exceptions. Use of *tert*-butyl 2-bromobenzoate leads to both diminished yield and stereocontrol (Table 7-2, entry 5). The decrease in stereocontrol may be due to the carbonyl coordinating to palladium and thus changing the transition state conformation. The low yield was due to competing Heck arylation. Additionally, the use of 1-benzenesulfonyl-3-bromo-indole lead to lower stereocontrol, although the origin of this result is not well understood (Table 7-2, entry 14). Finally, the use of a substrate bearing a *gem*-disubstituted olefin also lead to low stereocontrol (Table 7-2, entry 15). However, the stereoisomers were separable by flash chromatography. All other attempts to use disubstituted olefins were unsuccessful for the generation of isoxazolidines.

In order to evaluate if the enantiopurity of the substrate was retained in the product of the palladium catalyzed carboamination, an enantiopure substrate was synthesized. The necessary homoallylic alcohol was resolved using lypase. This enantioenriched alcohol was then converted to the hydroxylamine substrate in the same

manner as the racemic substrate (Scheme 7-7). After generation of the isoxazolidine product, the enantiopurity was the same as the hydroxylamine substrate (eq 7). Thus, the palladium catalyzed reaction does not lead to the erosion of enantiopurity.



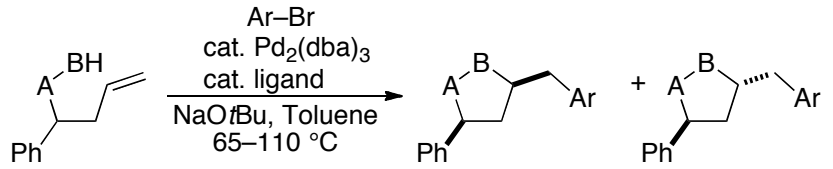
7.4 Carboetherification versus Carboamination

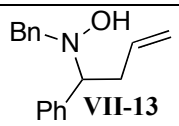
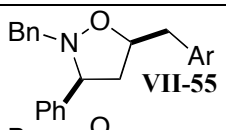
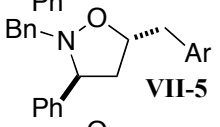
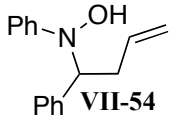
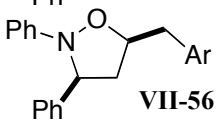
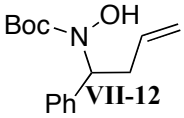
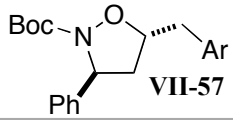
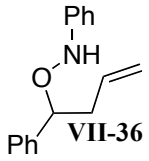
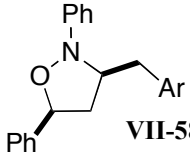
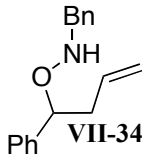
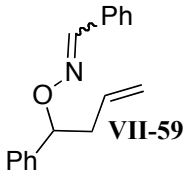
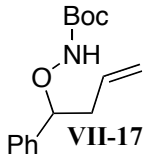
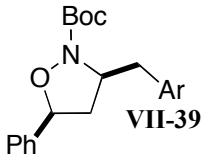
With the scope of carboamination investigated, we noted that the stereocontrol was better with this system than with carboetherification. We wanted to understand the origin of this difference. However, the nitrogen substituent was different in the two systems. Additionally, the optimal phosphine ligand for each process was different. Thus, in order to eliminate extra variables, it was necessary to synthesize both the *N*- and the *O*-butenyl hydroxylamines which had the same nitrogen substituent (Boc, Ph, and Bn). With these substrates in hand, we conducted experiments using the same phosphine ligands (Table 7-3). These studies were conducted in conjunction with Natalie Giampietro; studies by her are identified in the footnotes of Table 7-3.

P(*t*-Bu)$_3$ was not an efficient ligand for the carboetherification reaction. However, DPE-Phos and Xantphos were found to be suitable ligands for most of the desired transformation and thus were used for this study. Benzyl was not tolerated as a nitrogen protecting group in the carboamination reaction, as β-hydride elimination generated an oxime ether, thus preventing cyclization (Table 7-3, entries 9 and 10).

Comparison of the various examples leads to a few trends. In all cases with *N*-phenyl, the stereoselectivity is low (Table 7-3, entries 3, 4, 7, and 8). The carboetherification with **VII-13** where the nitrogen has a benzyl protecting group also proceeds with little stereocontrol. However, with Boc as the protecting group, the stereocontrol is improved in both cyclizations (Table 7-3, entries 6, 11, and 12). Based on the results with the *N*-phenyl substituent, which all result in the 3,5-*cis* isoxazolidine stereochemistry, we concluded that the identity of the cyclizing atom (oxygen versus nitrogen) did not have an inherent influence on the stereoselectivity of the cyclization reaction. As only the carboetherification with *N*-benzyl was successful, this system could not be used as a direct comparison. As the *N*-Boc series lead to different major diastereomers, we did not draw conclusions about the nature of the heteroatom cyclization from this system.

Table 7-3: Diastereoselectivity in Carboetherification versus Carboamination



entry	ligand	substrate	major product	dr[b]	isoxazolidine yield (%)[c]
1[d]	Dpe-phos	 **VII-13**	 **VII-55**	4:1	83[f]
2[d]	Xantphos	**VII-13**	 **VII-5**	1:2	69[g]
3[e]	Dpe-phos	 **VII-54**	 **VII-56**	3:1	79[f]
4[e]	Xantphos	**VII-54**	**VII-56**	1:1	75[f]
5[d,j]	Dpe-phos	 **VII-12**	—	—	0[h]
6[d,j]	Xantphos	**VII-12**	 **VII-57**	1:7	33[h]
7[e,k]	Dpe-phos	 **VII-36**	 **VII-58**	1:1	22–46[i]
8[e,k]	Xantphos	**VII-36**	**VII-58**	2:1	38[i]
9	Dpe-phos	 **VII-34**	 **VII-59**	—	0
10	Xantphos	**VII-34**	**VII-59**	—	0
11[e]	Dpe-phos	 **VII-17**	 **VII-39**	12:1	66[f]
12[e]	Xantphos	**VII-17**	**VII-39**	12:1	71[f]

[a] Conditions: 1.0 equiv hydroxylamine, 1.2–1.4 equiv ArBr, 1.2–1.4 equiv NaO*t*Bu, toluene (0.25 M), 65 °C or 110 °C. [b] Diastereomeric ratio observed in the crude reaction mixture. [c] Isolated yield of the major

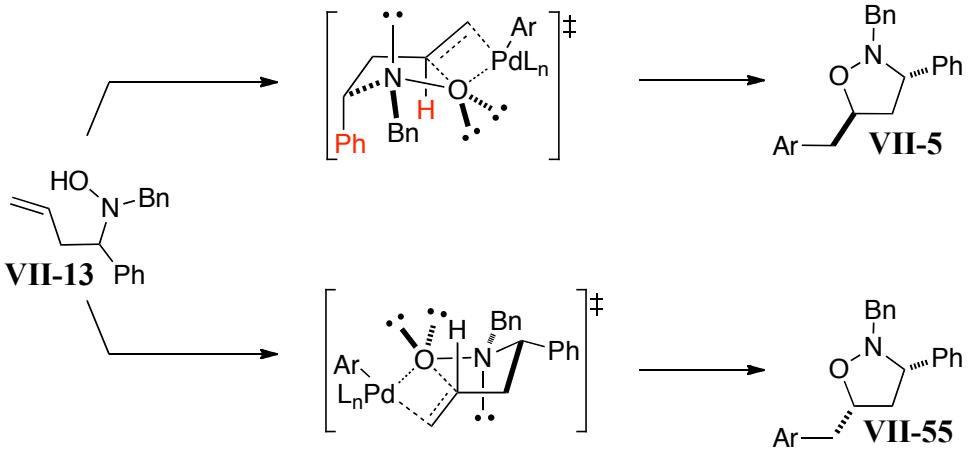
diastereomer (average of two experiments). [d] Ar = Ph. [e] Ar = 2-naphthyl. [f] Isolated dr is the same as the crude dr. [g] From reference 3; we have obtained nearly identical results. [h] A mixture of products resulting from either Heck arylation or isomerization of the starting alkene was obtained. [i] Significant amounts of products derived from substrate N–O bond cleavage were also formed.[j] These experiments were conducted by Natalie Giampietro. [k] These experiments were conducted in conjunction with Natalie Giampietro.

7.5 Discussion

7.5.1 Proposed Transition States

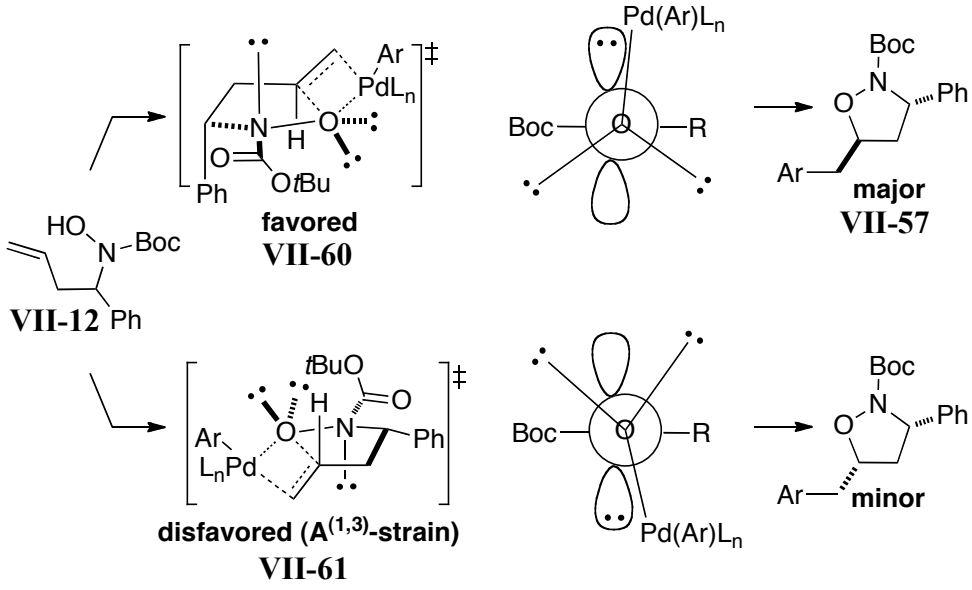
The difference between the low diastereoselectivity with benzyl or phenyl substituents as compared with the higher diastereocontrol with the Boc protecting group are likely due to stereoelectronic effects. In previous carboetherification and carboamination reactions for the formation of tetrahydrofurans and pyrrolidines, the diastereocontrol for the formation of 2,4-disubstituted products was low, as there was little energy difference between the two transition states.[6] This trend continued with the phenyl and benzyl substituted hydroxylamines in the synthesis of isoxazolidines (Scheme 7-8). In the transition state which leads to the *trans* diastereomer **VII-5**, the phenyl group is pseudo-axial, resulting in one diaxial interaction between the phenyl and the shown hydrogen (Scheme 7-9). However, this does not lead to a large energy difference between the two transition states, thus leading to the low diastereoselectivity.

Scheme 7-9: Stereodefining Transition States for Oxypalladation of VII-13



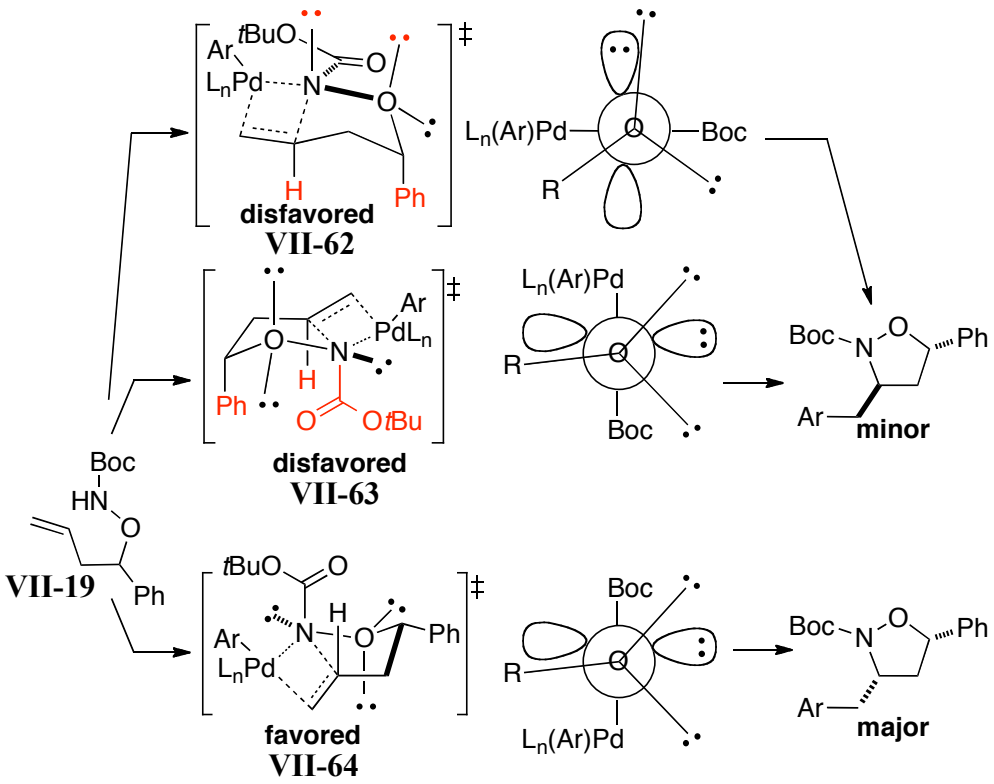
The higher stereocontrol with Boc in the carboetherification and carboamination arise from two causes. In the carboetherification reaction, the presence of the Boc group creates allylic strain with the phenyl side chain in the transition state **VII-61** leading to the *cis* substitution pattern (Scheme 7-10). Minimization of allylic strain in transition state **VII-60** leads to the formation of the 3,5-*trans* substituted isoxazolidine product **VII-57**. Similar transition states were reported in the synthesis of pyrazolidines.[7]

Scheme 7-10: Stereodefining Transition States for Oxypalladation of VII-12



The high stereocontrol in the carboamination generation of isoxazolidines with *N*-Boc-*O*-butenyl hydroxylamines is likely due to a combination of both steric and electronic effects (Scheme 7-11). Transition state **VII-62** is disfavored as there is lone pair repulsion between the lone pair on the nitrogen with one on the oxygen. This transition state also has one diaxial interaction. Transition states **VII-63** and **VII-64** have the electronic repulsions minimized. However, transition state **VII-63** has a diaxial interaction between the phenyl side chain and the Boc group, thus this transition state is disfavored for steric reasons. In contrast, this steric strain is minimized in transition state **VII-64** by allowing the phenyl side chain to be in a pseudoequatorial position. As the first two transitions states lead to the *trans* isomer and transition state **VII-64** leads to the *cis* isomer, this model is in agreement with the experimental data.

Scheme 7-11: Stereodefining Transition States for Aminopalladation of VII-19

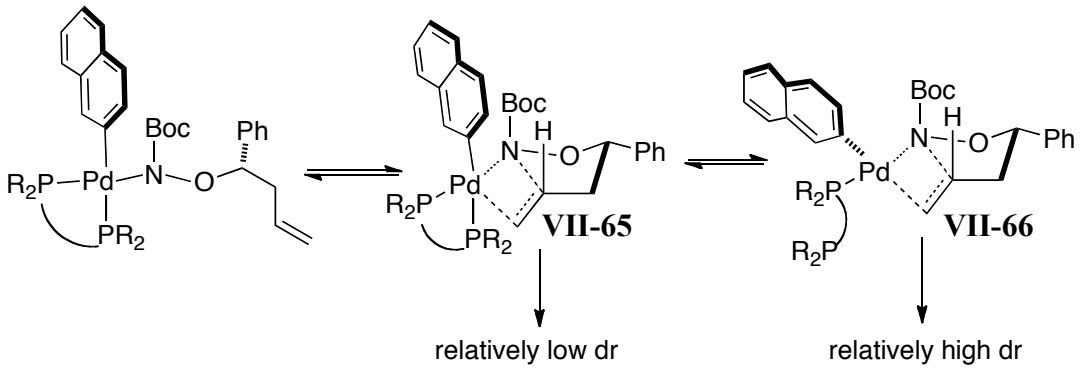


7.5.2 Ligand Effects

As discussed above, the choice of phosphine ligand has a large effect on the stereoselectivity in the carboamination reaction of **VII-19** (Table 7-1). Although the ligand also plays a role in the stereocontrol of the carboetherification reaction of **VII-13**, the change in selectivity is not as dramatic.[2,3]

We propose that the difference in ligand stereocontrol using bidentate ligands arises from a difference in palladium coordination number. Tightly chelating ligands, such as dppe and BINAP likely proceed via a five-coordinate transition state such as **VII-65** (Scheme 7-12). However, molecular models suggest that **VII-65** will have a steric interaction between the aryl group on Pd and the Boc group on nitrogen. This will raise the energy of transition state **VII-64**, but have little effect on transition state **VII-62**, thereby bringing the two transition states closer in energy and reducing the selectivity. In contrast, ligands with larger bite angles should be better able to dissociate one arm of the ligand, allowing for a four-coordinate transition state **VII-66**. This reduces the steric interaction between the aryl and Boc groups, resulting in greater difference in energy between transition states **VII-62** and **VII-64** (Scheme 7-11), and diastereoselectivity. Biaryl ligands, which are hemilabile, have diastereocontrol similar to bidentate ligands with large bite angles. This is consistent with a four-coordinate transition state being operative.

Scheme 7-12: Four vs. Five Coordinate Palladium Coordination



The effect of monodentate ligands is less clear at this point. Both sterics and electronics play a large role in the stereocontrol. P(*o*-tol)$_3$ has a larger cone angle than P*t*Bu$_3$ (194º versus 182º), yet P(*o*-tol)$_3$ is more electron poor and leads to low stereoselectivity (2:1 dr).[5] In the trialkyl series, small changes in cone angle lead to dramatically different levels of stereocontrol. PCy$_3$ has a cone angle of 174º and leads to little selectivity (2:1 dr), while P*t*Bu$_3$ has a cone angle of 182º, which is only slightly larger and leads to high stereoselectivity (28:1 dr).[5] The cause of these observations is currently not well understood.

7.6 Conclusion

We have developed a highly diastereoselective palladium catalyzed carboamination reaction for the synthesis of isoxazolidines. This reaction can be used with a broad scope of electrophilic coupling partners. The diastereocontrol is higher than many other isoxazolidine forming reactions. Ligand choice is critical for good stereocontrol and this has not been previously observed. We have extended the electrophilic coupling partners from only aryl bromides to now include alkenyl bromides for the carboetherification of **VII-13**, **VII-15**, and **VII-17**. In addition, we compared the carboamination and carboetherification reaction using analogous substrates and found

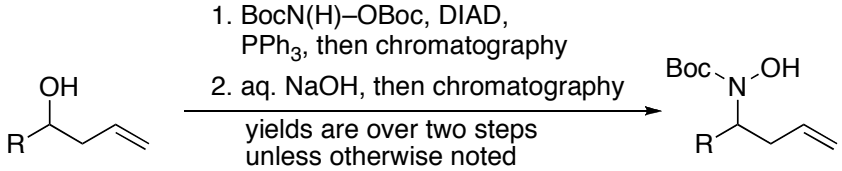
that the Boc protecting group on nitrogen is important for establishing good diastereoselectivity. This result will help direct selection of nitrogen substituent choice in future palladium catalyzed cyclization reactions.

7.7 Experimental

General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. $Pd(OAc)_2$, $Pd_2(dba)_3$, phosphine ligands, aryl bromides, and common reagents were obtained from commercial sources and used as obtained. *N*-phenyl hydroxylamine,[8] *N*-Boc-hydroxylamine,[9] *N*,*O*-bis-(Boc)-hydroxylamine (**VII-10**),[10] 1-phenylbut-3-en-1-ol (**VII-9**),[11] 1-(4-methoxyphenyl)-3-buten-1-ol (**VII-24**),[12] *N*-benzyl-*N*-(1-phenylbut-3-enyl)hydroxylamine (**VII-13**),[2] pyrrolidin-1-ol[13] and 2-allylpiperidin-1-ol (**VII-17**)[3] were prepared according to literature procedures. (–)-(*S*)-1-phenybut-3-en-1-ol was obtained in 96% ee via enzymatic resolution of the racemic alcohol according to a slightly modified literature procedure in which toluene was used in place of hexane as solvent.[14] Toluene, diethyl ether, methylene chloride, and THF were purified using a column solvent purification system. Ratios of diastereomers were determined by ^{1}H NMR analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis. The yields reported in the supporting information describe the result of a single experiment, whereas the yields reported in eq 1–3 and 7 and Tables 7-2 and 7-3 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in eq 1–3 and 7 and Tables 7-2 and 7-3.

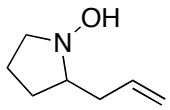
7.7.1 Preparation of Substrates

General Procedure 1: Synthesis of *N*-Boc-*O*-butenyl hydroxylamine derivatives. An oven- or flame-dried flask was cooled under a stream of nitrogen and charged with the homoallylic alcohol (1 equiv), triphenylphosphine (1.2 equiv), *N*-hydroxyphthalimide (1.2 equiv), and THF (8 mL/mmol homoallylic alcohol). The resulting mixture was cooled to 0 ºC then diethyl azodicarboxylate or diisopropyl azodicarboxylate (1.2 equiv) was added dropwise over 30 min. The resulting dark red solution was warmed to rt until the starting material was consumed as judged by GC analysis. Hydrazine monohydrate (2.3 equiv) was added, the mixture was stirred at rt for 1 h, then the resulting suspension was filtered through a pad of Celite. The solution was transferred to a dry, nitrogen-filled flask and di-*tert*-butyl dicarbonate (2 equiv) was added. The reaction mixture was stirred at rt for ca. 24 h, and then concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford the *N*-butenylhydroxylamine product. If column chromatography failed to remove all *tert*-butyl-containing byproducts of the Boc-protection step, the impure product was stirred in a mixture of THF (50 mL) and 1 M aqueous NaOH (50 mL) for 7.5 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo, and filtered through a plug of silica gel using EtOAc as the eluant. Concentration of the resulting solution afforded pure material.



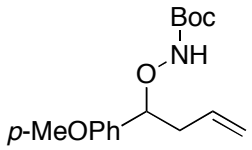
General Procedure 2: Synthesis of *N*-Boc-*N*-butenyl hydroxylamine derivatives. A flame-dried flask was cooled under a stream of nitrogen and charged with the homoallylic alcohol (1 equiv), triphenylphosphine (1.2 equiv), *N*,*O*-bis-(Boc)-hydroxylamine (1.2 equiv), and THF (0.2 M). The mixture was cooled to 0 ºC, diisopropyl azodicarboxylate (1.2 equiv) was added dropwise, and the resulting solution was warmed to rt until the starting material was consumed as judged by TLC analysis. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel to afford an *N*,*O*-bis-(Boc)-*N*-butenylhydroxylamine derivative.

A round-bottom flask was purged with nitrogen and charged with the *N*,*O*-bis-(Boc)-*N*-butenylhydroxylamine derivative (1 equiv) and methanol (0.1 M). Aqueous sodium hydroxide (2.5 equiv, 1 M) was added, and the resulting solution was stirred at rt until the starting material was consumed as judged by TLC analysis. The reaction mixture was concentrated *in vacuo* and the resulting material was diluted with water and extracted with ether. The layers were separated, the aqueous layer was acidified with $KHSO_4$ until pH = 2 and was then extracted with ethyl acetate. The ether extracts and the ethyl acetate extracts were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude *N*-Boc-*N*-butenylhydroxylamine product was purified by flash chromatography on silica gel.



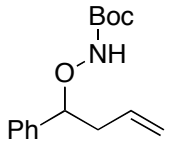
(±)-**2-allylpyrrolidin-1-ol (VII-15)**.[2]

A flame-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and was charged with pyrrolidin-1-ol[13] (1.31 g, 15 mmol, 1 equiv) and methylene chloride (60 mL, 4 mL/mmol). The reaction was cooled to 0 ºC. Mercury (I) oxide, yellow (6.50 g, 30 mmol, 2 equiv) was added in one portion. The reaction was warmed to rt and stirred 45 min at this temperature. The reaction mixture was filtered through a plug of Celite. The filtrate was concentrated *in vacuo*. The crude nitrone was purged with nitrogen, then diluted with THF (30 mL, 2 mL/mmol). The reaction was cooled to 0 ºC and allyl magnesium bromide in diethyl ether (1 M, 30 mL, 30 mmol) was added dropwise over 25 min. The reaction was warmed to rt and stirred 2.25 h. The reaction was then quenched with saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 954 mg (50%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 7.05 (bs, 1 H), 5.83 (ddt, J = 10.0, 14.0, 7.0, 1 H), 5.12–5.01 (m, 2 H), 3.30–3.25 (m, 1 H), 2.86–2.76 (m, 2 H), 2.27–2.51 (m, 1 H), 2.19–2.10 (m, 1 H), 1.99–1.89 (m, 1 H), 1.84–1.63 (m, 2 H), 1.48–1.35 (m, 1 H).

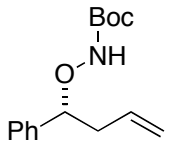


(±)-*tert*-Butyl 1-(4-methoxyphenyl)but-3-enyloxycarbamate (VII-29).[15] The conversion of 1-(4-methoxyphenyl)-3-buten-1-ol (**VII-24**)[12] **(**0.500 g, 2.81 mmol) to the title compound was conducted according to General Procedure 1. After flash chromatography, the product was recrystallized from ether and hexanes to yield 370 mg

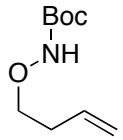
(45%) of the title compound as a white solid, mp 83.0–85.5 ºC (mp not previously reported in the literature). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2 H), 6.91–6.88 (m, 2 H), 6.84 (s, br, 1 H), 5.82–5.73 (m, 1 H), 5.11–5.01 (m, 2 H), 4.74 (t, J = 7.0 Hz, 1 H), 3.81 (s, 3 H), 2.77–2.69 (m, 1 H), 2.51–2.43 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 133.9, 131.7, 128.6, 117.4, 113.9, 86.6, 81.5, 55.3, 39.5, 28.2 (one carbon signal is absent due to incidental equivalence); IR (film) 3312, 2979, 1716 cm^{-1}. MS (ESI) 316.1512 (316.1525 calcd for $C_{16}H_{23}NO_4$, M + Na^+)



(±)-*tert*-Butyl 1-phenylbut-3-enyloxycarbamate (VII-19).[16] The conversion of 1-phenyl-3-buten-1-ol (**VII-22**)[11] **(**2.46 g, 16.6 mmol) to the title compound was conducted according to General Procedure 1. This procedure afforded 2.34 g (54%) of the title compound as a white solid, mp 30.5–33.0 ºC (mp not previously reported in the literature). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H), 6.89 (s, 1 H), 5.86–5.74 (m, 1 H), 5.13–5.05 (m, 2 H), 4.80 (t, J = 6.8 Hz, 1 H), 2.77–2.68 (m, 1 H), 2.53–2.44 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 139.8, 133.8, 128.5, 128.2, 127.2, 117.4, 87.1, 81.6, 39.7, 28.2. IR (film) 3299, 2980, 1722 cm^{-1}. MS (ESI) 286.1416 (286.1419 calcd for $C_{15}H_{21}NO_3$, M + Na^+).

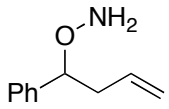


(+)-(*R*)-*tert*-Butyl 1-phenylbut-3-enyloxycarbamate (VII-19). The conversion of (–)-(*R*)-1-phenylbut-3-en-1-ol[14] **(**400 mg, 2.7 mmol, 96% ee) to the title compound was conducted according to General Procedure 1. This procedure afforded 549 mg (77%) of the title compound as a clear oil. The enantiopurity was determined to be 96% ee by chiral HPLC analysis (Chiracel AD 0.46 cm x 25 cm, 1% isopropanol/hexanes, 0.4 mL/min, RT= 33.8 and 37.1 min); $[\alpha]^{23}_{D}$ +139.6 (*c* 0.16, CH_2Cl_2). NMR data were identical to those reported above for (±)-**VII-19**.

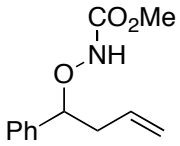


***tert*-Butyl but-3-enyloxycarbamate (VII-40).** [17] A flame-dried flask was charged with 95% NaH (288 mg, 12 mmol) in a nitrogen-filled glovebox. The flask was capped with a rubber septum and removed from the glovebox, then THF (6 mL) was added via syringe. A solution of *N*-Boc-hydroxylamine[9] (1.33 g, 10 mmol) in THF (3 mL) was added slowly dropwise over 15 min, and the resulting mixture was stirred at rt for 1 h. A solution of tetrabutylammonium iodide (370 mg, 1 mmol) and 4-bromo-1-butene (1.49 g, 1.1 mL, 11 mmol) in THF (1 mL) was then added to the reaction mixture in one portion, and an additional portion of tetrabutylammonium iodide (370 mg, 1 mmol) was added as a solid. The resulting mixture was stirred at rt for ca. 24 h, then was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine (1 x 15 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 420 mg (22%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1 H), 5.88–5.77 (m, 1 H), 5.13 (dq, *J*

= 1.6, 17.2 Hz, 1 H), 5.06 (dq, *J* = 1.2, 10.0 Hz, 1 H), 3.91 (t, *J* = 6.8 Hz, 2 H), 2.40 (dq, *J* = 1.2, 6.8 Hz, 2 H), 1.48 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 134.4, 116.8, 81.7, 75.7, 32.5, 28.2; IR (film) 3288, 2980, 1722 cm^{-1}. MS (ESI) 210.1102 (210.1106 calcd for $C_9H_{17}NO_3$, M + Na^+).

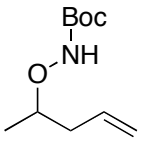


(±)-*O*-(1-Phenylbut-3-enyl)hydroxylamine (VII-35).[16] The conversion of 1-phenyl-3-buten-1-ol (**VII-22**)[11] (593 mg, 4.0 mmol), to the title compound was accomplished according to General Procedure 1 except the Boc-protection step was omitted. This modified procedure afforded 540 mg (83%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 2 H), 7.34–7.28 (m, 3 H), 5.81–5.71 (m, 1 H), 5.09–5.01 (m, 2 H), 4.57 (dd, *J* = 6.0, 7.5 Hz, 1 H), 2.63–2.56 (m, 1 H), 2.45–2.38 (m, 1 H) (the NH_2 signal was not detected due to broadening); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 128.5, 127.9, 126.8, 117.1, 86.7, 40.5 (one carbon signal is absent due to incidental equivalence); IR (film) 3317, 3076, 2906, 1583 cm^{-1}. MS (ESI) 164.1078 (164.1075 calcd for $C_{10}H_{13}NO$, M + H^+).



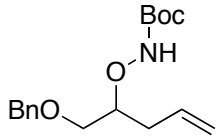
(±)-Methyl 1-phenylbut-3-enyloxycarbamate (VII-33).[16] A flame-dried flask was charged with *O*-(1-phenylbut-3-enyl)hydroxylamine (**VII-35**) (742 mg, 4.55 mmol) and potassium carbonate (755 mg, 5.46 mmol). The flask was purged with nitrogen, anhydrous THF (4.5 mL) and methyl chloroformate (0.70 mL, 9.10 mmol) were added,

and the reaction mixture was stirred at rt for 5.5 h. TLC analysis of the reaction mixture indicated the starting material was not completely consumed, and two additional portions of methyl chloroformate (0.35 mL, 4.55 mmol) were added (one after 5.5 h and one after 19h). After stirring for 3 additional h, the reaction mixture was quenched with aqueous 1M HCl (10 mL) and extracted with EtOAc (4 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 837 mg (83%) of the title compound as a white solid (mp 59.5–62.5 ºC; mp not previously reported in the literature). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5 H), 7.04 (s, br, 1 H), 5.84–5.74 (m, 1 H), 5.14–5.04 (m, 2 H), 4.81 (t, J = 7.0 Hz, 1 H), 3.73 (s, 3 H), 2.78–2.70 (m, 1 H), 2.54–2.45 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 139.4, 133.5, 128.6, 128.4, 127.2, 117.6, 87.3, 52.7, 39.5; IR (film) 3276, 2954, 1734 cm^{-1}. MS (ESI) 244.0950 (244.0950 calcd for $C_{12}H_{15}NO_3$, M + Na^+).

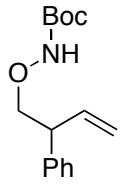


(±)-*tert*-Butyl pent-4-en-2-yloxycarbamate (VII-28).[15] The conversion of 4-penten-2-ol (0.50 mL, 0.42 g, 5.0 mmol) to the title compound was conducted according to General Procedure 1. This procedure afforded 0.84 g (83%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1 H), 5.88–5.76 (m, 1 H), 5.13–5.03 (m, 2 H), 3.94 (m, 1 H), 2.44–2.38 (m, 1 H), 2.38–2.19 (m, 1 H), 1.47 (s, 9 H), 1.20 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 134.3, 117.2, 81.5, 80.9, 39.1, 28.2, 18.1; IR

(film) 3296, 2979, 1721 cm^{-1}. MS (ESI) 224.1259 (224.1263 calcd for $C_{10}H_{19}NO_3$, M + Na^+)

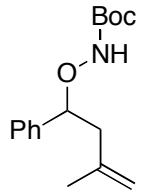


(±)-*tert*-Butyl 1-(benzyloxy)pent-4-en-2-yloxycarbamate (VII-30). The conversion of 1-(benzyloxy)pent-4-en-2-ol (**VII-24**)[18] **(**0.62 g, 3.21 mmol) to the title compound was conducted according to General Procedure 1. This procedure afforded 0.76 g (77%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 4 H), 7.31–7.27 (m, 1 H), 7.25 (s, br, 1 H), 5.91–5.82 (m, 1 H), 5.14–5.05 (m, 2 H), 4.55 (s, br, 2 H), 4.02–3.96 (m, 1 H), 3.61–3.58 (m, 2 H), 2.48–2.34 (m, 2 H), 1.47 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 138.0, 134.0, 128.4, 127.71, 127.69, 117.4, 83.5, 81.6, 73.4, 70.6, 34.6, 28.2; IR (film) 3307, 2979, 1731 cm^{-1}. MS (ESI) 330.1677 (330.1677 calcd for $C_{17}H_{25}NO_4$, M + Na^+).

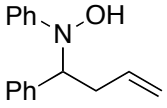


(±)-*tert*-Butyl 2-phenylbut-3-enyloxycarbamate (VII-31). The conversion of 2-phenyl-3-buten-1-ol (**VII-26**)[19] (1.66 g, 11.2 mmol) to the title compound was conducted via a modification of General Procedure 1. After cleavage of the phthalimide group with hydrazine, *O*-(2-phenylbut-3-enyl)hydroxylamine (1.20 g, 66%) was isolated via flash chromatography on silica gel. This compound was dissolved in CH_2Cl_2 (10 mL) and di-*tert*-butyl dicarbonate (1.66 g, 7.36 mmol) was added. The resulting solution was stirred

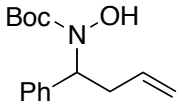
at rt overnight and then the reaction mixture was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 1.56 g (81%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2 H), 7.24–7.21 (m, 3 H), 7.12 (s, 1 H), 6.07–5.99 (m, 1 H), 5.19–5.14 (m, 2 H), 4.17–4.09 (m, 2 H), 3.76 (q, J = 7.5 Hz, 1 H), 1.47 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 140.5, 138.2, 128.6, 128.0, 126.8, 116.4, 81.7, 79.2, 48.2, 28.2; IR (film) 3293, 2979, 1720 cm^{-1}. MS (ESI) 286.1417 (286.1419 calcd for $C_{15}H_{21}NO_3$, M + Na^+).



(±)-*tert*-Butyl 3-methyl-1-phenylbut-3-enyloxycarbamate (VII-32). The conversion of 3-methyl-1-phenylbut-3-en-1-ol (**VII-27**)[20] (2.43 g, 15.0 mmol) to the title compound was conducted according to General Procedure 1. This procedure afforded 3.55 g (85%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5 H), 6.86 (s, br, 1 H), 4.94 (dd, J = 6.5, 7.5 Hz, 1 H), 4.79 (m, 2 H), 2.71 (dd, J = 7.5, 14.5 Hz, 1 H), 2.39 (dd, J = 6.5, 14.5 Hz, 1 H), 1.77 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 141.4, 140.1, 128.4, 128.2, 127.2, 113.2, 86.0, 81.5, 43.7, 28.1, 22.7; IR (film) 3307, 1747 cm^{-1}. MS (ESI) 300.1578 (300.1576 calcd for $C_{16}H_{23}NO_3Na$, M + Na^+).

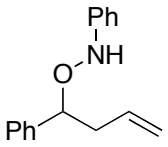


(±)-*N*-phenyl-*N*-(1-phenylbut-3-enyl)hydroxylamine (VII-54).[21] A flame-dried flask was cooled under a stream of nitrogen and charged with *N*-benzylideneaniline *N*-oxide[8] (200 mg, 1.0 mmol, 1 equiv) and THF (2 mL). The mixture was cooled to 0 °C and a solution of allylmagnesium bromide in diethyl ether (1 M, 2.0 mL, 2 equiv) was added dropwise over 30 minutes. The resulting mixture was stirred at 0 ºC for 1 h and then warmed to rt and stirred for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 213 mg (88%) of the title compound as a white solid, mp 88.5–91.5 ºC (mp not previously reported in the literature). ^{1}H NMR (500 MHz, C_6D_6) δ 7.24–7.21 (m, 2 H), 7.18–7.16 (m, 2 H), 7.14–7.07 (m, 3 H), 7.06–7.03 (m, 2 H), 6.84–6.80 (m, 1 H), 5.79–5.70 (m, 1 H), 5.02–4.92 (m, 2 H), 4.46 (t, J = 8.0 Hz, 1 H), 4.09 (s, 1 H), 2.84–2.76 (m, 1 H), 2.73–2.65 (m, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 152.1, 138.9, 136.2, 129.5, 128.8, 128.1, 127.6, 122.4, 118.2, 116.6, 71.1, 35.6; IR (KBr) 3234, 3065, 2920, 1598 cm^{-1}. MS (EI) 239.1313 (239.1310 calcd for $C_{16}H_{17}NO$).



(±)-*tert*-Butyl *N*-hydroxy(1-phenylbut-3-enyl)carbamate (VII-12). The conversion of 1-phenylbut-3-en-1-ol (**VII-9**)[11] (1.0 g, 6.8 mmol) to the title compound was conducted according to General Procedure 2. This procedure afforded 0.83 g (47%) of the title compound as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2 H), 7.35–7.26 (m,

3 H), 5.90–5.80 (m, 1 H), 5.21–5.17 (m, 1 H), 5.08–5.06 (m, 2 H), 2.98–2.90 (m, 1 H), 2.64–2.59 (m, 1 H), 1.43 (s, 1 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 139.7, 135.1, 128.3, 127.5, 117.4, 82.0, 62.2, 36.1, 28.3; IR (film) 3214, 2978, 1689 cm^{-1}. MS (ESI) 286.1419 (286.1419 calcd for $C_{15}H_{21}NO_3$, M + Na^+).

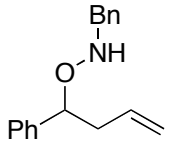


(±)-*N*-Phenyl-*O*-(1-phenylbut-3-enyl)hydroxylamine (VII-36). An oven-dried Schlenk flask was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (952 mg, 1.04 mmol), (2-biphenyl)di-*tert*-butylphosphine (745 mg, 2.50 mmol), sodium *tert*-butoxide (2.40 g, 25.0 mmol), and *N*-Boc hydroxylamine (2.77 g, 20.8 mmol). The flask was evacuated and refilled with nitrogen (3 x), then bromobenzene (2.6 mL, 25.0 mmol) and THF (42 mL) were added via syringe. The resulting mixture was heated to 65 ºC with stirring for 2 h, then was cooled to rt. Saturated aqueous ammonium chloride (75 mL) was added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel, and then further purified by recrystallization from Et_2O/hexanes to afford 2.44 g (56%) of *N*-Boc-*N*-phenyl hydroxylamine as a tan solid, mp 87.5–91.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2 H), 7.37–7.31 (m, 2 H), 7.17–7.12 (m, 1 H), 7.10 (s, br, 1 H), 1.53 (s, 9 H).

A flame-dried flask was cooled under a stream of nitrogen and charged with 1-phenylbut-3-en-1-ol (**VII-9**) (150 mg, 1.01 mmol), *N*-Boc-*N*-phenyl hydroxylamine (339 mg, 1.62

mmol), and triphenylphosphine (425 mg, 1.62 mmol). The flask was purged with nitrogen, THF (8.0 mL) was added, and the reaction mixture was cooled to 0 ºC. Diisopropyl azodicaroxylate (0.32 mL, 1.62 mmol) was added dropwise over 15 min, then the reaction mixture was warmed to rt, stirred for 1 h, then heated to 55 ºC with stirring for 19.5 h. The reaction mixture was then cooled to rt and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 164 mg (48%) of *tert*-butyl phenyl(1-phenylbut-3-enyloxy)carbamate as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.25 (m, 9 H), 7.15–7.11 (m, 1 H), 5.71–5.62 (m, 1 H), 5.05–4.97 (m, 2 H), 4.79 (t, J = 7.0 Hz, 1 H), 2.86–2.79 (m, 1 H), 2.61–2.54 (m, 1 H), 1.42 (s, 9 H).

A portion of the *tert*-butyl phenyl(1-phenylbut-3-enyloxy)carbamate (339 mg, 1.00 mmol) was dissolved in CH_2Cl_2. The resulting solution was cooled to 0 °C and trifluoroacetic acid (2.5 mL) was added. The mixture was stirred at 0 ºC for 5 min then was quenched at 0 °C with saturated Na_2CO_3. The reaction mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography to yield 86 mg (37%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.31 (m, 5 H), 7.25–7.21 (m, 2 H), 6.96–6.89 (m, 3 H), 6.76 (s, br, 1 H), 5.92–5.81 (m, 1 H), 5.16–5.07 (m, 2 H), 4.85–4.80 (m, 1 H), 2.81–2.72 (m, 1 H), 2.58–2.49 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 140.9, 134.2, 128.9, 128.6, 128.1, 127.0, 121.9, 117.6, 114.5, 85.6, 40.4. IR (film) 3291, 3032, 2909, 1602 cm^{-1}. MS (ESI) 240.1390 (240.1388 calcd for $C_{16}H_{17}NO$, M + H^+).

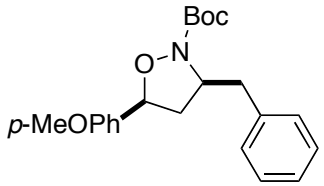


(±)-*N*-Benzyl-*O*-(1-phenylbut-3-enyl)hydroxylamine (VII-34). A flame-dried flask was charged with *O*-(1-phenylbut-3-enyl)hydroxylamine (**VII-35**) (238 mg, 1.6 mmol) and potassium carbonate (445 mg, 3.2 mmol). The flask was purged with nitrogen, anhydrous DMF (1.6 mL) and benzyl bromide (0.19 mL, 1.61 mmol) were added, and the reaction mixture was stirred at rt for 4 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (10 mL), diluted with H_2O (15 mL), and then extracted with 1:1 EtOAc/hexanes (3 x 17 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 160 mg (39%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 10 H), 5.72–5.61 (m, 1 H), 5.04–4.95 (m, 2 H), 4.61 (t, J = 7.2 Hz, 1 H), 4.01 (q, J = 12.8 Hz, 2 H), 2.61–2.52 (m, 1 H), 2.41–2.32 (m, 1 H) (the NH signal was not detected due to broadening); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 137.5, 134.7, 129.1, 128.3, 127.5, 127.3, 126.8, 116.8, 84.8, 56.5, 40.4 (one carbon signal is absent due to incidental equivalence); IR (film) 3260, 3030, 2908, 1641 cm^{-1}. MS (ESI) 254.1555 (254.1545 calcd for $C_{17}H_{19}NO$, M + H$^+$).

7.7.2 Synthesis of Isoxazolidines via Pd-Catalyzed Carboamination (Tables 7-2 and 7-3)

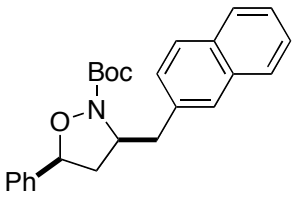
General Procedure 3: Pd-Catalyzed Synthesis of *N*-Boc Isoxazolidines from *N*-Boc-*O*-Butenyl Hydroxylamines: A flame- or oven- dried Schlenk tube equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol% complex, 2 mol% Pd), P*t*Bu$_3$·HBF$_4$ (4 mol%), sodium *tert*-butoxide (1.2 equiv),

and the aryl or alkenyl bromide if solid (1.2 equiv). The Schlenk tube was evacuated and refilled with nitrogen (3x). The *O*-butenyl hydroxylamine substrate (1.0 equiv) was added as a solution in toluene (4 mL solvent/mmol substrate), along with the aryl bromide if liquid. The resulting mixture was heated to 65 °C until the starting material was consumed as judged by GC analysis. The reaction mixture was cooled to rt and treated with saturated aqueous ammonium chloride (2 mL) and ethyl acetate (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

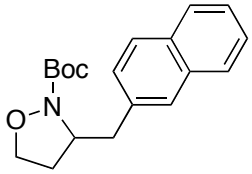


(±)-(3*S,5*S**)-*tert*-Butyl 3-benzyl-5-(4-methoxyphenyl)isoxazolidine-2-carboxylate (VII-37).** The reaction of **VII-29** (73 mg, 0.25 mmol) with bromobenzene (32 μL, 0.30 mmol) was conducted for 2.5 h at 65 ºC according to General Procedure 3. This procedure afforded 68 mg (74%) of the title compound as a clear oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.21 (m, 7 H), 6.90–6.85 (m, 2 H), 4.81 (dd, *J* = 6.4, 10.4 Hz, 1 H), 4.56–4.48 (m, 1 H), 3.80 (s, 3 H), 3.19 (dd, *J* = 6.4, 13.6 Hz, 1 H), 2.85 (dd, *J* = 7.6, 13.2 Hz, 1 H), 2.66–2.58 (m, 1 H), 2.05–1.97 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.7, 157.5, 138.1,

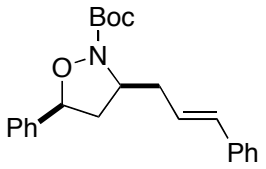
129.5, 129.1, 128.4, 128.1, 126.4, 113.8, 82.8, 81.7, 61.9, 55.3, 42.5, 42.3, 28.1; IR (film) 2978, 1728, 1614 cm^{-1}. MS (ESI) 392.1825 (392.1838 calcd for $C_{22}H_{27}NO_4$, M + Na^+).



(±)-(3*S,5*S**)-3-Napthalen-2-ylmethyl-5-phenylisoxazolidine-2-carboxylic acid *tert*-butyl ester (VII-39).** The reaction of **VII-19** (66 mg, 0.25 mmol) with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted for 1.25 h at 65 ºC according to General Procedure 3. This procedure afforded 90 mg (92%) of the title compound as a clear oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 28:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 3 H), 7.68 (s, 1 H), 7.48–7.38 (m, 3 H), 7.35–7.30 (m, 5 H), 4.89 (dd, *J* = 6.4 , 10.0 Hz, 1 H), 4.67–4.58 (m, 1 H), 3.37 (dd, *J* = 6.4, 13.2 Hz, 1 H), 2.99 (dd, *J* = 8.0, 13.2 Hz, 1 H), 2.73–2.64 (m, 1 H), 2.12 (m, 1 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 137.4, 135.5, 133.4, 132.2, 128.4, 128.3, 128.0, 127.8, 127.7, 127.52, 127.46, 126.5, 125.9, 125.4, 82.9, 81.8, 61.9, 42.8, 42.4, 28.1; IR (film) 2978, 1729 cm^{-1}. MS (ESI) 412.1880 (412.1889 calcd for $C_{25}H_{27}NO_3$, M + Na^+).

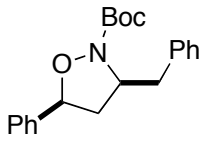


(±)-*tert*-Butyl 3-(naphthalen-2-ylmethyl)isoxazolidine-2-carboxylate (VII-41). The reaction of **VII-40** (47 mg, 0.25 mmol) with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted for 3 h at 65 ºC according to General Procedure 3. This procedure afforded 49 mg (62%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.77 (m, 3 H), 7.68 (s, 1 H), 7.48–7.42 (m, 2 H), 7.38 (dd, *J* = 2.0, 8.5 Hz, 1 H), 4.51–4.44 (m, 1 H), 4.08 (dt, *J* = 3.5, 8.0 Hz, 1 H), 3.77 (q, *J* = 8.0 Hz, 1 H), 3.26 (dd, *J* = 6.5, 13.5 Hz, 1 H), 2.87 (dd, *J* = 8.0, 13.5 Hz, 1 H), 2.31–2.24 (m, 1 H), 2.11–2.03 (m, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 135.7, 133.5, 132.2, 128.0. 127.77, 127.71, 127.57, 127.49, 125.9, 125.4, 81.7, 69.0, 60.3, 41.7, 34.0, 28.1; IR (film) 2978, 1727, 1367 cm^{-1}. MS (ESI) 336.1577 (336.1576 calcd for $C_{19}H_{23}NO_3$, M + Na^+).



(±)-(*E*)-(3*S,5*S**)-*tert*-Butyl 3-cinnamyl-5-phenylisoxazolidine-2-carboxylate (VII-42).** The reaction of **VII-19** (66 mg, 0.25 mmol) with β-bromostyrene (65 μL, 0.50 mmol, ca. 7:1 *E*:*Z*) and sodium *tert*-butoxide (48 mg, 0.50 mmol) was conducted for 5 h at 90 ºC according to a modified version of General Procedure 3 using a catalyst composed of $Pd_2(dba)_3$ (3.4 mg, 0.0038 mmol) and P*t*Bu_3·HBF_4 (6.5 mg, 0.023 mmol). This procedure afforded 53 mg (58%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a >20:1 mixture of diastereomers (epimeric at C5) and a ca. 20:1 mixture of *E*:*Z* alkene isomers; the isolated product was obtained as a 35:1 mixture of diastereomers (epimeric at C5) and a 20:1 mixture of *E*:*Z* alkene isomers following purification. Data are for the major

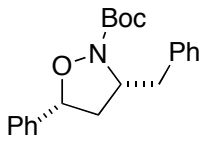
stereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 9 H), 7.25–7.20 (m, 1 H), 6.50 (d, *J* = 15.5 Hz, 1 H), 6.27 (dt, *J* = 7.0, 15.5 Hz, 1 H), 4.89 (dd, *J* = 6.5, 10.0 Hz, 1 H), 4.51–4.44 (m, 1 H), 2.83–2.76 (m, 1 H), 2.75-2.68 (m, 1 H), 2.62–2.54 (m, 1 H), 2.10–2.03 (m, 1 H), 1.53 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 137.37, 137.32, 132.8, 128.5, 128.4, 127.2, 126.7, 126.1, 126.0, 83.1, 81.8, 60.4, 42.5, 39.6, 28.3 (one carbon signal is absent due to incidental equivalence); IR (film) 2978, 1731, 1703 cm^{-1}. MS (ESI) 388.1891 (388.1889 calcd for $C_{23}H_{27}NO_3$, M + Na^+).



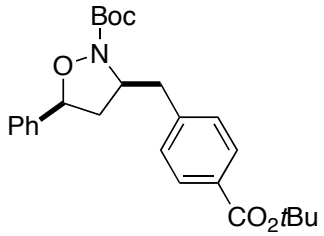
(±)-(3*S,5*S**)-*tert*-butyl 3-benzyl-5-phenylisoxazolidine-2-carboxylate (VII-21).** The reaction of **VII-19** (66 mg, 0.25 mmol) with iodobenzene (34 μL, 0.30 mmol) was conducted at for 2 h at 65 ºC according to General Procedure 3. This procedure afforded 58 mg (68%) of the title compound as a pale yellow oil. ^{1}H NMR analysis indicated the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data were identical to those provided below.

(±)-(3*S,5*S**)-*tert*-butyl 3-benzyl-5-phenylisoxazolidine-2-carboxylate (VII-21)**. The reaction of **VII-19** (66 mg, 0.25 mmol) with bromobenzene (32 μL, 0.30 mmol) was conducted at for 2.5 h at 65 ºC according to General Procedure 3. This procedure afforded 64 mg (75%) of the title compound as a pale yellow oil. ^{1}H NMR analysis indicated the product was formed as a >20:1 mixture of diastereomers; the isolated

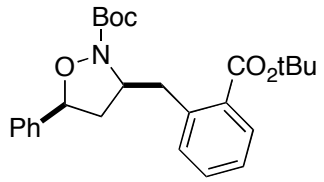
product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.21 (m, 10 H), 4.87 (dd, *J* = 6.5, 10.0 Hz, 1 H), 4.56–4.49 (m, 1 H), 3.19 (dd, *J* = 9.5, 13.5 Hz, 1 H), 2.84 (dd, *J* = 8.0, 13.5 Hz, 1 H), 2.70–2.64 (m, 1 H), 2.05–1.98 (m, 1 H), 1.46 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 138.0, 137.4, 129.4, 128.5, 128.4, 128.3, 126.5, 126.4, 82.9, 81.8, 61.9, 42.7, 42.2, 28.1; IR (film) 2978, 1731 cm^{-1}. MS (ESI) 362.1718 (362.1732 calcd for $C_{21}H_{25}NO_3$, M + Na^+).



(+)-(3*R*,5*R*)-*tert*-butyl 3-benzyl-5-phenylisoxazolidine-2-carboxylate (VII-21). The reaction of **(+)-VII-19** (66 mg, 0.25 mmol) with bromobenzene (32 μL, 0.30 mmol) was conducted for 2 h at 65 ºC according to General Procedure 3. This procedure afforded 76 mg (90%) of the title compound as a pale yellow solid. ^{1}H NMR analysis indicated the product was formed as a 25:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. The enantiopurity was determined to be 97% by chiral HPLC analysis (Chiracel OD-H 0.46 cm x 15 cm, 0.8% isopropanol/hexanes, 0.1 mL/min, RT= 87.7 and 106.7 min); $[\alpha]^{23}_{D}$ +7.30 (*c* 0.16, CH_2Cl_2). NMR data were identical to those provided above for **(±)-VII-21**.

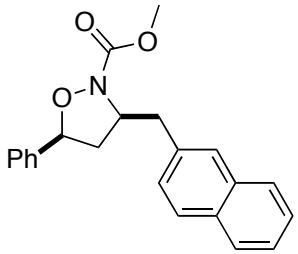


(±)-(3*S,5*S**)-*tert*-Butyl 3-[4-(*tert*-butoxycarbonyl)benzyl]-5-phenylisoxazolidine-2-carboxylate (VII-43).** The reaction of **VII-19** (66 mg, 0.25 mmol) with *tert*-butyl-4-bromobenzoate (77 mg, 0.30 mmol) was conducted for 1.5 h at 65 ºC according to General Procedure 3. This procedure afforded 87 mg (79%) of the title compound as a white solid, mp 117.0–119.5 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2 H), 7.37–7.27 (m, 7 H), 4.87 (dd, *J* = 7.0, 10.0 Hz, 1 H), 4.58–4.51 (m, 1 H), 3.21 (dd, *J* = 6.5, 13.5 Hz, 1 H), 2.88 (dd, *J* = 7.5, 13.5 Hz, 1 H), 2.72–2.64 (m, 1 H), 2.03–1.95 (m, 1 H), 1.59 (s, 9 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 157.5, 142.8, 137.3, 130.4, 129.6, 129.3, 128.5, 128.4, 126.5, 82.9, 82.0, 80.8, 61.6, 42.6, 42.1, 28.19, 28.16; IR (film) 2977, 1731, 1710 cm^{-1}. Anal. calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19. Found: C, 71.33; H, 7.65; N, 3.22.



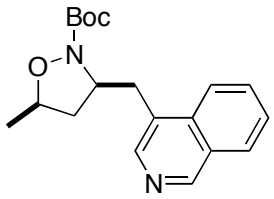
(±)-(3*S,5*S**)-*tert*-butyl 3-[2-(*tert*-butoxycarbonyl)benzyl]-5-phenylisoxazolidine-2-carboxylate (VII-44).** The reaction of **VII-19** (66 mg, 0.25 mmol) with *tert*-butyl-2-bromobenzoate (77 mg, 0.30 mmol) was conducted for 2.25 h at 65 ºC according to

General Procedure 3. This procedure afforded 47 mg (43%) of the title compound as a clear oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 6:1 mixture of diastereomers; the isolated product was obtained with 8:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) 7.84 (dd, *J* = 1.0, 7.5 Hz, 1 H), 7.43–7.30 (m, 7 H), 7.29–7.23 (m, 1 H), 4.88 (dd, *J* = 6.5, 10.0 Hz, 1 H), 4.70–4.63 (m, 1 H), 3.46 (dd, *J* = 4.5, 13.0 Hz, 1 H), 3.09 (dd, *J* = 9.5, 13.0 Hz, 1 H), 2.88 (ddd, *J* = 7.0, 8.5, 12.0 Hz, 1 H), 2.03 (ddd, *J* = 6.0, 10.0, 12.5 Hz, 1 H), 1.59 (s, 9 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 157.2, 139.8, 137.7, 132.7, 131.7, 131.2, 130.4, 128.4, 128.3, 126.7, 126.3, 83.0, 81.3, 81.1, 61.8, 43.4, 40.8, 28.2, 27.9; IR (film) 2977, 1730, 1711 cm^{-1}. MS (ESI) 462.2249 (462.2256 calcd for $C_{26}H_{33}NO_5$, M + Na^+).



(±)-(3*S,5*S**)-methyl 3-(naphthalen-2-ylmethyl)-5-phenylisoxazolidine-2-carboxylate (VII-45).** The reaction of **VII-33** (55 mg, 0.25 mmol) with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted for 2.5 h at 65 ºC according to General Procedure 3. This procedure afforded 74 mg (86%) of the title compound as a clear oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.74 (m, 3 H), 7.68–7.66 (m, 1 H), 7.47–7.38 (m, 3 H), 7.32–7.25 (m, 5

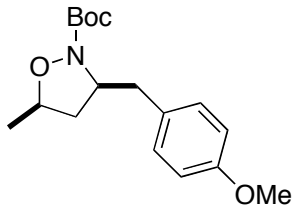
H), 4.89 (dd, J = 6.8, 10.0 Hz, 1 H), 4.75–4.67 (m, 1 H), 3.79 (s, 3 H), 3.40 (dd, J = 5.6, 13.6 Hz, 1 H), 3.03 (dd, J = 8.0, 13.6 Hz, 1 H), 2.69–2.61 (m, 1 H), 2.14–2.06 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 136.9, 135.0, 133.4, 132.3, 128.52, 128.49, 128.1, 127.9, 127.7, 127.6, 127.5, 126.5, 126.0, 125.5, 83.5, 61.7, 53.4, 42.6, 41.9; IR (film) 3056, 1719 cm^{-1}. MS (ESI) 370.1415 (370.1419 calcd for $C_{22}H_{21}NO_3$, M + Na^+).



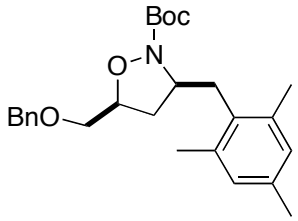
(±)-(3*S,5*S**)-*tert*-Butyl 3-(isoquinolin-4-ylmethyl)-5-methylisoxazolidine-2-carboxylate (VII-46).**

The reaction of **VII-28** (50 mg, 0.25 mmol) with 4-bromoisoquinoline (63 mg, 0.30 mmol) was conducted for 3 h at 65 ºC according to General Procedure 3. This procedure afforded 56 mg (69%) of the title compound as a brown solid, mp 91–94 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 17:1 mixture of diastereomers; the isolated product was obtained with 20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1 H), 8.40 (s, 1 H), 8.14 (d, J = 8.5 Hz, 1 H), 7.97 (d, J = 8.0 Hz, 1 H), 7.76–7.72 (m, 1 H), 7.65–7.58 (m, 1 H), 4.56–4.48 (m, 1 H), 4.03–3.93 (m, 1 H), 3.57 (dd, J = 6.5, 13.5 Hz, 1 H), 3.05 (dd, J = 6.5, 14.0 Hz, 1 H), 2.39–2.33 (m, 1 H), 1.74–1.67 (m, 1 H), 1.38 (d, J = 6.0 Hz, 3 H), 1.29 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 143.6, 134.9, 130.4, 128.4, 128.2, 127.8, 127.0, 123.2, 81.6, 77.8, 60.7, 42.5, 36.8, 28.0, 17.7 (one carbon signal is

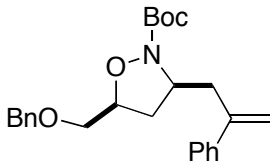
absent due to incidental equivalence); IR (film) 2978, 1726 cm^{-1}. MS (ESI) 351.1685 (351.1685 calcd for $C_{19}H_{24}N_2O_3$, M + Na^+).



(±)-(3*S,5*S**)-*tert*-Butyl 3-(4-methoxybenzyl)-5-methylisoxazolidine-2-carboxylate (VII-47).** The reaction of **VII-28** (50 mg, 0.25 mmol) with 4-bromoanisole (38 μL, 0.30 mmol) was conducted for 6 h at 65 ºC according to General Procedure 3. This procedure afforded 54 mg (70%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2 H), 6.85–6.81 (m, 2 H), 4.35–4.28 (m, 1 H), 4.03–3.96 (m, 1 H), 3.79 (s, 3 H), 3.05 (dd, *J* = 6.5, 14.0 Hz, 1 H), 2.66 (dd, *J* = 8.0, 13.5 Hz, 1 H), 2.38–2.32 (m, 1 H), 1.60–1.54 (m, 1 H), 1.43 (s, 9 H), 1.32 (d, *J* = 5.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 130.3, 113.8, 81.5, 77.6, 61.9, 55.3, 41.9, 41.3, 28.2, 17.8 (two carbon signals are absent due to incidental equivalence); IR (film) 2976, 1727 cm^{-1}. MS (ESI) 330.1667 (330.1681 calcd for $C_{17}H_{25}NO_4$, M + Na^+).

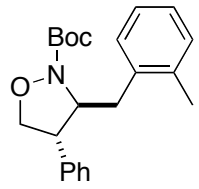


(±)-(3*S,5*S**)-*tert*-Butyl 5-(benzyloxymethyl)-3-(2,4,6-trimethylbenzyl)isoxazolidine-2-carboxylate (VII-48).** The reaction of **VII-30** (77 mg, 0.25 mmol) with 2-bromomesitylene (46 μL, 0.30 mmol) was conducted for 9 h at 65 ºC according to General Procedure 3. This procedure afforded 54 mg (65%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 20:1 mixture of diastereomers; the isolated product was obtained with 20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 4 H), 7.31–7.26 (m, 1 H), 6.81 (s, 2 H), 4.64 (s, 2 H), 4.50–4.42 (m, 1 H), 4.21–4.13 (m, 1 H), 3.76 (dd, *J* = 3.6, 11.2 Hz, 1 H), 3.69 (dd, *J* = 5.2, 11.6 Hz, 1 H), 3.05 (dd, *J* = 9.2, 14.0 Hz, 1 H), 2.75 (dd, *J* = 6.0, 14.0 Hz, 1 H), 2.42–2.29 (m, 7 H), 2.23 (s, 3 H), 1.97–1.89 (m, 1 H), 1.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 138.0, 136.8, 135.4, 132.4, 128.8, 128.3, 127.66, 127.61, 81.5, 80.8, 73.5, 69.2, 59.2, 36.4, 35.1, 27.8, 20.7, 20.3; IR (film) 2976, 1728 cm^{-1}. MS (ESI) 448.2458 (448.2464 calcd for $C_{26}H_{35}NO_4$, M + Na^+).



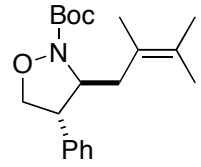
(±)-(3*S,5*S**)-*tert*-Butyl 5-(benzyloxymethyl)-3-(2-phenylallyl)isoxazolidine-2-carboxylate (VII-49).** The reaction of **VII-30** (77 mg, 0.25 mmol) with α-bromostyrene (39 μL, 0.30 mmol) was conducted for 7 h at 65 ºC according to General Procedure 3. This procedure afforded 54 mg (65%) of the title compound as a white solid, mp 59–62 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 17:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following

purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2 H), 7.36–7.26 (m, 8 H), 5.36 (s, 1 H), 5.11 (s, 1 H), 4.61 (s, 2 H), 4.31–4.24 (m, 1 H), 4.17–4.10 (m, 1 H), 3.70 (dd, *J* = 3.5, 11.5 Hz, 1 H), 3.62 (dd, *J* = 4.5, 11.0 Hz, 1 H), 3.15 (dd, *J* = 6.0, 14.5 Hz, 1 H), 2.54 (dd, *J* = 9.5, 14.0 Hz, 1 H), 2.25–2.18 (m, 1 H), 1.91–1.85 (m, 1 H), 1.46 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 144.7, 140.2, 138.0, 128.4, 128.4, 127.7, 127.66, 127.63, 126.1, 115.1, 81.7, 80.5, 73.5, 69.3, 58.5, 41.4, 35.8, 28.2; IR (film) 2978, 1732, 1706 cm^{-1}. MS (ESI) 432.2151 (432.2151 calcd for $C_{25}H_{31}NO_4$, M + Na^+).

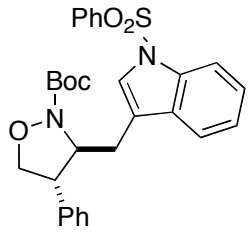


(±)-(3*S,4*S**)-*tert*-Butyl 3-(2-methylbenzyl)-4-phenylisoxazolidine-2-carboxylate (VII-50).** The reaction of **VII-31** (66 mg, 0.25 mmol) with 2-bromotoluene (51 mg, 36 μL, 0.30 mmol) was conducted for 4 h at 65 ºC according to General Procedure 3. This procedure afforded 66 mg (75%) of the title compound as a white solid, mp 60.5–65.0 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 13:1 mixture of diastereomers; the isolated product was obtained with 14:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, C_6D_6) δ 7.10–7.03 (m, 1 H), 7.02–6.96 (m, 4 H), 6.95–6.88 (m, 4 H), 4.70–4.62 (m, 1 H), 4.00 (t, *J* = 8.5 Hz, 1 H), 3.76 (t, *J* = 8.5 Hz, 1 H), 3.22 (dt, *J* = 5.0, 8.3 Hz, 1 H), 3.14 (dd, *J* = 7.0, 13.8 Hz, 1 H), 2.77 (dd, *J* = 7.5, 13.8 Hz, 1 H), 2.12 (s, 3 H), 1.34 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 139.5, 136.5, 136.1, 130.4, 130.1, 128.8, 127.2, 127.7, 126.6, 125.7,

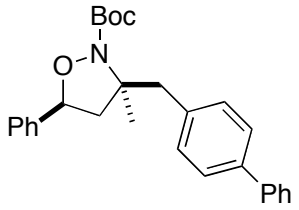
81.8, 76.6, 67.9, 54.3, 39.0, 28.0. 19.4; IR (film) 2978, 1731 cm^{-1}. MS (ESI) 376.1884 (376.1889 calcd for $C_{22}H_{27}NO_3$, M + Na^+).



(±)-(3*S,4*S**)-*tert*-Butyl 3-(2,3-dimethylbut-2-enyl)-4-phenylisoxazolidine-2-carboxylate (VII-51).** The reaction of **VII-31** (66 mg, 0.25 mmol) with 2-bromo-3-methyl-2-butene (35 µL, 0.30 mmol) was conducted for 7 h at 65 ºC according to General Procedure 3. This procedure afforded 54 mg (65%) of the title compound as a yellow solid, mp 32–34 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2 H), 7.26–7.21 (m, 1 H), 7.16–7.12 (m, 2 H), 4.36 (t, *J* = 8.0 Hz, 1 H), 4.28 (dt, *J* = 5.0, 8.0 Hz, 1 H), 3.83 (t, *J* = 9.0 Hz, 1 H), 3.43–3.38 (m, 1 H), 2.53 (dd, *J* = 7.0, 13.5 Hz, 1 H), 2.42 (dd, *J* = 7.5, 11.5 Hz, 1 H), 1.71 (s, 3 H), 1.59 (s, 3 H), 1.53–1.50 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 139.8, 128.8, 127.34, 127.32, 127.1, 123.9, 81.7, 76.7, 66.9. 54.3, 39.9, 28.3, 20.8, 20.5, 18.6. IR (film) 2979, 1732, 1705 cm^{-1}. MS (ESI) 354.2040 (354.2045 calcd for $C_{20}H_{29}NO_3$, M + Na^+).



(±)-(3*S,4*S**)-*tert*-Butyl 4-phenyl-3-{[1-(phenylsulfonyl)-indol-3-yl]methyl}isoxazolidine-2-carboxylate (VII-52).** The reaction of **VII-31** (66 mg, 0.25 mmol) with 3-bromo-1-(phenylsulfonyl)-indole (101 mg, 0.30 mmol) was conducted for 5.5 h at 90 ºC according to a modified version of General Procedure 3 using a catalyst composed of $Pd_2(dba)_3$ (3.4 mg, 0.0038 mmol) and P*t*Bu_3·HBF_4 (6.5 mg, 0.023 mmol). This procedure afforded 88 mg (67%) of the title compound as a white solid, mp 165–170 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 5:1 mixture of diastereomers; the isolated product was obtained with 5:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 1 H), 7.88–7.80 (m, 2 H), 7.54–7.38 (m, 5 H), 7.33–7.15 (m, 5 H), 7.08–7.02 (m, 2 H), 4.51 (dd, *J* = 6.4, 11.6 Hz, 1 H), 4.35 (t, *J* = 8.0 Hz, 1 H), 3.84 (t, *J* = 8.8 Hz, 1 H), 3.51–3.44 (m, 1 H), 3.13 (dd, *J* = 7.2, 14.8 Hz, 1 H), 3.00 (dd, *J* = 6.4, 15.2 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHZ, $CDCl_3$) δ 157.2, 138.9, 138.3, 135.0, 133.7, 131.1, 129.2, 129.0, 127.4, 127.3, 126.7, 124.7, 124.1, 123.1, 119.5, 119.0, 113.5, 82.3, 76.6, 67.4, 54.8, 30.7, 28.1; IR (film) 2978, 1729, 1448 cm^{-1}. MS (ESI) 541.1777 (541.1773 calcd for $C_{29}H_{30}N_2O_5S$, M + Na^+).

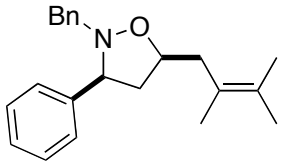


(±)-(3*S,5*S**)-*tert* Butyl-3-(biphenyl-4-ylmethyl)-3-methyl-5-phenylisoxazolidine-2-carboxylate (VII-53).** The reaction of **VII-32** (69 mg, 0.25 mmol) with 4-bromobiphenyl (70 mg, 0.30 mmol) was conducted for 8 h at 65 ºC according to General Procedure 3.

This procedure afforded 59 mg (55%) of the title compound as a pale yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 4:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.0 Hz, 2 H), 7.54 (d, *J* = 6.5 Hz, 2 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.29–7.26 (m, 5 H), 7.16–7.14 (m, 2 H), 5.10 (dd, *J* = 6.0, 10.0 Hz, 1 H), 3.35 (d, *J* = 13.5 Hz, 1 H), 3.15 (d, *J* = 13.0 Hz, 1 H), 2.57 (dd, *J* = 10.0, 12.5 Hz, 1 H), 2.32 (dd, *J* = 6.0, 12.5 Hz, 1 H), 1.68 (s, 3 H), 1.60 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 140.8, 139.5, 137.9, 136.3, 131.0, 128.7, 128.3, 128.1, 127.1, 126.9, 126.8, 126.5, 81.2, 78.8, 66.0, 49.4, 44.0, 28.5, 25.3; IR (film) 2977, 1683 cm^{-1}. MS (ESI) 452.2201 (452.2202 calcd for $C_{27}H_{29}NO_3Na$, M + Na^+).

General Procedure 4: Pd-catalyzed Synthesis of Isoxazolidines via Carboetherification vs. Carboamination as Shown in eq 1–3 and Table 7-3. A flame- or oven- dried Schlenk tube equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with either $Pd_2(dba)_3$ (1 mol% complex, 2 mol% Pd) or $Pd(OAc)_2$ (2 mol%), DPE-Phos or Xantphos (2–4 mol%), sodium *tert*-butoxide (1.4 equiv), and the aryl or alkenyl bromide if solid (1.2–1.4 equiv). The Schlenk tube was evacuated and refilled with nitrogen (3x). The hydroxylamine substrate (1.0 equiv) was added as a solution in THF or toluene (4 mL solvent/mmol substrate), along with the aryl or alkenyl bromide if liquid. The resulting mixture was heated to 65 °C or 110 ºC until the starting material was consumed as judged by GC or NMR analysis. The reaction

mixture was cooled to rt and treated with saturated aqueous ammonium chloride (2 mL) and ethyl acetate (5 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

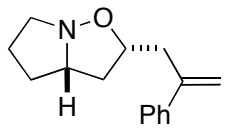


(±)-(3*S,5*S**)-2-benzyl-5-(2,3-dimethylbut-2-enyl)-3-phenylisoxazolidine (VII-14)**

The reaction of 63 mg (0.25 mmol) of **VII-13** with 2-bromo-3-methyl-2-butene (45 mg, 35 μL, 0.30 mmol) was conducted in THF (8 mL/mmol hydroxylamine) for 3 h at 65 ºC according to the General Procedure 4 using a catalyst composed of $Pd(OAc)_2$ (1.1 mg, 0.0050 mmol, 2 mol%) and DPE-Phos (3.0 mg, 0.0050 mmol, 2 mol%). This procedure afforded 63 mg (79%) of the title compound as a pale yellow solid, mp 33–36 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 6:1 mixture of diastereomers; the isolated product was obtained with 6:1 dr following purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2 H), 7.36–7.30 (m, 4 H), 7.29–7.17 (m, 4 H), 4.36–4.28 (m, 1 H), 3.96 (d, *J* = 14.4 Hz, 1 H), 3.87 (t, *J* = 8.4 Hz, 1 H), 3.79 (d, *J* = 14.0 Hz, 1 H), 2.73 (dt, *J* = 12.4, 7.2 Hz, 1 H), 2.54 (dd, *J* = 7.2, 13.6 Hz, 1 H), 2.30 (dd, *J* = 6.4, 13.2 Hz, 1 H), 2.06–1.95 (m, 1 H), 1.60 (s, 6 H), 1.57 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.9, 128.9, 128.5, 128.0, 127.5, 127.4, 126.9, 126.5, 124.4,

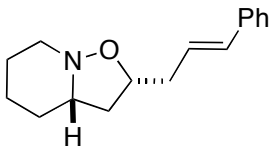
76.5, 70.6, 60.2, 45.2, 40.2, 20.6, 20.5, 19.0. IR (film) 2917, 1603 cm^{-1}. MS (ESI) 322.2168 (322.2171 calcd for $C_{22}H_{27}NO$, $M + H^+$).



(±)-(2*S,3a*S**)-2-(2-phenylallyl)hexahydropyrrolo[1,2-b]isoxazole (VII-16)**

The reaction of 32 mg (0.25 mmol) of **VII-15** with α-bromostyrene (92 mg, 65 μL, 0.50 mmol) was conducted in THF (5 mL/mmol hydroxylamine) with NaO*t*Bu (48 mg, 0.50 mmol) for 15.5 h at 65 ºC according to the a modified General Procedure 4 using a catalyst composed of $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 4 mol%) and DPE-Phos (10.8 mg, 0.020 mmol, 8 mol%). This procedure afforded 37 mg (69%) of the title compound as a red oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 7:1 mixture of diastereomers; the isolated product was obtained with 8:1 dr following purification.

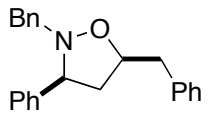
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2 H), 7.34–7.29 (m, 2 H), 7.29–7.23 (m, 1 H), 5.35–5.32 (m, 1 H), 5.17–5.14 (m, 1 H), 4.17–4.10 (m, 1 H), 3.75–3.68 (m, 1 H), 3.14–3.04 (m, 2 H), 2.93 (dd, *J* = 6.0, 14.0 Hz, 1 H), 2.62 (dd, *J* = 7.5, 14.5 Hz, 1 H), 2.16–2.09 (m, 1 H), 1.97–1.87 (m, 2 H), 1.87–1.77 (m, 1 H), 1.68–1.59 (m, 1 H), 1.49–1.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 140.8, 128.3, 128.2, 127.5, 126.1, 114.6, 75.1, 64.9, 57.0, 42.1, 40.0, 31.5, 24.2; IR (film) 2963, 1626 cm^{-1}. MS (ESI) 252.1363 (252.1136 calcd for $C_{15}H_{19}NO$, $M + Na^+$).



(±)-(2*R,3a*S**)-2-cinnamylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (VII-18)**

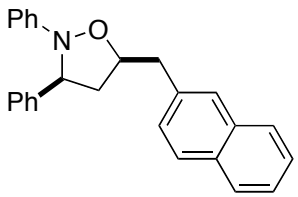
The reaction of 35 mg (0.25 mmol) of **VII-17** with β-bromostyrene (92 mg, 64 μL, 0.30 mmol) was conducted in THF (5 mL/mmol hydroxylamine) with NaO*t*Bu (48 mg, 0.50 mmol) for 16 h at 65 ºC according to a modification of General Procedure 4 using a catalyst composed of $Pd(OAc)_2$ (1.1 mg, 0.0050 mmol) and DPE-Phos (5.4 mg, 0.010 mmol). This procedure afforded 50 mg (82%) of the title compound as an orange oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2 H), 7.32–7.27 (m, 2 H), 7.22–7.17 (m, 1 H), 6.46 (d, *J* = 15.5 Hz, 1 H), 6.27–6.19 (m, 1 H), 4.20–4.11 (m, 1 H), 3.28–3.42 (m, 1 H), 2.71–2.64 (m, 1 H), 2.47-2.36 (m, 3 H), 2.27–2.19 (m, 1 H), 1.97-1.90 (m, 1 H), 1.84–1.65 (m, 4 H), 1.47–1.34 (m, 1 H), 1.27-1.15 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 131.9, 128.4, 127.0, 126.7, 126.1, 75.6, 67.4, 55.3, 41.0, 40.6, 29.2, 24.8, 23.7; IR (film) 3025, 2936, 1494 cm^{-1}. MS (ESI) 244.1701 (244.1703 calcd for $C_{16}H_{21}NO$, M + H$^+$).



(±)-(3*S,5*S**)-2,5-Dibenzyl-3-phenylisoxazolidine (VII-55, Table 7-4, Entry 1).** The reaction of **VII-13** (63.3 mg, 0.25 mmol) with bromobenzene (38 μL, 0.36 mmol) was

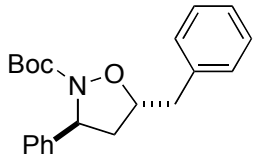
conducted in toluene at 65 ºC according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and DPE-Phos (2.7 mg, 0.0050 mmol). This procedure afforded 70 mg (85%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 4:1 mixture of diastereomers; the isolated product was obtained with 4:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2 H), 7.39–7.16 (m, 11 H), 7.14–7.10 (m, 2 H), 4.41 (quint, J = 6.8 Hz, 1 H), 3.98 (d, J = 13.6 Hz, 1 H), 3.89 (t, J = 8.4 Hz, 1 H), 3.79 (d, J = 14.0 Hz, 1 H), 3.18 (dd, J = 6.8, 13.2 Hz, 1 Hz), 2.83–2.70 (m, 2 H), 2.16–2.08 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 138.5, 138.0, 129.4, 128.8, 128.6, 128.2, 128.0, 127.52, 127.47, 126.9, 126.1, 77.8, 70.6, 60.0, 45.1, 41.9; IR (film) 3028, 2865, 1602 cm^{-1}. MS (ESI) 330.1850 (330.1858 calcd for $C_{23}H_{23}NO$, M + H$^+$).



(±)-(3*S,5*S**)-5-(Naphthalen-2-ylmethyl)-2,3-diphenylisoxazolidine (VII-56, Table 7-3, entry 3).** The reaction of **VII-54** (60 mg, 0.25 mmol) with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted in toluene for 4 h at 65 ºC according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and DPE-Phos (2.7 mg, 0.005 mmol). This procedure afforded 72 mg (79%) of the title compound as a pale yellow solid, mp 96–108 ºC. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 3:1 mixture of diastereomers; the isolated product was obtained

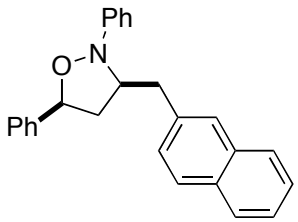
with 10:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.79 (m, 3H), 7.72 (s, 1H), 7.55–7.20 (m, 10 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 6.93 (t, *J* = 7.0 Hz, 1 H), 4.77 (t, *J* = 8.0 Hz, 1 H), 4.57–4.50 (m, 1 H), 3.36 (dd, *J* = 7.0, 14.0 Hz, 1 H), 3.07 (dd, *J* = 6.5, 14.0 Hz, 1 H), 2.89–2.83 (m, 1 H), 2.28–2.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 142.9. 135.3, 133.5, 132.2, 128.9, 128.8, 128.0, 127.6, 127.53, 127.51, 127.3, 126.1, 126.0, 125.5, 121.2, 113.9, 79.5, 70.9, 46.1, 39.4 (one carbon signal is absent due to incidental equivalence); IR (film) 3057, 1598 cm^{-1}. MS (ESI) 366.1852 (366.1858 calcd for $C_{26}H_{23}NO$, M + H^+).

(±)-(3*S,5*S**)-5-(Naphthalen-2-ylmethyl)-2,3-diphenylisoxazolidine (VII-56, Table 7-3, entry 4).** The reaction of **VII-54** (47 mg, 0.20 mmol) with 2-bromonapthalene (49.7 mg, 0.24 mmol) was conducted at 110 ºC according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.0020 mmol) and Xantphos (4.6 mg, 0.0080 mmol). This procedure afforded 57 mg (78%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 1:1 mixture of diastereomers; the isolated product was obtained with 1:1 dr following purification.



(±)-(3*R,5*R**)-*tert*-Butyl 5-(naphthalene-2-ylmethyl)-3-phenylisoxazolidine-2-carboxylate (VII-57, Table 7-3, entry 6).** The reaction of **VII-12** (38.9 mg, 0.15 mmol) with bromobenzene (19 μL, 0.18 mmol) was conducted according to General Procedure 4

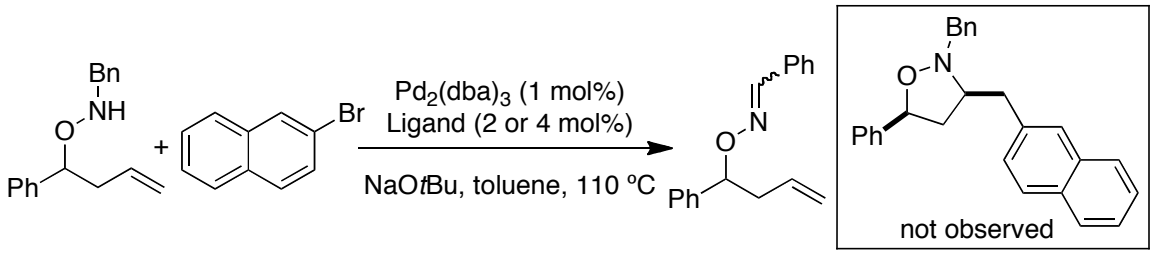
using a catalyst composed of $Pd_2(dba)_3$ (1.4 mg, 0.002 mmol) and Xantphos (3.5 mg, 0.006 mmol). This procedure afforded 19 mg (37%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 7:1 mixture of diastereomers; the isolated product was obtained with 13:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 6 H), 7.25–7.21 (m, 4 H), 5.28–5.25 (m, 1 H), 4.56–4.50 (m, 1 H), 3.15–3.10 (dd, *J* = 6.4, 13.6 Hz, 1 H), 2.74–2.69 (dd, *J* = 6.8, 14.0 Hz, 1 H), 2.53–2.47 (m, 1 H), 2.34–2.28 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 141.8, 137.3, 129.2, 128.5, 127.2, 126.7, 125.9, 81.8, 80.8, 61.8, 42.5, 39.7, 28.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2917, 1698 cm^{-1}. MS (ESI) 362.1726 (362.1732 calcd for $C_{21}H_{25}NO_3$, M + Na^+).



(±)-(3*S,5*S**)-3-(Naphthalen-2-ylmethyl)-2,5-diphenylisoxazolidine (VII-58, Table 7-3, Entry 7).** The reaction of **VII-35** (24 mg, 0.1 mmol) with 2-bromonapthalene (25 mg, 0.12 mmol) was conducted at 65 ºC according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (1.0 mg, 0.001 mmol) and DPE-Phos (1.1 mg, 0.002 mmol). This procedure afforded 8 mg (22%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 1:1 mixture of diastereomers; the isolated cis-disubstituted product was obtained with >20:1 dr following purification. Data are for the cis-diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.83–7.78 (m, 3 H), 7.74 (s, br, 1 H), 7.52–7.43 (m, 8 H), 7.22–7.16 (m, 2 H), 6.94–6.88 (m, 3 H), 5.13 (dd, J = 7.2, 9.2 Hz, 1 H), 4.28–4.21 (m, 1 H), 3.47 (dd, J = 8.0, 13.6 Hz, 1 H), 3.11 (dd, J = 6.4, 13.2 Hz, 1 H), 2.82 –2.75 (m, 1 H), 2.23–2.16 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9. 138.7, 136.5, 135.6, 132.2, 129.0, 128.6, 128.2, 128.1, 127.93, 127.87, 127.6, 126.6, 126.0, 125.4, 121.4, 114.0, 79.9, 69.6, 43.9, 43.1 (one carbon signal absent due to incidental equivalence); IR (film) 3057, 2919, 1597 cm^{-1}. MS (ESI) 366.1847 (366.1858 calcd for $C_{26}H_{23}NO$, M + H$^+$).

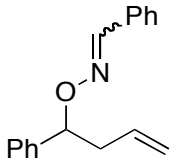
(±)-(3*S,5*S**)-3-(Naphthalen-2-ylmethyl)-2,5-diphenylisoxazolidine (VII-58, Table 7-3, Entry 8).** The reaction of **VII-35** (25 mg, 0.1 mmol) with 2-bromonapthalene (26 mg, 0.13 mmol) was conducted at 110 ºC according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (1.0 mg, 0.001 mmol) and Xantphos (2.5 mg, 0.004 mmol). This procedure afforded 15 mg (38%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 2:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. Data were identical to those provided above.



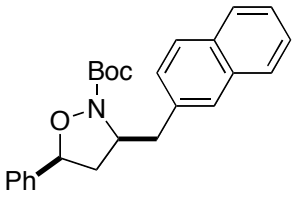
Attempted Synthesis of (±)-(3*S,5*S**)-2-Benzyl-3-(naphthalen-2-ylmethyl)-5-phenylisoxazolidine (Table 7-3, entry 9).** The reaction of **VII-34** (63 mg, 0.25 mmol)

with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted at 110 ºC for 12 h according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and Dpe-Phos (2.7 mg, 0.0050 mmol). Analysis of a sample removed from the crude reaction mixture indicated that benzaldehyde *O*-1-phenylbut-3-enyl oxime was the major product of this reaction. A number of minor products were also formed, but there was no indication that the desired isoxazolidine had been generated. After purification, 9.7 mg (15%) of benzaldehyde *O*-1-phenylbut-3-enyl oxime (**VII-59**) was isolated as a yellow oil which was judged to be ca. 90% pure by ^{1}H NMR analysis. The identity of this product was confirmed by independent synthesis as described below.

Attempted Synthesis of (±)-(3*S,5*S**)-2-Benzyl-3-(naphthalen-2-ylmethyl)-5-phenylisoxazolidine (Table 7-3, entry 10).** The reaction of **VII-34** (63 mg, 0.25 mmol) with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted at 110 ºC for 34.5 h according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and Xantphos (5.8 mg, 0.010 mmol). Analysis of a sample removed from the crude reaction mixture indicated that benzaldehyde *O*-1-phenylbut-3-enyl oxime was the major product of this reaction. A number of minor products were also formed, but there was no indication that the desired isoxazolidine had been generated. After purification, 9.0 mg (14%) of **VII-59** was isolated as a yellow oil which was judged to be ca. 90% pure by ^{1}H NMR analysis. The identity of this product was confirmed by independent synthesis as described below. In addition, 28.8 mg (45%) of the starting material (**VII-34**) was recovered in 90% purity (as determined by ^{1}H NMR analysis).



Independent Synthesis of Benzaldehyde *O*-1-phenylbut-3-enyl oxime (VII-59). A round-bottom flask was charged with *O*-(1-phenylbut-3-enyl)hydroxylamine (**VII-35**) (36 mg, 0.22 mmol), benzaldehyde (0.22 mL, 2.20 mmol) and silica gel (22 mg). The flask was attached to a rotary evaporator, placed under vacuum, and heated with spinning in a 37 ºC water bath for 1 h. The flask was then removed from the rotary evaporator, attached to a vacuum manifold, and excess benzaldehyde was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 29 mg (52%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 7.56–7.51 (m, 2 H), 7.38–7.31 (m, 7 H), 7.29–7.26 (m, 1 H), 5.86–5.77 (m, 1 H), 5.25 (t, J = 6.5 Hz, 1 H), 5.13–5.03 (m, 2 H), 2.84–2.78 (m, 1 H), 2.66–2.59 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 141.5, 134.2, 132.4, 129.7, 128.6, 128.2, 127.5, 127.1, 126.9, 117.3, 84.9, 40.4 IR (film) 3062, 1447 cm^{-1}. MS (ESI) 252.1382 (252.1388 calcd for $C_{17}H_{17}NO$, $M + H^+$)



(±)-(3*S,5*S**)-3-Napthalen-2-ylmethyl-5-phenylisoxazolidine-2-carboxylic acid *tert*-butyl ester (VII-39, Table 7-3, entry 11).** The reaction of **VII-19** (66 mg, 0.25 mmol) with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted at 65 ºC for 6 h according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and

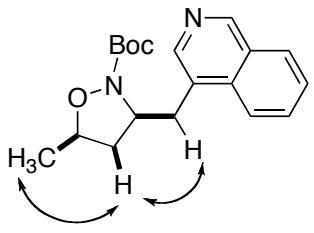
Dpe-Phos (0.0050 mg, 2.7 mmol). This procedure afforded 66 mg (67%) of the title compound as a white solid. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 12:1 mixture of diastereomers; the isolated product was obtained with 10:1 dr following purification. Data were identical to those provided above.

(±)-(3*S,5*S**)-3-Napthalen-2-ylmethyl-5-phenylisoxazolidine-2-carboxylic acid *tert*-butyl ester (VII-39, Table 7-3, entry 12).** The reaction of **VII-19** (99 mg, 0.38 mmol) with 2-bromonapthalene (93 mg, 0.45 mmol) was conducted at 65 ºC for 1.25 h according to General Procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (3.4 mg, 0.038 mmol) and Xantphos (4.3 mg, 0.0075 mmol). This procedure afforded 105 mg (72%) of the title compound as a white solid. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 12:1 mixture of diastereomers; the isolated product was obtained with 12:1 dr following purification. Data were identical to those provided above.

7.7.3 Assignment of Stereochemistry

***cis*-3,5-Disubstituted isoxazolidines VII-21, VII-39, and VII-42–49**

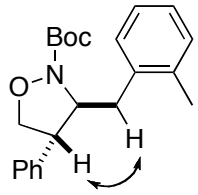
The relative stereochemistry of isoxazolidine **VII-46** was determined based on the nOe signals depicted below.



The stereochemistry of other *cis*-3,5-disubstituted isoxazolidine products was assigned based on analogy to the above molecule.

***trans*-4,5-Disubstituted isoxazolidines VII-50–52**

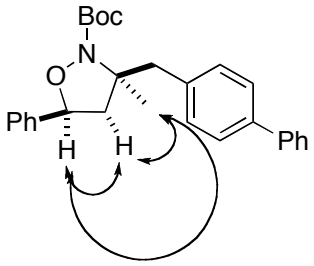
The relative stereochemistry of isoxazolidine **VII-50** was determined based on the nOe signals depicted below.



The stereochemistry of other *trans*-4,5-disubstituted isoxazolidine products was assigned based on analogy to the above molecule.

3,5,5-Trisubstituted Isoxazolidine VII-53

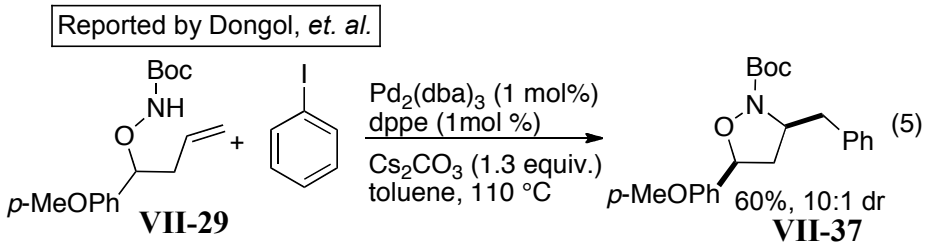
The relative stereochemistry of isoxazolidine **VII-53** was determined based on the nOe signals depicted below.



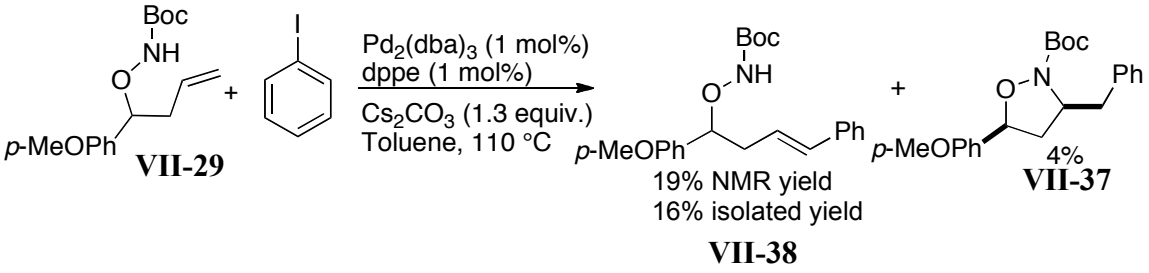
7.7.4 Efforts to Reproduce the Results of Reference 4.

Examination of Conditions Reported by Dongol, K., *et. al.* in *Tetrahedron Lett.*, 2006, *47*, 927–930.

In the paper cited above, Dongol reported that treatment of **VII-29** with iodobenzene and Cs_2CO_3 in the presence of 1 mol% $Pd_2(dba)_3$ and 1 mol% dppe afforded isoxazolidine **VII-37** in 60% yield with 10:1 dr (eq 5). *Note: these conditions employ only 0.5 equivalents of ligand relative to palladium, as the catalyst precursor is a dinuclear complex with 2 Pd atoms per equivalent.*



In our hands, efforts to employ the conditions described above for the conversion of **VII-29** to **VII-37** instead afforded a complex mixture of products (as determined by ^{1}H NMR analysis of the crude material obtained after workup of this reaction). The major product was alkene **VII-38** (19% NMR yield), which results from Heck arylation of the starting material. The isoxazolidine **VII-37** was formed in 4% yield as judged by ^{1}H NMR analysis using phenanthrene as an internal standard. The remainder of the mixture was composed of a number of other unidentified products. After workup and purification of the complex mixture, we isolated **VII-38** in 16% yield. This experiment was run a total of four times by two different coworkers, and similar results were obtained in all four runs.



(*E*)-*tert*-Butyl-1,4-diphenylbut-3-enyloxycarbamate (VII-38).[4] A flame-dried Schlenk tube was cooled under a stream of N_2 and charged with $Pd_2(dba)_3$ (3.1 mg, 0.0034 mmol), dppe (1.4 mg, 0.0034 mmol), and Cs_2CO_3 (145 mg, 0.44 mmol). The tube was evacuated and refilled with N_2 (3 x). A solution of **VII-29** (100 mg, 0.34 mmol) in toluene (3 mL) was added, followed by iodobenzene (49 μL, 0.44 mmol,), and additional toluene (2 mL). The resulting mixture was heated in a 110 ºC oil bath for 20 h. The reaction was removed from the oil bath and cooled to rt. The crude reaction mixture was filtered through silica gel, the silica gel was rinsed with ethyl acetate, and the resulting solution was concentrated *in vacuo*. ^{1}H NMR analysis of the crude product indicated that a complex mixture had formed. The major product was **VII-38** (19% NMR yield using phenanthrene as internal standard), and a small amount of **VII-37** (4%) was also detected. The crude product was purified by flash chromatography on silica gel to obtain 20 mg (16%) of the title compound (Heck arylation product) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.22 (m, 7 H), 6.91–6.89 (m, 2 H), 6.42 (d, J = 15.6 Hz, 1 H), 6.12 (dt, J = 16.0, 7.2 Hz, 1 H), 4.81 (t, J = 7.2 Hz, 1 H), 3.81 (s, 3 H), 2.93–2.85 (m, 1 H), 2.69–2.60 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 132.5, 128.8, 128.7, 128.4, 127.1, 126.1, 125.4, 113.9, 86.7, 81.6, 55.3, 38.5, 28.2 (two signals are absent due to incidental equivalence); IR (film) 3304, 2977, 1716 cm^{-1}. MS (ESI) 392.1840 (392.1838 calcd for $C_{22}H_{27}NO_4$, M + Na^+).

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