Development of Reactions for the Stereoselective Synthesis of Heterocycles and Enantioselective Synthesis of Diols and Amino-Alcohols

by

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To Mom and Dad

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I’d like to thank my parents for their constant love and support. I would not have been able to achieve any of this without them. They have always taught me to work hard and to do my best in all aspects of life, and they’ve encouraged me through the most difficult parts of this process. Mom and Dad, I love you and am grateful for all you do for me.

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List of Abbreviations

Ac ..... acetyl

Ar ..... aryl

BINAP ..... 2,2’-bis(diphenylphosphino)-1,1’-biphenyl

BINOL ..... 1,1’-bi-2-naphthol

Bn ..... benzyl

Boc ..... *tert*-butyloxycarbonyl

Box ..... bisoxazoline

Bpy ..... 2,2’-bipyridine

Bu ..... butyl

Bz ..... benzoyl

ca. ..... approximately

CAN ..... cerium ammonium nitrate

Cy ..... cyclohexyl

dba ..... dibenzylideneacetone

DCC ..... *N*,*N*’-dicyclohexylcarbodiimide

DIAD ..... diisopropyl azodicarboxylate

DIEA .....diisopropylethylamine

DMAP .....dimethylaminopyridine

DMF .....dimethylformamide

Dpe-phos ..... bis(2-diphenylphosphinophenyl)ether

dppb..... 1,4-bis(diphenylphosphino)butane

dppe.....1,2-bis(diphenylphosphino)ethane

dppf .....1,1'-bis(diphenylphosphino)ferrocene

dr .....diastereomeric ratio

EDC.....1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

ee ..... enantiomeric excess

eq.....equation

equiv..... equivalents

ESI.....electrospray ionization

Et ..... ethyl

h.....hour(s)

HMDS .....hexamethyldisilazane

HMPA ..... hexamethylphosphoramide

HPLC .....high performance liquid chromatography

i-Pr..... isopropyl

LAH .....lithium aluminum hydride

LDA .....lithium diisopropylamide

Ln ..... ligand

M .....molarity

MAO ..... monoamine oxidase

Me ..... methyl

Ms .....mesyl

Mts .....mesitylenesulfonyl

NMR .....nuclear magnetic resonance

nOe.....nuclear Overhauser effect

tol .....tolyl

Pg .....protecting group

Ph .....phenyl

PMB .....*para*-methoxybenzyl

PMP.....*para*-methoxyphenyl

Pr .....propyl

rt .....room temperature

Tf.....trifluoromethanesulfonyl

TFA .....trifluoroacetic acid

TFAA ..... trifluoroacetic anhydride

THF ..... tetrahydrofuran

TMS ..... trimethylsilyl

Xantphos 9,9-dimethyl-bis-4,5-diphenylphosphinoxantphene

XPhos ..... 2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Abstract

Part One of this thesis describes the synthesis of heterocycles containing two heteroatoms via palladium-catalyzed carboamination and carboetherification reactions. The development of a new stereoselective synthesis of *cis*- and *trans*-disubstituted pyrazolidines from *N*-butenyl hydrazine derivatives is described. The products are generated with good to excellent diastereoselectivity and chemical yield and can be transformed to synthetically useful pyrazolines or 1,3-diamines via oxidation or reduction. Importantly, these experiments also demonstrate that allylic strain interactions can be manipulated through a simple substrate modification (N^2-protection vs. no N^2-protection) to allow for control of relative stereochemistry in Pd-catalyzed reactions. Upon completion of this work, we became interested in whether manipulation of allyic strain as a means to control product stereochemistry would be applicable in the synthesis of other heterocycles. Thus, application of this concept in isoxazolidine synthesis is described. A new method for pyrrolidinone synthesis via Pd-catalyzed carboamination of γ,δ-unsaturated amides with aryl or alkenyl bromides is also described. The pyrrolidinone products are accessed in good to excellent yields, and have the potential to be useful precursors in a variety of other interesting transformations.

Part Two of this thesis describes new methods for the enantioselective synthesis of diols and amino-alcohols. The research presented in Chapters VI-VII describe development of a tandem reaction sequence towards a new method for the formation of enantioenriched α-alkyl-α,β-dihydroxy esters (Wittig rearrangement/aldol reactions) and

α-alkyl-α-hydroxy-β-amino esters (Wittig rearrangement/Mannich reactions) involving reaction of chiral glycolate esters with various electrophilic coupling partners. The asymmetric Wittig/Aldol reactions are the first examples of tandem reactions involving enolate [1,2]-Wittig rearrangements that afford nonracemic products, and are also the first asymmetric aldol reactions of α-alkyl-α-hydroxy ester enolates that generate unprotected diol products with both high *syn*:*anti* selectivity and high ee. In addition, these results have led to the development of the first asymmetric Mannich reactions of ester enolates that afford both *syn*- and *anti*-α-alkyl-α-hydroxy-β-amino esters with both high dr and ee. These are also the first examples of asymmetric Mannich reactions that proceed via tetrasubstituted enolboronate intermediates.

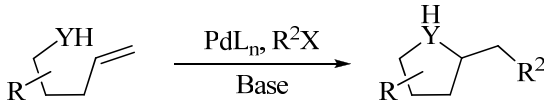
Part One

Synthesis of Heterocycles with Two Adjacent Heteroatoms via Palladium-Catalyzed Carboamination and Carboetherification Reactions

Chapter I

Mechanism and Stereochemistry of Carboamination Reactions that Provide Pyrrolidine Products

Over the past several years, research in the Wolfe group has been focused on the development of transition-metal catalyzed processes to construct various types of saturated heterocycles,[1] which are key components in many biologically active compounds and natural products. In its simplest form, this methodology involves transformation of γ-amino or γ-hydroxy alkene substrates **I-1** into heterocyclic products **I-2** such as pyrrolidines[2] or tetrahydrofurans[3] using a transition metal catalyst and an aryl or vinyl halide coupling partner (eq 1). These cross-coupling reactions, termed "carboamination" (when the cyclizing heteroatom is nitrogen) and "carboetherification" (when the cyclizing heteroatom is oxygen) have proven to be some of the most concise methods to construct saturated heterocycles in a highly stereoselective fashion.



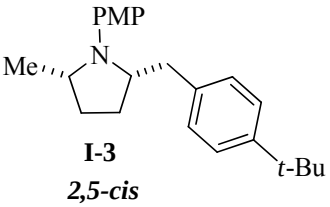
(1)

I-1
Y = NR^1, O
X= Br, Cl, I

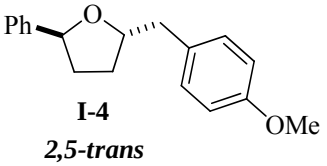
I-2
R^2 = Aryl, vinyl

To date, catalysts composed of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and various phosphine ligands allow for successful cyclization of a wide variety of substrates, and many different 5- and 6-memebered nitrogen- and oxygen-containing heterocycles have been accessed in good yields and in with good to excellent selectivities (Figure I-1). For example, pyrrolidines[2] **I-3**, tetrahydrofurans[3] **I-4**, isoxazolidines[4] **I-5**, piperazines[5] **I-6**, and imidazolidin-2-ones[6] **I-7** have all been prepared in a highly stereoselective fashion via carboamination or carboetherification processes. This methodology is not only interesting from a synthetic standpoint, in that key carbon-heteroatom bonds are formed via a novel *syn*-heteropalladation process, but it also serves as a straightforward method for the construction of biologically significant molecules from relatively simple alcohol or amine precursors. Although there are many existing methods for the synthesis of pyrrolidines[7] and tetrahydrofurans,[8] few allow for simultaneous construction of the core heterocycle as well as a carbon-carbon bond adjacent to the newly formed ring, which is a highlight of carboamination and carboetherification methodology.

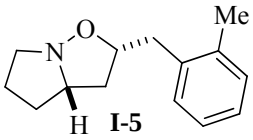
Figure I-1. Recent Products of Palladium-Catalyzed Carboamination and Carboetherification Reactions



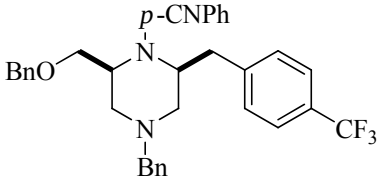
I-3
2,5-cis
Pyrrolidine
66%, >20:1 dr



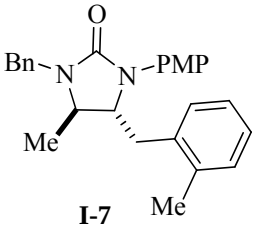
I-4
2,5-trans
Tetrahydrofuran
62%, >20:1 dr



I-5
3,5-cis
Isoxazolidine
82%, >20:1 dr



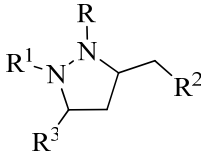
I-6
2,6-cis
Piperazine
69%, 14:1 dr



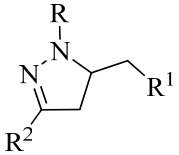
I-7
4,5-trans
Imidazolidin-2-one
71%, 12:1 dr

The research presented in Chapters II–IV of this thesis will describe the extension of carboamination and carboetherification processes towards development of new routes for formation of pyrazolidines[9] **I-8**, pyrazolines[9] **I-9**, isoxazolidines[10] **I-10**, and pyrrolidinones[11] **I-11** (Figure I-2). These heterocycles are interesting from a biological standpoint,[12,13,14,15] and the methodology developed for their construction is mechanistically related to carboamination reactions for the synthesis of substituted pyrrolidines.

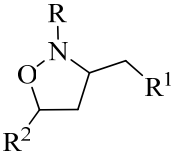
Figure I-2. Target Heterocycles of Studies in Chapters II–IV



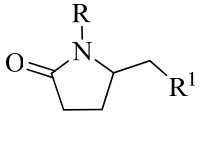
I-8
Pyrazolidine



I-9
Pyrazoline



I-10
Isoxazolidine

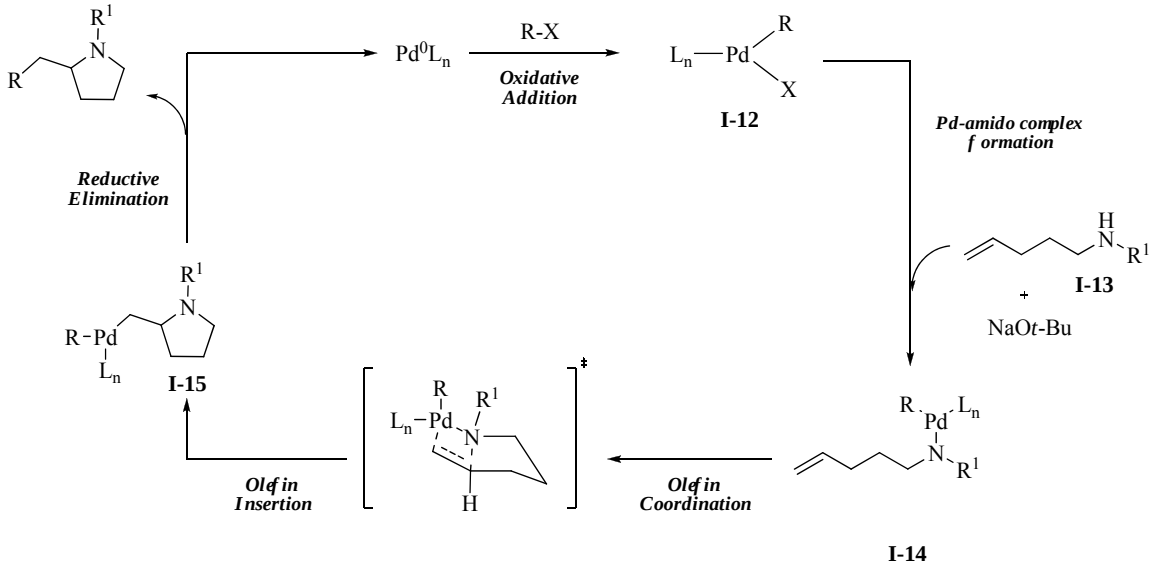


I-11
Pyrrolidinone

I.1 Mechanism of Palladium-Catalyzed Carboamination Reactions

The mechanism of pyrrolidine-forming carboamination reactions is shown in Scheme I-1, and begins with oxidative addition of an aryl or alkenyl halide to a Pd(0) catalyst, to afford complex **I-12**. Subsequent deprotonation and coordination of the γ-amino alkene substrate **I-13** to **I-12** results in formation of Pd-amido complex **I-14**. Coordination of the alkene followed by *syn*-insertion of the alkene into the Pd-nitrogen bond results in formation of the key C–N bond and the core of the pyrrolidine. Reductive elimination from **I-15** leads to formation of a C–C bond, installing the aryl or alkenyl moiety, and regenerating the Pd(0) catalyst.

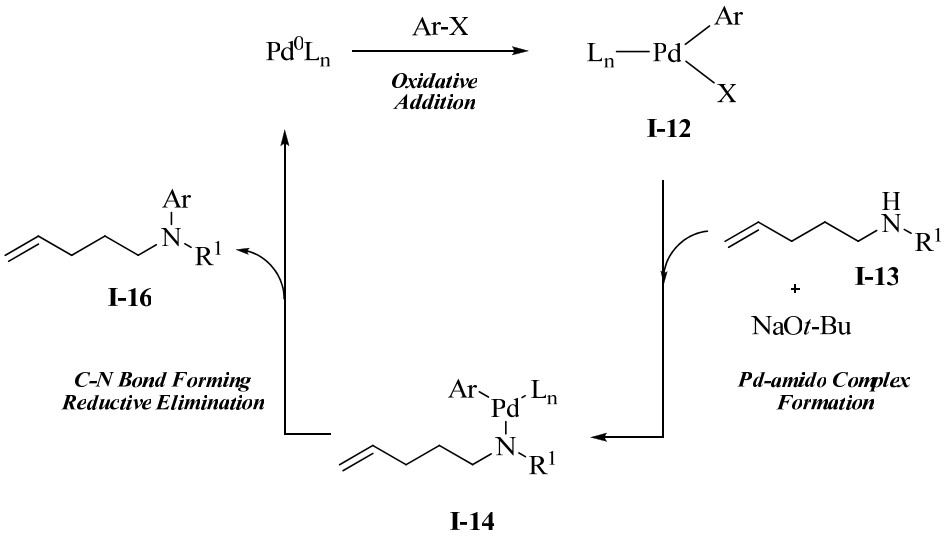
Scheme I-1. Palladium-Catalyzed Carboamination Catalytic Cycle



Previous studies have shown that side products arising from *N*-arylation of the γ-amino alkene substrate are occasionally formed in these reactions, and *N*-arylation reactions of amines are known to proceed via intermediates similar to those accessed in

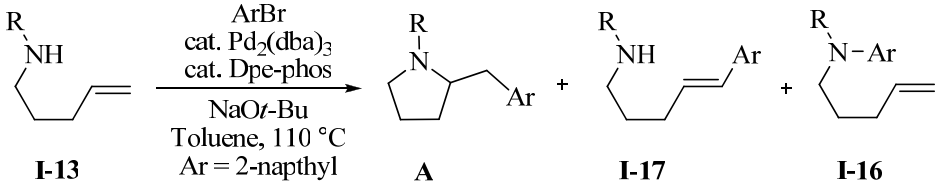
the carboamination process.[1] For example, C-N bond forming reductive elimination form **I-14** can occur to generate **I-16** (Scheme I-2). Manipulation of the nucleophilicity of the amine substrate can serve as a means to circumvent this issue, as less nucleophilic amines undergo relatively slow reductive elimination.[16]

Scheme I-2. Mechanism of Formation of *N*-Arylated Side-Products



Substrates bearing aromatic groups on nitrogen have been found to be viable coupling partners in the carboamination process,[2a] and since these initial studies, more traditional nitrogen protecting groups such as acetyl and Boc have been utilized (Table I-1).[2b] The nature of the phosphine ligand also has a large influence on product distribution. Typically chelating phosphines with wide bite angles such as Dpe-phos[17] have provided good results, although studies have shown that the optimal ligand for a given transformation is often dependant on substrate structure.[1]

Table I-1. *N*-Substituent Effects and Side Product Formation



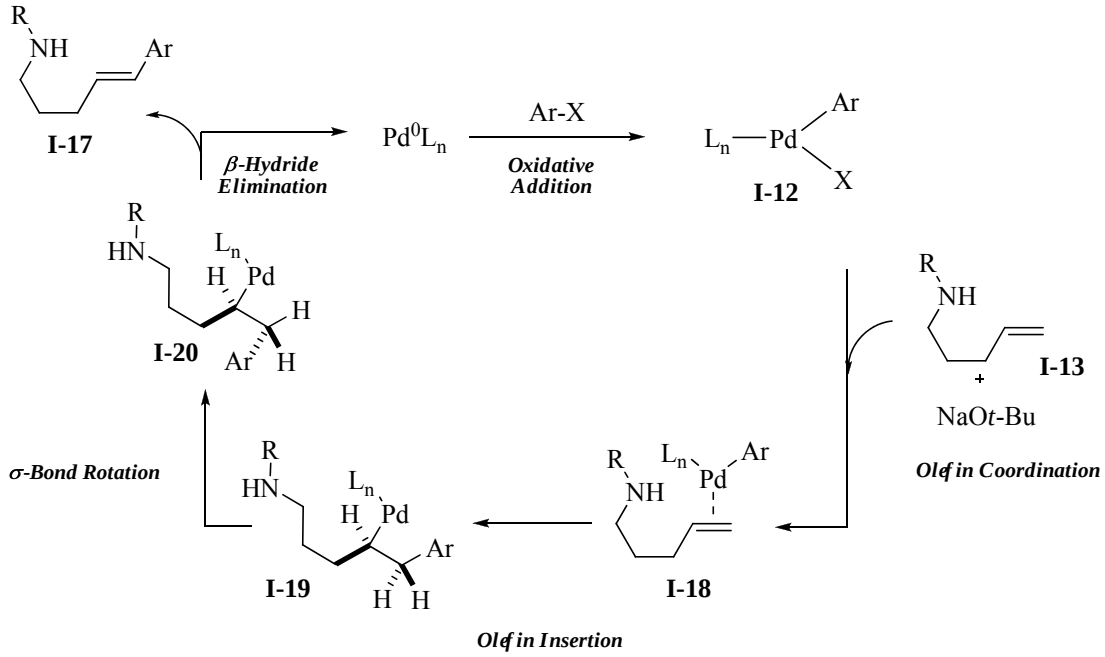
I-13 **A** **I-17** **I-16**

N-Substituent (R)	GC Ratio		
	A	**I-17**	**I-16**
Bn[a]	-	40[b]	34
Ph	75[c-d]	-	25
Ac[a]	88	12	-
Boc[a]	82	4[b]	-

[a] Other minor, unidentified side products were also observed. [b] Mixtures of alkene regioisomers were obtained. [c] This product was obtained as a 15:1 mixture of regioisomers. [d] Use of dppb as a ligand provided a 94% isolated yield of **A** as a 25:1 mixture of regioisomers. See Ref. 2a.

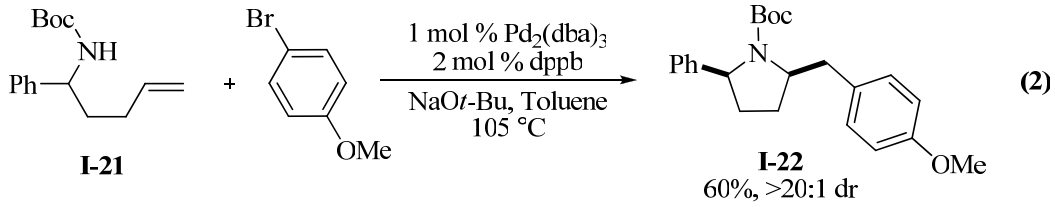
Along with competing *N*-arylation pathways, side products resulting from Heck arylation of the substrate may also be formed under carboamination reaction conditions. Heck-arylated products **I-17** are seen in the case of the acetyl and Boc protected substrates (Table I-1). The mechanism for formation of **I-17** involves coordination of the alkene to oxidative addition complex **I-12** (Scheme I-3).[2b] Once coordinated, *syn*-addition of the olefin into the Pd-Ar bond of complex **I-18** occurs to afford **I-19**, followed by bond rotation to intermediate **I-20**. Termination of the catalytic cycle via *cis*-β-hydride elimination from **I-20** regenerates the catalyst, and affords Heck arylation product **I-17**.

Scheme I-3. Mechanism of Heck-Arylated Side Product Formation



I.2 Stereoselectivity in Carboamination Reactions

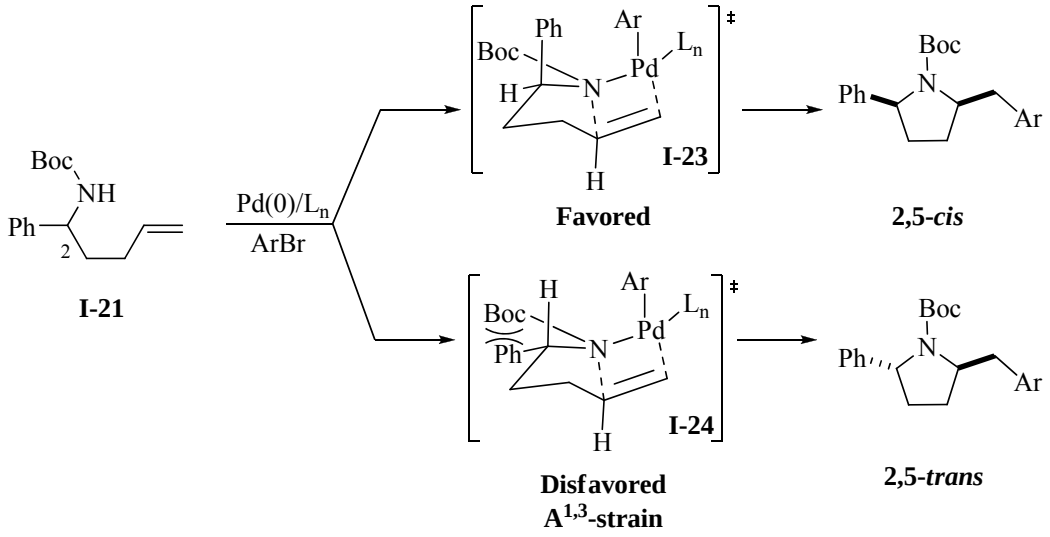
Carboamination reactions of starting materials containing a stereocenter adjacent to the nitrogen atom provide *cis*-2,5-disubstituted pyrrolidines with high diastereoselectivity. For example, treatment of phenyl-substituted γ-amino alkene substrate **I-21** with 4-bromoanisole, sodium *tert*-butoxide and a catalyst composed of $Pd_2(dba)_3$ and dppb affords **I-22** in 60% yield and with >20:1 dr (eq 2).[2b]



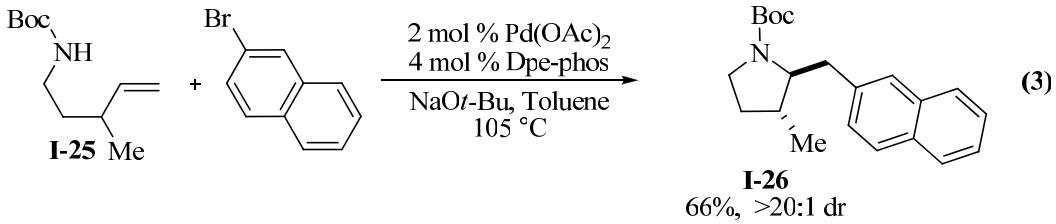
(2)

Carboamination reactions of substrates such as **I-21** are believed to proceed via transition state **I-23**, in which the C2-substituent lies in a pseudoaxial position (Scheme I-4). The alternative transition state **I-24**, with the C2-substituent in a pseudoequatorial position is disfavored since a significant $A^{1,3}$-strain interaction would arise between the R-group and the Boc protecting group on nitrogen. In principle, the selectivity of this reaction could be reversed by employing primary amine substrates. This would alleviate the $A^{1,3}$-strain interactions and provide the *trans*-2,5-disubstituted product. However, all attempts to employ primary amines have led only to *N*-arylated products.[2b]

Scheme I-4. Transition States for 2,5-Disubstituted Pyrrolidine Synthesis

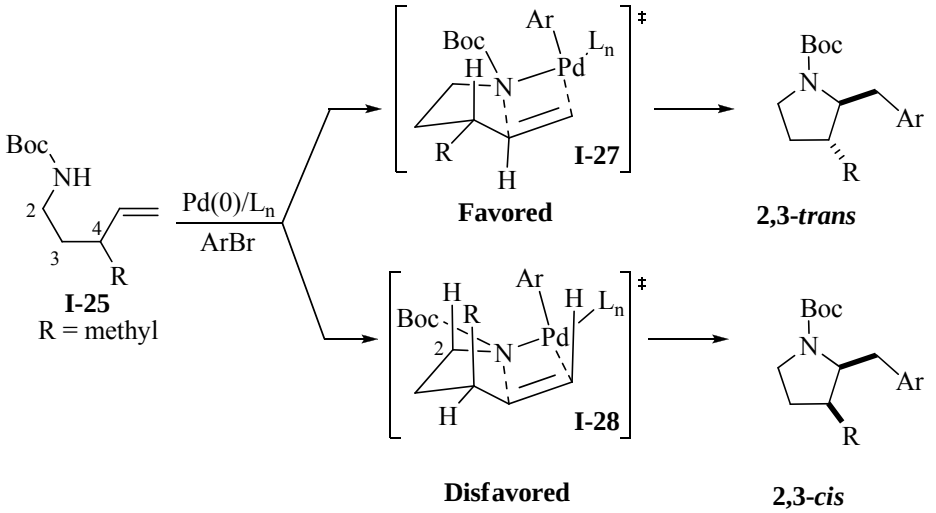


Carboamination reactions have also proven to be very stereoselective for formation of *trans*-2,3-disubstituted pyrrolidine products. For example, the reaction of **I-25** with 2-bromonaphthalene in the presence of a catalyst composed of $Pd(OAc)_2$ and Dpe-phos provides **I-26** in 66% yield and with >20:1 dr (eq 3).

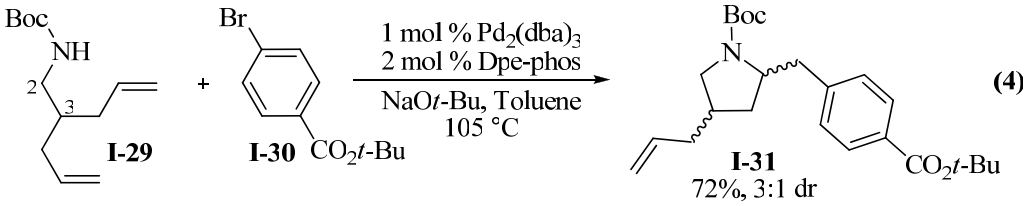


The high selectivity observed for *trans*-2,3-disubstituted pyrrolidine products with substrates of this type is believed to arise via transition state **I-27**, in which the R-group lies in a pseudoequatorial position (Scheme I-5). The alternative transition state (**I-28**) suffers from an unfavorable 1,3-diaxial interactions between the R-group and the hydrogen atoms on C2. In addition, this transition state also suffers from $A^{(1,3)}$-strain between the R-group and the illustrated hydrogen atom of the alkene.

Scheme I-5. Transition States for 2,3-Disubstituted Pyrrolidine Synthesis



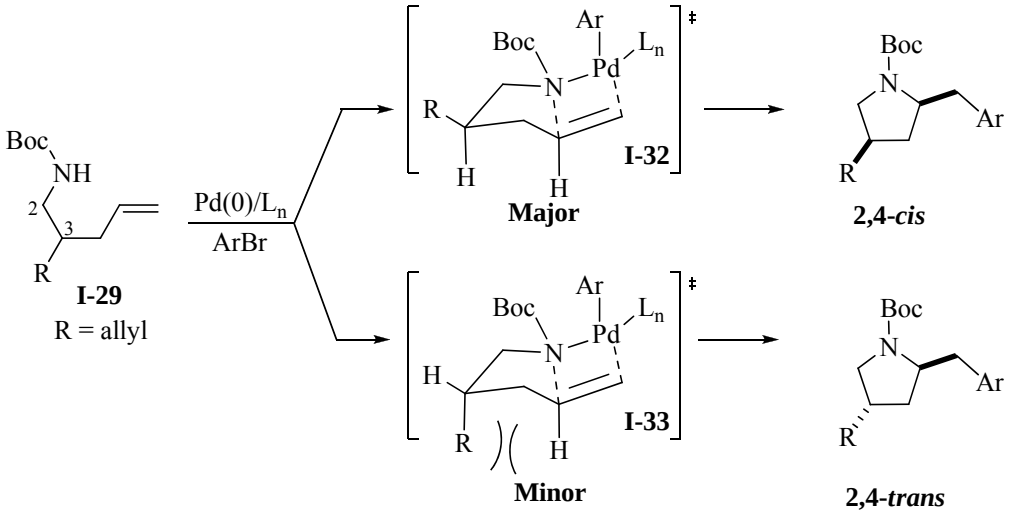
In contrast to transformation of substrates substituted at C2 or C4, the reaction of C3-substituted γ-amino alkene substrate **I-29** with aryl halide **I-30** provides **I-31** with only modest diastereoselectivity (eq 4).



(4)

Transition states leading to *cis*- or *trans*- **I-31** are illustrated in Scheme I-6. The observed modest selectivity suggests these transition states are fairly close in energy. In transition state **I-33** only a single unfavorable 1,3-diaxial interaction is present.

Scheme I-6. Transition States for 2,4-Disubstituted Pyrrolidine Synthesis



Issues of allyic strain and stereoselective synthesis will be a primary focus of studies discussed in subsequent chapters of this thesis. The development of methodology

for the construction of substituted pyrazolidines, pyrazolines, isoxazolidines, and pyrrolidinones will be described, as well as the scope and limitations of these methods.

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[16] *N*-arylated side-products are observed in carboamination reactions of Ph- and Bn-protected γ-amino alkene substrates. Installation of Boc and Ac protecting groups on nitrogen render γ-amino alkene substrates less nucleophilic. Therefore, *N*-arylated side-product formation is eliminated in carboamination reactions of these substrates.

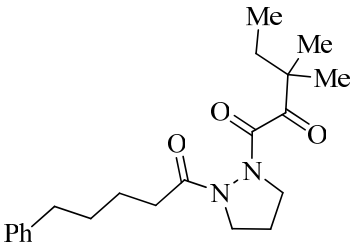
[17] Dpe-phos = bis(2-diphenylphosphino)phenyl ether.

Chapter II

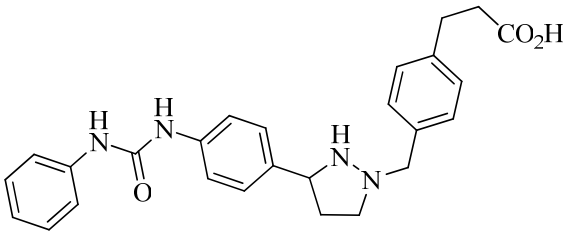
Diastereoselective Synthesis of Pyrazolidines via Palladium-Catalyzed Carboamination Reactions

Pyrazolidines are a core functional unit found in a variety of biologically active molecules.[1,2a,3] Most known biologically active pyrazolidines are structurally similar to compound **II-1**, which lacks substitution along the backbone (Figure II-1). This FKBP12 ligand and potent neuroprotective agent has the potential to be useful in therapy to treat degenerative disorders of the nervous system such as Parkinson's disease.[3c]

Figure II-1. Biologically Active Pyrazolidines



II-1
FKBP12 antagonist

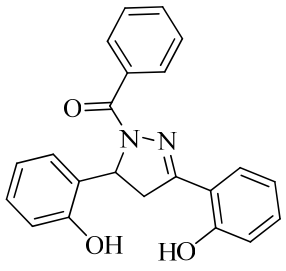


II-2
VLA-4 antagonist

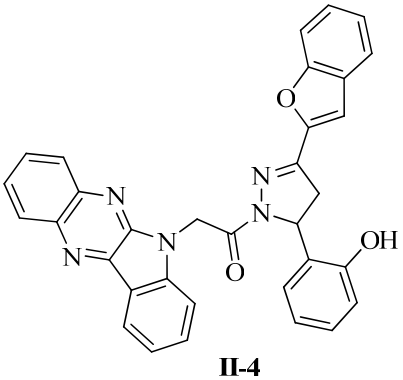
Although many different unsubstituted pyrazolidines such as **II-1** have been synthesized and assayed for biological activity, far fewer have been examined that bear substitution along the backbone of the heterocycle.[4] Compound **II-2** is one example in which substitution along the heterocycle's backbone was important in rendering it a potent VLA-4 antagonist (Figure II-1). It should be expected that more of these types of substituted pyrazolidine derivatives will be screened in the future.[3a]

Pyrazolidines can be oxidized to afford pyrazolines,[5,6] or pyrazoles,[7,8] which are useful in medicinal chemistry applications. Some examples of pyrazolines with interesting biological properties include **II-3**, a known monoamine oxidase inhibitor, and compound **II-4** which has been shown to exhibit antibacterial activity against *Escherichia coli* (Figure II-2).[9] Additionally, the N–N bond of pyrazolidines can be cleaved under reducing conditions to afford synthetically useful 1,3-diamines such as the HIV protease inhibitor **II-5** (Figure II-2).[2c-d,10]

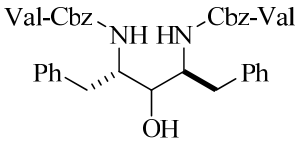
Figure II-2. Biologically Active Pyrazolines and 1,3-Diamines



II-3
MAO inhibitor



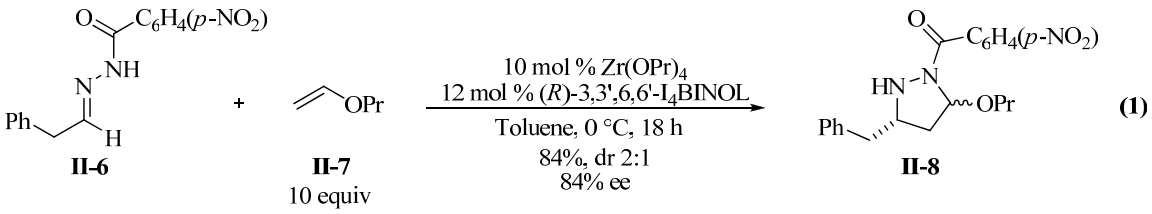
II-4
Antimicrobial Activity



II-5
HIV-1 Protease Inhibitor

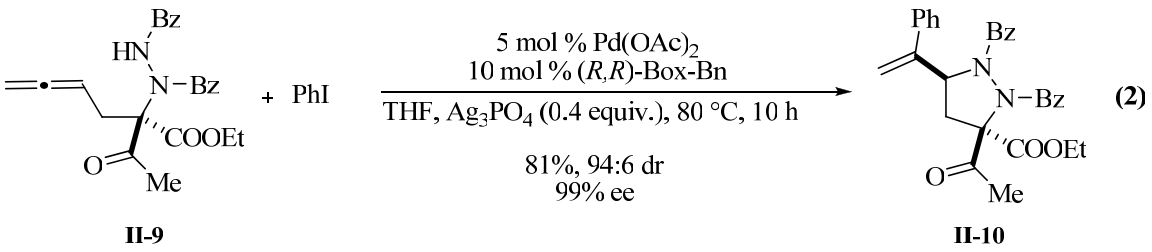
II.1 Methods of Pyrazolidine Synthesis

The most convergent method for 3,5-disubstituted pyrazolidine synthesis involves [3+2] cycloaddition of hydrazones to olefins. In a recent example from the Kobayaski group, hydrazone **II-6** can be reacted with electron rich olefins such as **II-7** and a zirconium catalyst to afford 3,5-disubstituted pyrazolidines **II-8** (eq 1).[11,12] Although this Lewis acid catalyzed cycloaddition reaction affords good overall yields of the desired pyrazolidine products, the levels of diastereoselectivity are quite modest (~2:1) and the requirement for a large excess of the olefinic coupling partner is a limitation of this methodology.



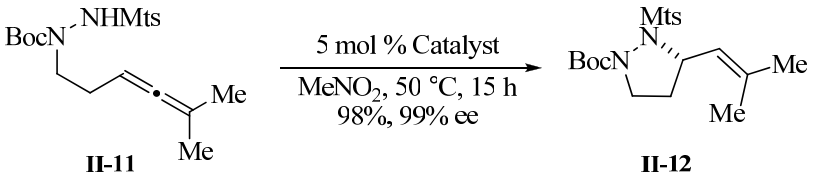
(1)

The palladium-catalyzed cyclization of allenylic hydrazine derivates has been found to generate enantiopure pyrazolidine products (eq 2).[13] For example, conversion of **II-9** to pyrazolidine **II-10** in 81% yield and 99% ee has been accomplished through use of a catalyst composed of $Pd(OAc)_2$ and (*R*,*R*)-Box-Bn. However, these reactions are limited to substrates bearing benzoyl protecting groups on both *N*-atoms and only aryl halides have been examined as coupling partners.

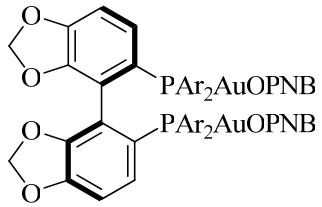


II-9 **II-10** **(2)**

Pyrazolidines have also been accessed asymmetrically via a Au(I)-catalyzed hydroamination process.[14] For example, the homoallenic hydrazine **II-11** can be converted to enantioenriched pyrazolidine product **II-12** in excellent yield and enantiopurity (eq 3). However, only monosubstituted products were generated via this method.



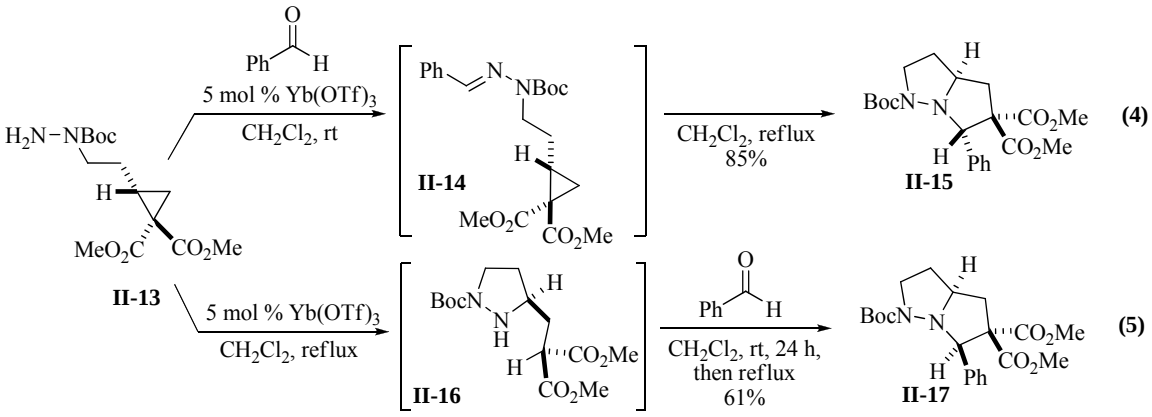
II-11 **II-12** **(3)**



Catalyst
Ar = 3,5-di-*tert*-butyl-4-methoxyphenyl
[(*R*)-DTBM-Segphos(AuOPNB)$_2$]

Fused bicyclic pyrazolidines have been accessed via an intramolecular hydrazone/cyclopropane annulation reaction sequence.[15] When cyclopropyldiester **II-13** is reacted in the presence of benzaldehyde followed by Yb(OTf)$_3$, the 2,5-*trans*-fused pyrazolidine **II-15** is formed in 85% yield via intermediate hydrazone **II-14** (eq 4). The

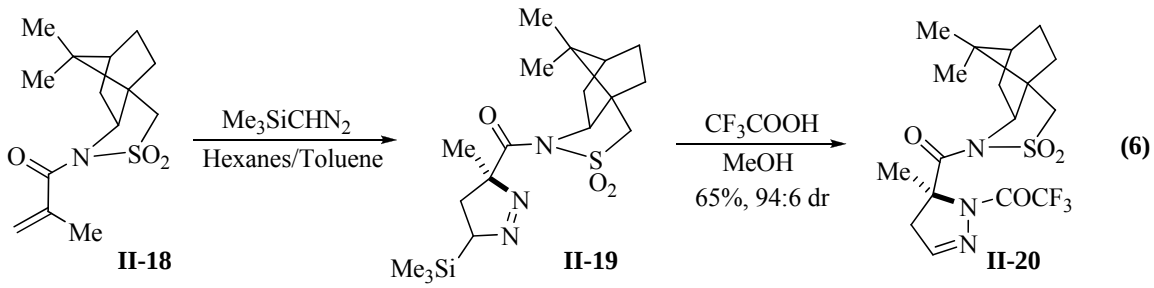
ability to access either 2,5-*trans*- or 2,5-*cis*- products is possible via controlling the order of addition of the catalyst and aldehyde. Subjection of **II-13** to $Yb(OTf)_3$ prior to addition of the aldehyde results in formation of the 2,5-*cis*-fused product **II-17** via intermediate pyrazolidine **II-16**.



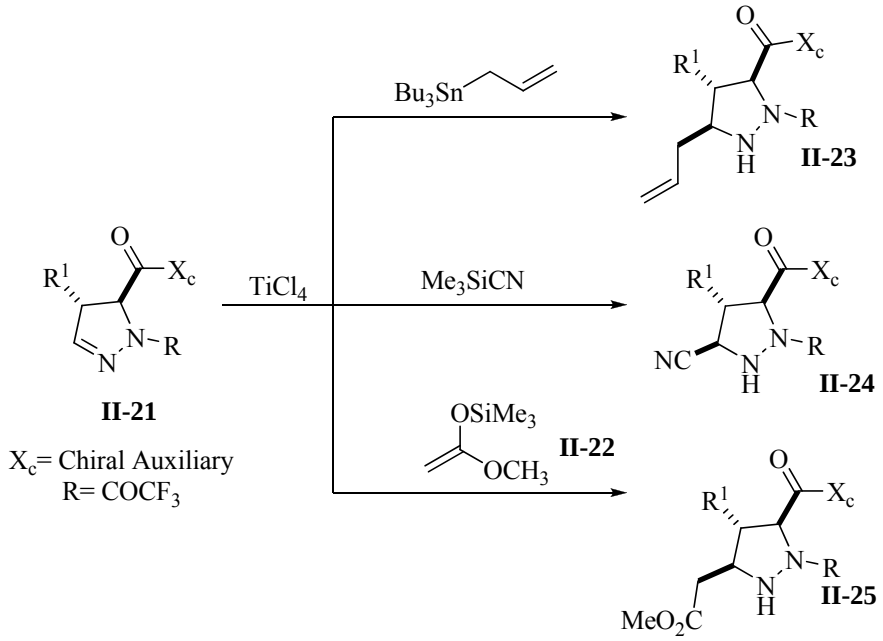
(4)

(5)

Leighton has described asymmetric dipolar cycloadditions of Me_3SiCHN_2 with dipolarophiles derived from a camphor sultam auxiliary to generate pyrazoline derivatives (eq 6).[16] For example, reaction of **II-18** with Me_3SiCHN_2 affords initially the Δ^1-pyrazoline **II-19**. Upon exposure of **II-19** to trifluoroacetic acid furnishes the Δ^2-pyrazoline in 65% yield and 94:6 diastereoselectivity. These pyrazoline products **II-20** are susceptible to diastereoselective addition reactions in the presence of $TiCl_4$.[17,18] Reaction of **II-21** with allyltributylstannane, trimethylsilyl cyanide, or the silyl ketene acetal **II-22** affords products of type **II-23**, **II-24**, and **II-25** respectively (Scheme II-1).

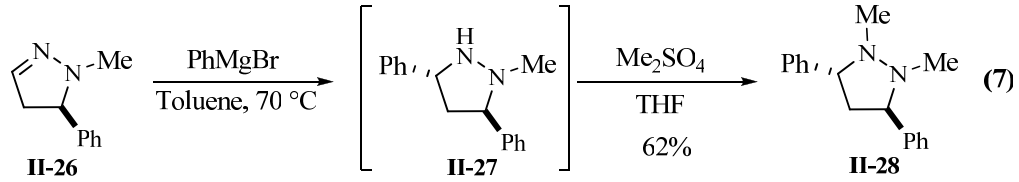


Scheme II-1. Additions to Pyrazolines to Afford Pyrazolidines

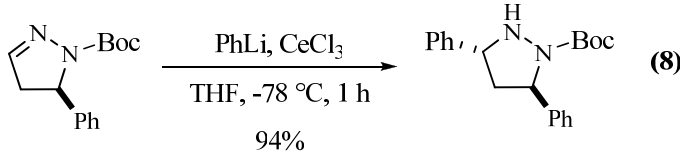


The transformations described in Scheme II-1 represent a relatively mild, nucleophilic method for addition to pyrazoline adducts. Other methods for nucleophilic additions to pyrazolines include the use of various Grignard and organocerium reagents, although reactivity of pyrazolines to these types of reagents varies from substrate to substrate.[19,20] Addition of phenylmagnesium bromide to pyrazoline **II-26**, followed by alkylation of the intermediate pyrazolidine **II-27** afforded **II-28** in 62% yield as a single

diastereomer (eq 7). Attempts to isolate the intermediate pyrazolidine were unsuccessful due to oxidation of the pyrazolidine to the pyrazoline during chromatography. Similarly, **II-30** was isolated in 94% yield as a single diastereomer through reaction of **II-29** with an in-situ generated organocerium reagent (eq 8). The success of these reactions is highly dependant on the quality and dryness of the cerium(III) chloride reagent.



II-26 **II-27** **II-28**

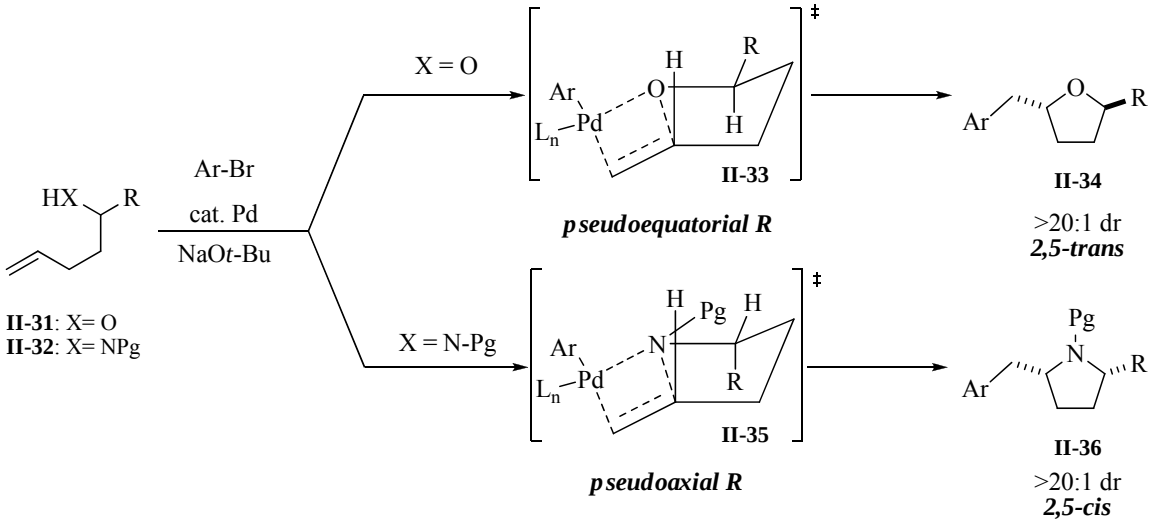


II-29 **II-30**

II.2 Stereochemical Hypothesis for Pyrazolidine Synthesis

As outlined in Chapter I, Pd-catalyzed reactions of γ-hydroxy- and γ-aminoalkenes with aryl bromides are efficient and convergent methods for the stereoselective construction of substituted oxygen- and nitrogen heterocycles.[21,22] However, the stereochemical outcome is substrate-controlled and it has not been possible to overcome inherent bias for formation of either *cis*- or *trans*- disubstituted products (Scheme II-2).

Scheme II-2. 2,5-Disubstituted Heterocycle Stereochemistry



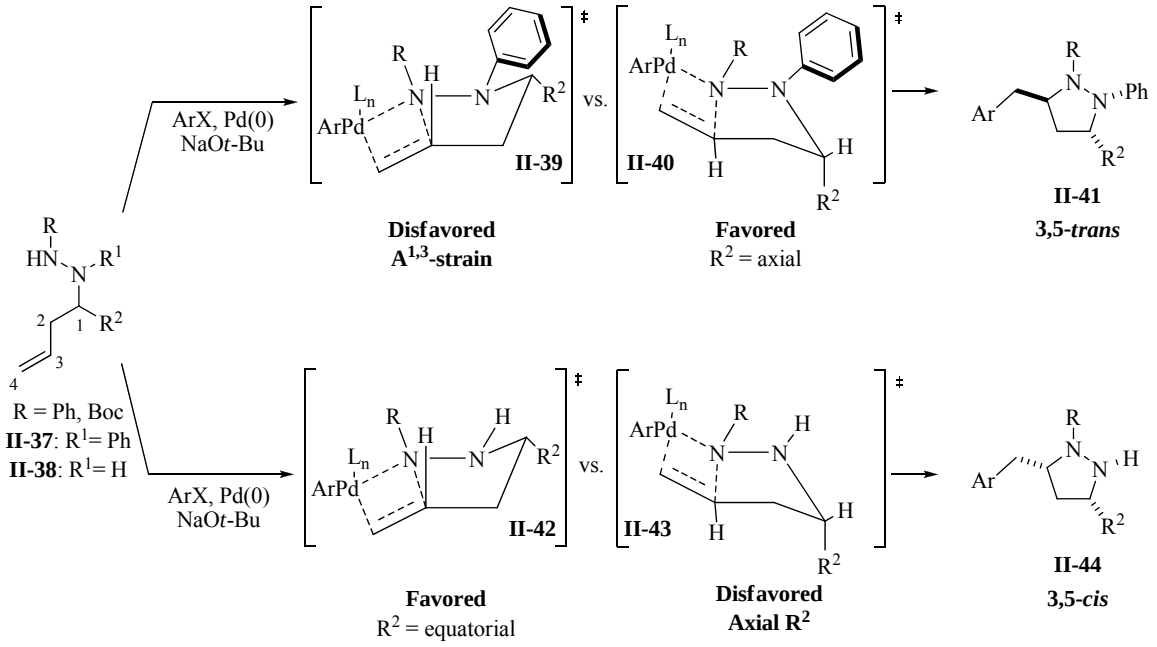
For example, secondary alcohol substrates **II-31** always afford *trans*-2,5-disubstituted tetrahydrofurans **II-34** via *syn*-oxypalladation through cyclic transition states **II-33** with pseudoequatorial orientation of the R-group (Scheme II-2).[22a,b] In contrast, reactions of analogous *N*-Boc or *N*-aryl amine substrates **II-32** provide *cis*-2,5-disubstituted pyrrolidines **II-36** via *syn*-heteropalladation with the R-group in a pseudoaxial position in the transition state **II-35** to minimize developing $A^{1,3}$-strain.[22c,d]

The model shown in Scheme II-2 suggests that product stereochemistry in Pd-catalyzed carboamination reactions could be controlled through variation of *N*-substituents to maximize or minimize $A^{1,3}$-strain, which would allow the synthesis of either stereoisomer of a heterocyclic target with only minor substrate modification. Although the impact of $A^{1,3}$-strain on stereoselective reactions is well-documented,[23] manipulation of $A^{1,3}$-strain to allow for selective generation of two different product

stereoisomers from closely related substrates is rare[24] and has not been demonstrated in Pd-catalysis.

As shown in Scheme II-3, it seemed that *trans*-3,5-disubstituted pyrazolidines **II-41** could be prepared from hydrazine substrates **II-37** bearing formally sp^2-hybridized N^2-atoms with π-accepting substituents, such as aryl groups or carbamates. These compounds should react via transition state **II-40** in which the C1 R^2-group is oriented in a pseudoaxial position to avoid unfavorable $A^{1,3}$-strain between the sp^2N–Ar group and the R^2-substituent that is present in transition state **II-39**. In contrast, we believed that selective synthesis of *cis*-3,5-disubstituted pyrazolidines **II-44** could be achieved through alleviation of unfavorable $A^{1,3}$-strain via cyclizations of substrates **II-38** lacking an N^2-substituent. This process should occur via transition state **II-42** with the R^2-group in a preferred pseudoequatorial position. The alternative transition state **II-43**, with the R^2-group in a pseudoaxial position, would be expected to be a higher energy transition state.

Scheme II-3. Transition States for Pyrazolidine Synthesis

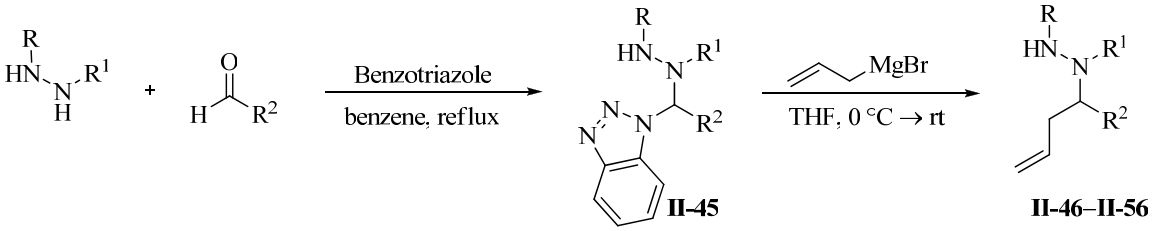


II.3 Synthesis of *N*-Butenyl Hydrazine Substrates

N-Butenyl hydrazines were initially selected as substrates for our studies on the effect of $A^{1,3}$-strain on product stereochemistry in Pd-catalyzed carboamination reactions, as the N^2-substituent of these compounds can be varied with minimal electronic perturbation to the cyclizing N^1-atom. Substrates for these studies were synthesized via a variety of simple methods. The first method involved a procedure developed by Katritzky[25] for formation of benzotriazole intermediates **II-45** via reaction of various hydrazines and aldehydes in the presence of benzotriazole (Table II-1). These intermediates then undergo nucleophilic substitution in the presence of allylmagnesium

bromide affording the desired *N*-butenyl hydrazine substrates **II-46–II-56** in good overall yields.

Table II-1. Synthesis of *N*-Butenyl Hydrazine Substrates

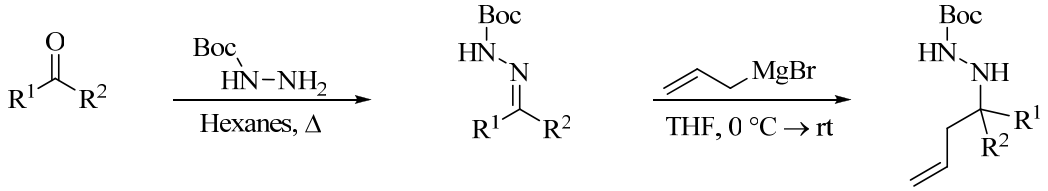


R	R^1	R^2	Product	Yield **II-46–II-56** Over 2 Steps
Ph	Ph	H	**II-46**	54%
Ph	Ph	C_3H_7	**II-47**	89%
Boc	Ph	H	**II-48**	85%
Boc	Ph	C_3H_7	**II-49**	55%
Boc	Ph	Ph	**II-50**	53%
Boc	Ph	$(CH_2)_4CH(OMe)_2$	**II-51**	54%
Boc	Ph	$(CH_2)_3CH{=}CH_2$	**II-52**	59%
Boc	PMP	C_3H_7	**II-53**	60%
Boc	PMP	Cy	**II-54**	51%
Boc	Me	C_3H_7	**II-55**	59%
Boc	Bn	C_2H_5	**II-56**	57%

A second method used to generate substrates lacking substitution on the internal nitrogen atom involved condensation of an appropriate aldehyde or ketone with *tert*-butyl carbazate followed by reaction of the intermediate hydrazones **II-57** with allyl magnesium bromide affording *N*-butenyl hydrazines **II-58** in good yield (Table II-2).[26] A

variety of substrates **II-59–II-64** could be synthesized through these methods, with a range of different substituents at the carbon atom α- to the internal nitrogen atom.

Table II-2. Synthesis of *N*-Butenyl Hydrazines Lacking Substitution on the Internal *N*-atom

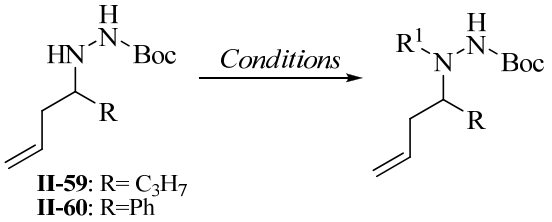


II-57 **II-58**

R^1	R^2	Yield **II-57**	Yield **II-58**	Product	Yield Over 2 Steps
C_3H_7	H	97%	74%	**II-59**	72%
Ph	H	96%	75%	**II-60**	72%
CH_3	CH_3	92%	51%	**II-61**	47%
-$(CH_2)_5$-		93%	71%	**II-62**	66%
Ph	CH_3	53%	42%	**II-63**	22%
CH_3	*t*-Bu	90%	47%	**II-64**	42%

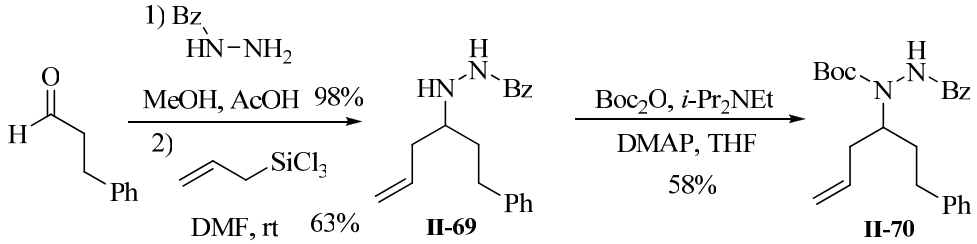
Substrates containing Boc-groups on both nitrogen atoms were synthesized via protection of **II-59** and **II-60** with Boc-anhydride to yield substrates **II-65** and **II-66** (Table II-3, Entries 1-2). Substrates with alternative protecting groups on N^2 were also synthesized. Treatment of **II-59** with Ac_2O and pyridine afforded **II-67** in 64% yield (Entry 3). Similarly, treatment of **II-59** with benzoyl chloride afforded **II-68** (Entry 4).

Table II-3. Synthesis of Substrates Bearing Carbamate Protecting Groups



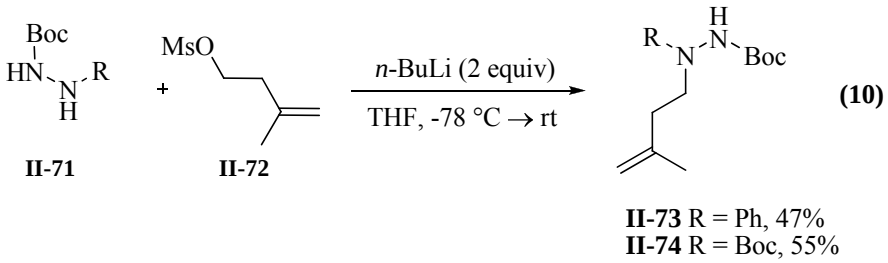
Entry	R	Conditions	Product	Yield	R^1
1	Ph	Boc_2O	**II-65**	96%	Boc
2	C_3H_7	Boc_2O	**II-66**	66%	Boc
3	C_3H_7	Ac_2O, pyr	**II-67**	64%	Ac
4	C_3H_7	BzCl, pyr	**II-68**	75%	Bz

In order to further probe the scope of substrate carbamate groups in our carboamination reactions, substrates bearing a N^1-benzoyl group were synthesized (eq 9). Upon formation of a benzoyl hydrazone, allylation with allyltrichlorosilane afforded **II-69** in good yield. A portion of this substrate was treated with Boc anhydride to give **II-70** as well.



We were also interested in examining substrates bearing substitution on the alkene, as these types of substrates would yield pyrazolidine products containing a

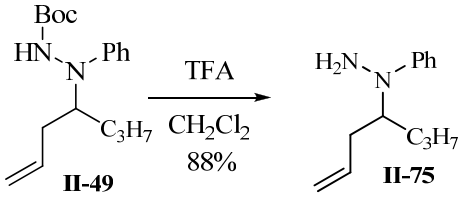
quaternary stereocenter. To this end, treatment of a hydrazine **II-71** with two equivalents of *n*-butyl lithium followed by reaction with mesylate **II-72** afforded **II-73** and **II-74** in moderate yields (eq 10).



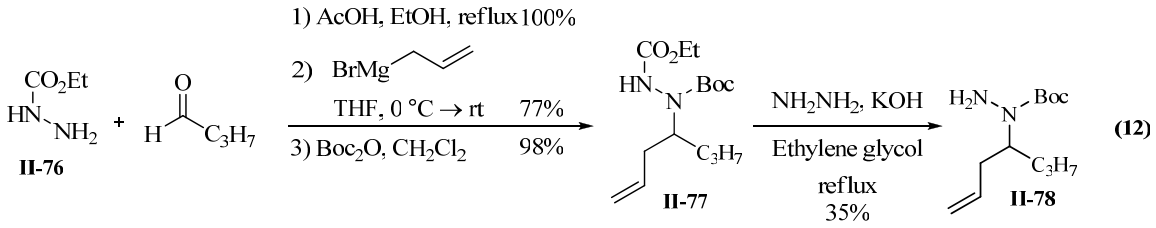
II-71 **II-72** **(10)**

II-73 R = Ph, 47%
II-74 R = Boc, 55%

Although substrates bearing free amines were not viable in previous carboamination reactions that afforded pyrrolidines,[21] we were interested in examining reactions of hydrazine substrates lacking N^1-substituents. A substrate of this type **II-75** bearing an N^2-phenyl group was accessed in 88% yield via treatment of **II-49** with trifluoroacetic acid in CH_2Cl_2 (eq 11). In order to access a substrate lacking an N^1-substituent but bearing an N^2-Boc group, a four step sequence was adoped (eq 12). Condensation of hydrazine **II-76** with butyraldehyde afforded a hydrazone which was subsequently treated with allylmagnesium bromide and Boc protected to yield **II-77** in excellent yield. Removal of the ethyl ester protecting group from N^1 was accomplished in moderate yield via treatment of **II-77** with hydrazine hydrate to afford **II-78**.



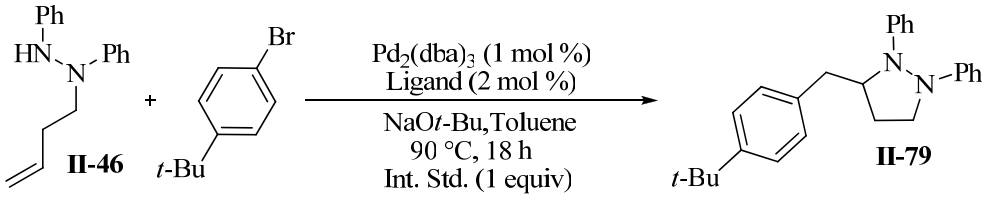
II-49 **II-75** **(11)**



II.4 Determining Reactivity: Ligand Study and Optimization

Prior to studying carboamination reactions of substrates **II-49** and **II-59**, we first elected to examine the reactivity of a simple *N*-butenyl hydrazine substrate. Thus, a ligand study was conducted involving the reaction of 1 equiv of *N,N'*-diphenyl hydrazine **II-46** with 1.7 equiv of 4-*tert*-butyl bromobenzene in the presence of 1 mol % $Pd_2(dba)_3$, and 1.7 equiv of NaO*t*-Bu (Table II-4). We were pleased to find that bidentate phosphine ligands facilitated the desired carboamination: dppe and Dpe-phos[27] provided the best overall yields of pyrazolidine **II-79**, as determined by ^{1}H NMR analysis. This initial ligand screen confirmed that *N*-butenyl hydrazines were viable substrates for pyrazolidine formation via a carboamination reaction and also that an active catalyst could be derived from several different ligands. Based on these results, a clear trend in ligand properties in terms of sterics/electronics was not evident. However, similar catalyst systems ($Pd(OAc)_2$/Dpe-phos or $Pd_2(dba)_3$/dppe) have been proven successful in related pyrrolidine and tetrahydrofuran reactions. Future work is merited in this area in terms of probing the influence of ligand sterics/electronics in carboamination reactions affording pyrazolidine products.

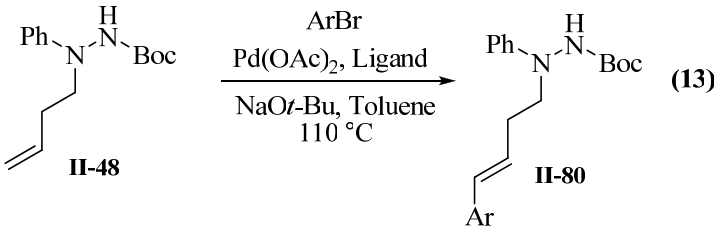
Table II-4. Palladium-Catalyzed Carboamination Ligand Screen



Ligand	^{1}H NMR Yield
dppb	66%
Dpe-phos	99%
dppe	88%
BINAP	64%
Xantphos	48%

Int. Std. = 1,3,5-trimethoxybenzene

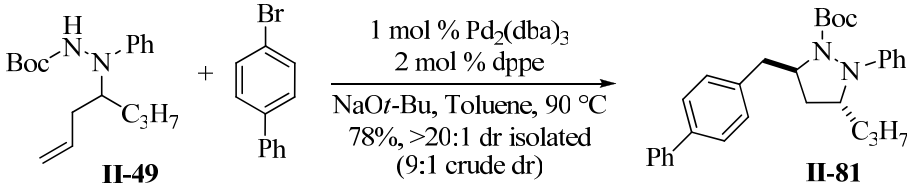
A substrate **II-48** bearing a Boc group on the cyclizing nitrogen atom was then examined with the two best ligands from the optimization study presented in Table II-4. However, attempts to cyclize **II-48** were unsuccessful and resulted in complex mixtures of products with a catalyst composed of $Pd_2(dba)_3$/dppe, and observation of Heck-arylated product **II-80** by crude ^{1}H NMR analysis with a catalyst composed of $Pd_2(dba)_3$/Dpe-phos (eq 13).



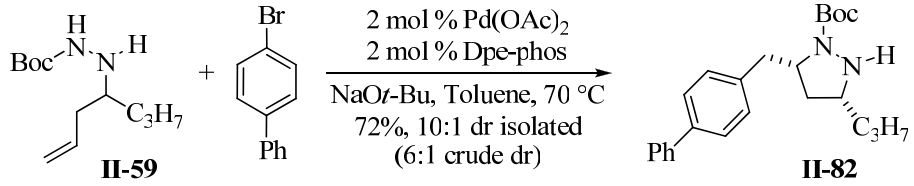
(13)

Ligand= dppe, Dpe-phos

We next elected to examine Pd-catalyzed carboamination reactions of 4-bromobiphenyl with N^2-butenylhydrazine derivatives **II-49** and **II-59** to test the hypothesis outlined in Scheme II-3. After some optimization, we found that treatment of **II-49** with 4-bromobiphenyl and NaO*t*-Bu in the presence of catalytic amounts of $Pd_2(dba)_3$ and dppe[27] afforded *trans*-3,5-disubstituted pyrazolidine **II-81** with 9:1 dr. Upon purification, **II-81** was obtained in 78% yield with >20:1 dr (eq 14). Use of dppe as ligand in the analogous reaction of **II-59** provided only trace amounts of pyrazolidine products, and afforded significant amounts of products resulting from Heck-arylation of the starting material. However, use of a $Pd(OAc)_2$/Dpe-phos catalyst provided satisfactory results, and led to the generation of *cis*-3,5-disubstituted pyrazolidine **II-82** with 6:1 dr. After column chromatography, **II-82** was obtained in 72% yield with 10:1 dr (eq 15). These results clearly demonstrate that product stereochemistry can be reversed by varying the degree of allylic strain in the transition state through a very simple modification of the substrate N^2-substituent.



(14)

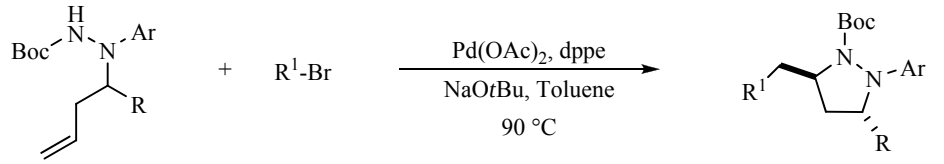


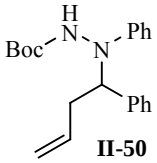
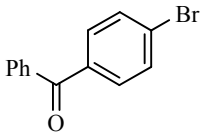
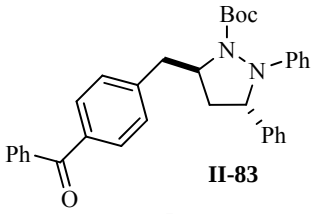
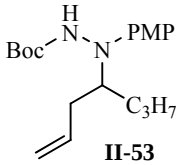
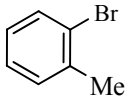
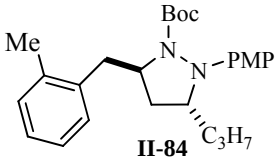
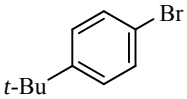
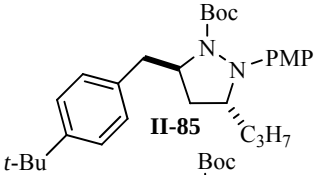
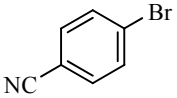
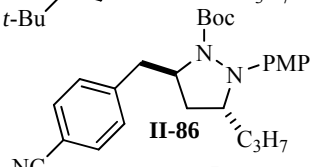
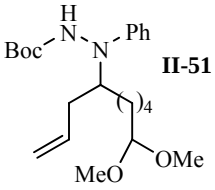
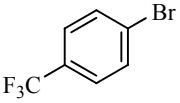
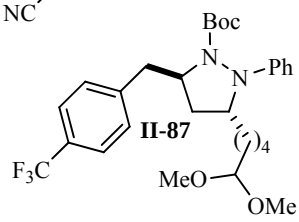
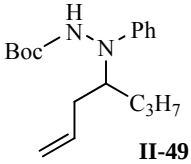
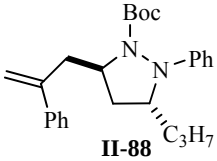
(15)

II.5 Stereoselective Synthesis of *trans*-3,5-Disubsititued Pyrazolidines

Having demonstrated that the stereoselective synthesis of *trans*-3,5-disubstituted pyrazolidines can be achieved using N^2-arylated substrates such as **II-49**, we proceeded to examine the scope of these transformations. As shown in Table II-5, the coupling reactions can be conducted with a variety of electron-rich, -neutral, and –poor aryl bromides and a number of functional groups are tolerated. Several substrates bearing aryl or unbranched alkyl substituents at C3 (**II-50**–**II-51** and **II-53**) were successfully transformed to *trans*-3,5-disubstituted pyrazolidines **II-83**–**II-87** in moderate to good yield. Pyrazolidines bearing differentially substituted nitrogen atoms (N^1-Boc, N^2-PMP) can be prepared in a straightforward manner and good to excellent levels of diastereoselectivity are obtained. Both $Pd_2(dba)_3$ and $Pd(OAc)_2$ precatalysts provided similar results in these reactions. Curiously, although the coupling of 4-bromobiphenyl with hydrazine **II-49** proceeded with good diastereoselectivity (9:1 dr, eq 14), use of α-bromostyrene as an electrophilic coupling partner with this substrate (Table II-5, Entry 6) led to the formation of **II-88** with only 2:1 dr. However, partial separation of diastereomers was achieved during purification and **II-88** was isolated in 70% yield as a 10:1 mixture of stereoisomers. The origin of the diminished diastereoselectivity in this reaction is not clear, although this effect has been previously observed in related Pd-catalyzed carboamination reactions of *N*-allylureas.[28]

Table II-5. Synthesis of *trans*-3,5-Disubstituted-N^2-Aryl Pyrazolidines[a]

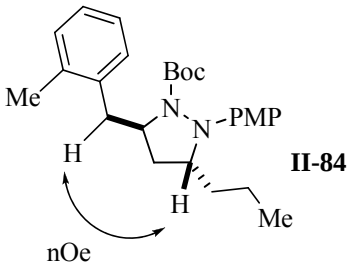


Entry	Hydrazine	ArBr	Product	Yield,[b] dr[c]
1	 **II-50**		 **II-83**	74%, 20:1 (11:1)
2	 **II-53**		 **II-84**	61%,[d] >20:1 (10:1)
3	**II-53**		 **II-85**	55%, >20:1 (8:1)
4	**II-53**		 **II-86**	63%, >20:1 (>20:1)
5	 **II-51**		 **II-87**	64%,[e] >20:1 (>20:1)
6	 **II-49**		 **II-88**	70%,[f] 10:1 (2:1)

[a] Conditions: 1.0 equiv hydrazine, 1.7 equiv ArBr, 1.7 equiv NaO*t*-Bu, 2 mol % $Pd(OAc)_2$, 2 mol % dppe, toluene (0.25 M), 90 °C, 3–12 h. [b] Isolated yield, average of two or more experiments. [c] Diastereomeric ratios are reported for the isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures. [d] The reaction was conducted using $Pd_2(dba)_3$ as precatalyst. [e] The reaction was conducted with 4 mol % P(2-furyl)$_3$ in place of dppe. [f] The reaction was conducted with 4 mol % Dpe-phos in place of dppe.

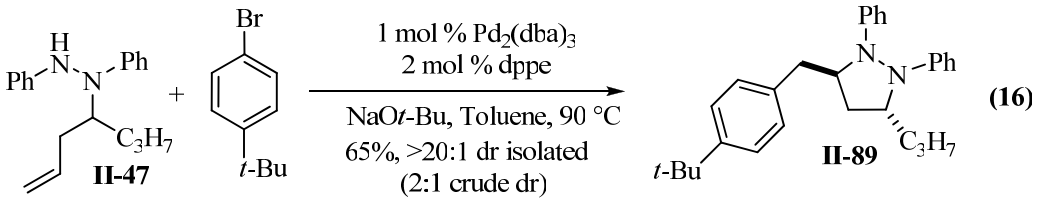
NMR techniques were used to establish product stereochemistry in this transformation. The 3,5-*trans* stereochemistry of **II-84** was assigned on the basis of nOe signals depicted in Figure II-3. The stereochemistry of the other *trans*-3,5-disubstituted pyrazolidine-1-carboxylate products was assigned based on analogy to **II-84**.

Figure II-3. Assignment of Stereochemistry of 3,5-*trans*-Disubstituted N^1-Boc-N^2-Aryl Pyrazolidines



II-84

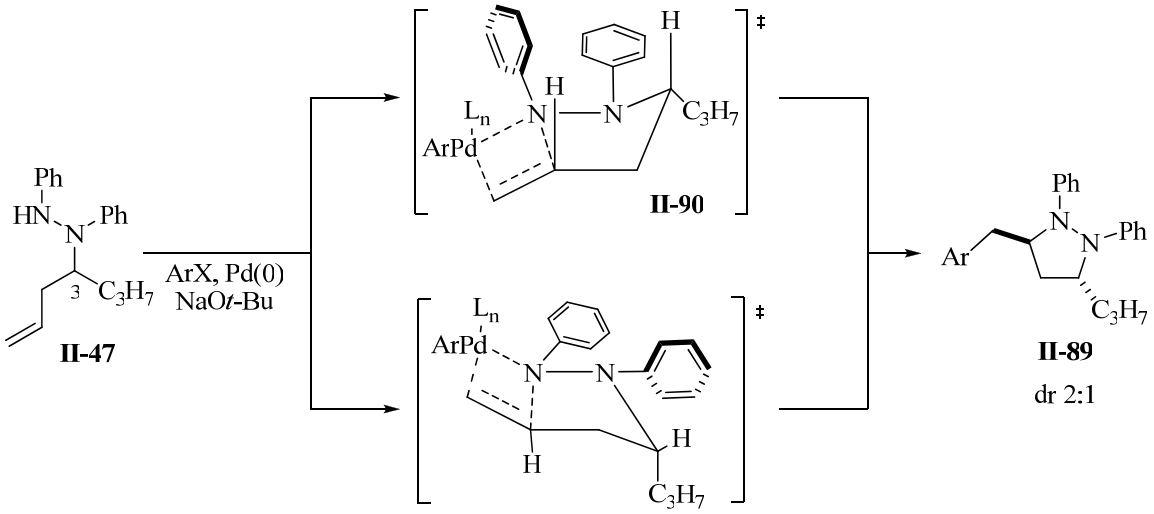
The presence of a Boc-group on N^1 was essential for the stereoselective preparation of *trans*-3,5-disubstituted N^2-aryl pyrazolidines. As shown in Equation 16, the carboamination of 1,2-diphenylhydrazine-derived substrate **II-47** with 4-bromo-*tert*-butylbenzene proceeded to yield **II-89** with only 2:1 diastereoselectivity. However, the minor diastereomer proved to be separable by chromatography.



(16)

The diminished stereoselectivity observed in this transformation may be due to an unfavorable steric interaction between the N^1-Ph group and the N^2-Ph group that leads to rotation of the N^2-Ph group and pyramidalization of the N^2-atom. This would decrease the allylic strain interaction present in transition state **II-90** (Figure II-4) and result in the formation of increased amounts of the minor stereoisomer.

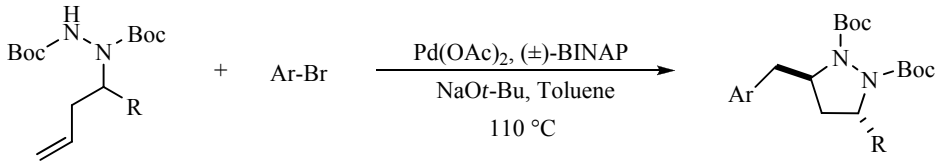
Scheme II-4. Diminished Selectivity in Reactions of *N*,*N*'-Di-Phenyl Hydrazine Carboamination

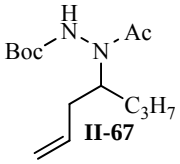
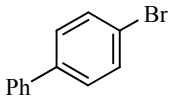
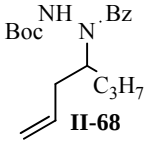
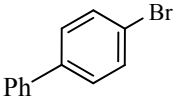
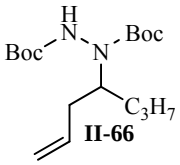
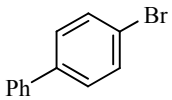
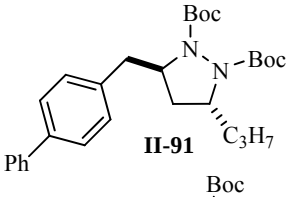
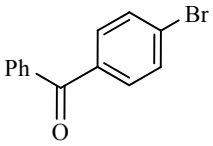
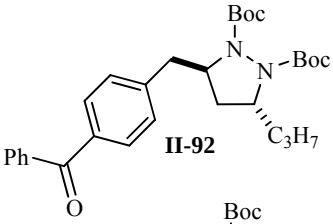
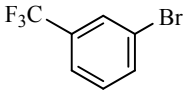
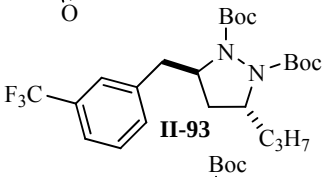
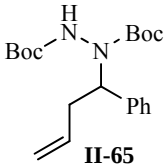
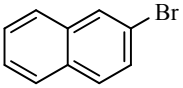
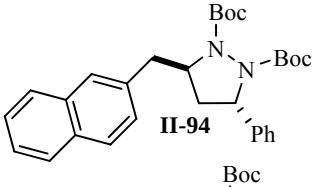
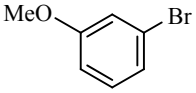
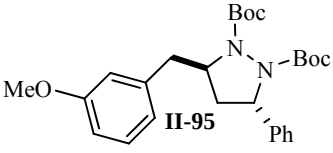


The hypothesis outlined in Scheme II-3 suggests that replacement of the N^2-aryl substituent on the substrate with other π-accepting groups should also allow for the construction of *trans*-3,5-disubstituted pyrazolidines. Therefore, the reactivity of several butenylhydrazine derivatives bearing N^2-carbonyl functionality was examined. Our initial attempts to employ substrates **II-67–II-68** analogous to **II-49** with N^2-Ac or Bz groups were unsuccessful and led to the formation of complex mixtures of products (Table II-6,

Entries 1-2). However, we were gratified to discover that the Pd/BINAP-catalyzed coupling of 4-bromobiphenyl with **II-66**, which contains Boc-groups on both N^1 and N^2, provided the desired pyrazolidine **II-91** in moderate yield (52%) but with >20:1 diastereoselectivity (Table II-6, Entry 3). The modest yield in this reaction was due to competing Heck arylation of **II-66**. The high diastereoselectivity observed in these reactions relative to transformations involving N^2-arylated substrates (Table II-5) may be due to the relatively high barrier to pyramidalization of the Boc-substituted N^2-atoms, which leads to greater differences in energy between transition states **II-39** and **II-40** (Scheme II-3). Interestingly, reactions of **II-66** with electron-poor aryl bromides were much cleaner and afforded pyrazolidines **II-92**–**II-93** in good yield with excellent dr (Entries 3–4). Coupling reactions of aryl bromides with the C3-phenyl substituted substrate **II-65** provided similar results to those obtained in transformations of **II-66** (Entries 5–6).

Table II-6. Synthesis of *trans*-3,5-Disubstituted-N^2-Boc Pyrazolidines[a]

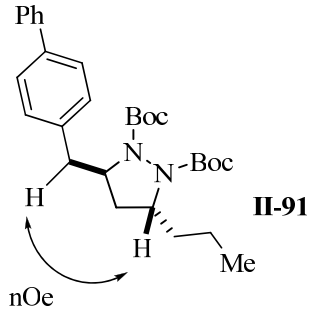


Entry	Hydrazine	ArBr	Product	Yield,[b] dr[c]
1	 **II-67**		---	0%[d]
2	 **II-68**		---	0%[d]
3	 **II-66**		 **II-91**	52%, >20:1 (>20:1)
4	**II-66**		 **II-92**	78%, >20:1 (>20:1)
5	**II-66**		 **II-93**	81%, >20:1 (>20:1)
6	 **II-65**		 **II-94**	55%, >20:1 (>20:1)
7	**II-65**		 **II-95**	47%, >20:1 (>20:1)

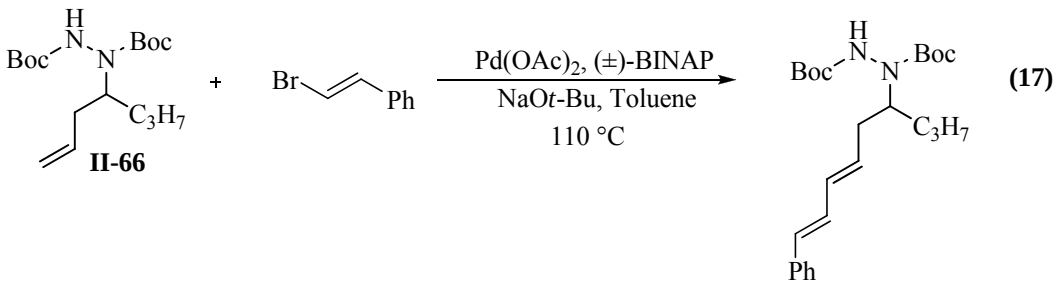
[a] Conditions: 1.0 equiv of substrate, 1.7 equiv of ArBr, 1.7 equiv of NaO*t*-Bu, 2 mol % $Pd(OAc)_2$, 2 mol % BINAP, toluene (0.25 M), 110 °C. Reactions were complete in 12–14 h; reaction times have not been minimized. [b] Isolated yield (average of two or more experiments). [c] Diastereomeric ratios are reported for the isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures. [d] Complex mixtures of products observed.

The 3,5-*trans* stereochemistry of **II-91** was assigned on the basis of nOe signals depicted in Figure II-4. The stereochemistry of the other *trans*-3,5-Di-*tert*-butyl-disubstituted pyrazolidine-1-carboxylate products was assigned based on analogy to **II-91**.

Figure II-4. Assignment of Stereochemistry of 3,5-*trans*-Disubstituted N^1-Boc-N^2-Boc Pyrazolidines

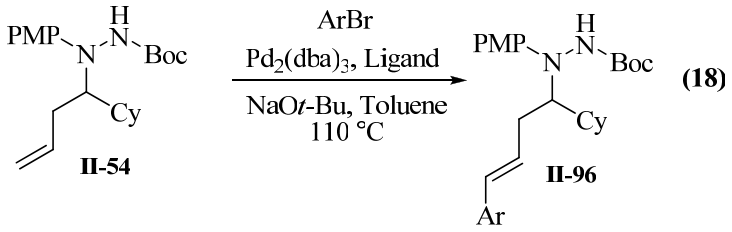


Although reaction of **II-65** and **II-66** with aryl bromides were effective for formation of disubstituted pyrazolidines, efforts to employ alkenyl bromides in carboamination reactions of **II-66** failed to generate the desired pyrazolidine products. Competing Heck alkenylation of the substrates was observed in this case (eq 17).



(17)

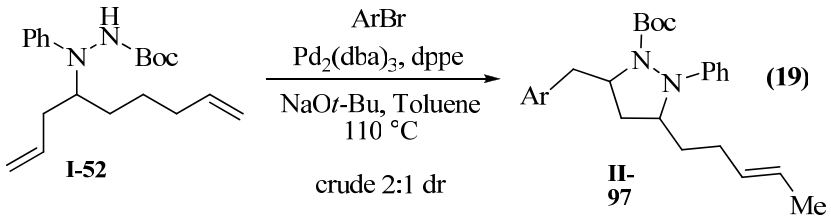
We next turned our attention to examining a substrate **I-54** bearing a branched substituent α to the internal nitrogen atom. However**, II-54** did not undergo the desired carboamination process and Heck-arylated product **II-96** formation was observed (eq 18).



(18)

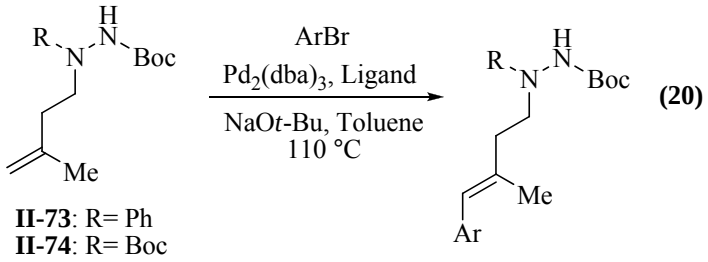
Ligand= dppe, Dpe-phos, P(*o*-tol)$_3$, Xantphos

Attempts to cyclize a substrate containing a pendant alkene **II-52** were plagued by isomerization of the pendant double bond as illustred in **II-97**, although pyrazolidine formation was observed in 2:1 diastereoselectivity (eq 19).



(19)

A brief examination of substituted alkene substrates **II-73**–**II-74** was made, but only Heck-arylation of the alkene resulted in the case of both substrates (eq 20).

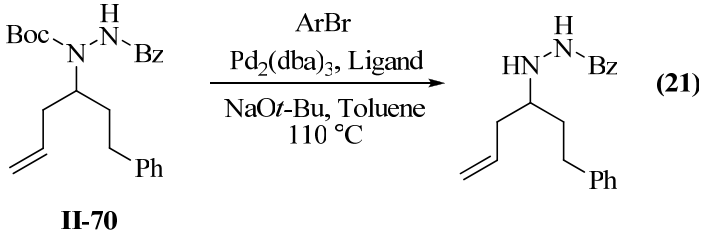


(20)

II-73: R= Ph
II-74: R= Boc

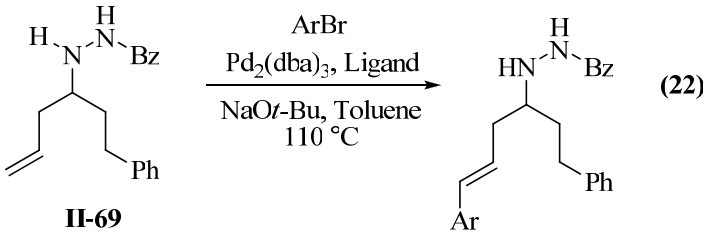
Ligand= dppe, Dpe-phos, P(2-furyl)$_3$, P(*o*-tol)$_3$, Xantphos

Reactions of *N*-butenyl hydrazine substrates with alternative carbamate protecting groups on N^1 were also conducted. When benzoyl protected substrate **II-70** was subjected to carboamination reaction conditions loss of the Boc group was observed (eq 21). Unfortunately, only Heck-alkenylation was observed in efforts to cyclize **II-69** (eq 22).



(21)

II-70

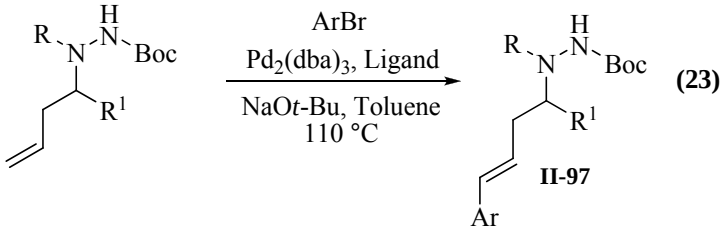


(22)

II-69

Ligand= dppe, Dpe-phos, P(2-furyl)$_3$, Xantphos

Substrates bearing a sp^3 hybridized N^2-substituent were also examined. To this end, substrates **II-55** and **II-56** bearing a methyl or benzyl group on N^2 were reacted under our optimized reaction conditions. Subjection of **II-55** to the reaction conditions led exclusively to Heck product **II-97** formation (eq 23). Similar results were observed in the case of benzyl-protected substrate **II-56**.



II-97 **(23)**

II-55: R= Me, R^1= C_3H_7
II-56: R= Bn, R^1= C_2H_5

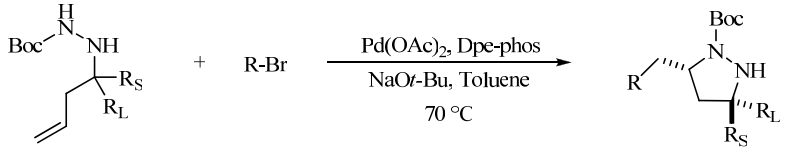
Ligand= dppe, Dpe-phos, Xantphos, BINAP, $P(2\text{-furyl})_3$, $P(o\text{-tol})_3$, NiXantphos

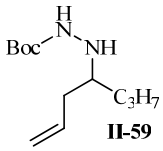
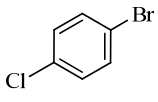
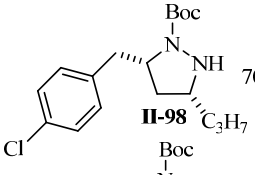
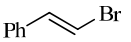
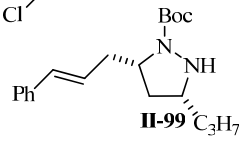
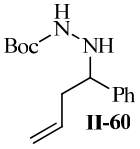
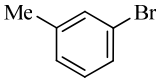
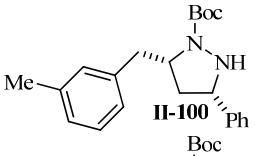
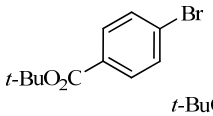
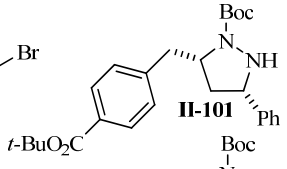
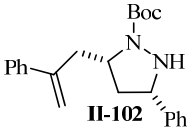
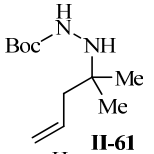
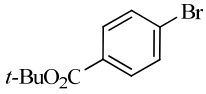
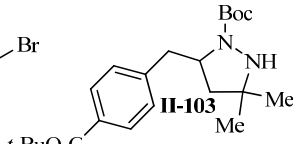
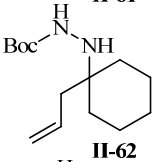
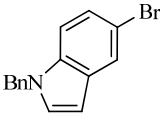
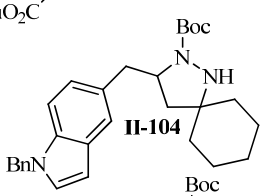
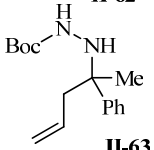
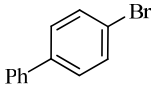
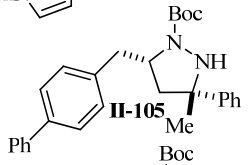
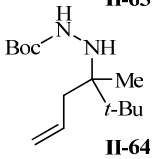
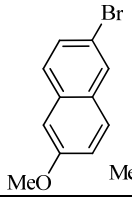
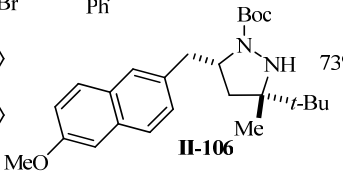
II.6 Stereoselective Synthesis of *cis*-3,5-Disubsititued Pyrazolidines and 3,3,5-Trisubstituted Pyrazolidines

In order to explore the scope of carboamination reactions of *N*-butenylhydrazine derivatives lacking N^2-substituents, substrates **II-59–II-64** were treated with various aryl or alkenyl bromides. These transformations proceeded with moderate to good yields and diastereoselectivities for several different substrate combinations (Table II-7). Both aryl and alkenyl halides can be employed as coupling partners, although reactions involving alkenyl halides proceeded with somewhat lower yields and diastereoselectivities. The reactions were effective with both aldehyde-derived substrates (**II-59** and **II-60**, Entries 1–5) and ketone-derived substrates (**II-61**–**II-64**, Entries 6–9**)**. Substrates **II-63**–**II-64**

bearing two different substituents at C3 were converted to trisubstituted pyrazolidines **II-105**–**II-106** with moderate to good stereocontrol (Entries 8–9).

Table II-7. Synthesis of *trans*-Disubstituted and –Trisubstituted Pyrazolidines[a]

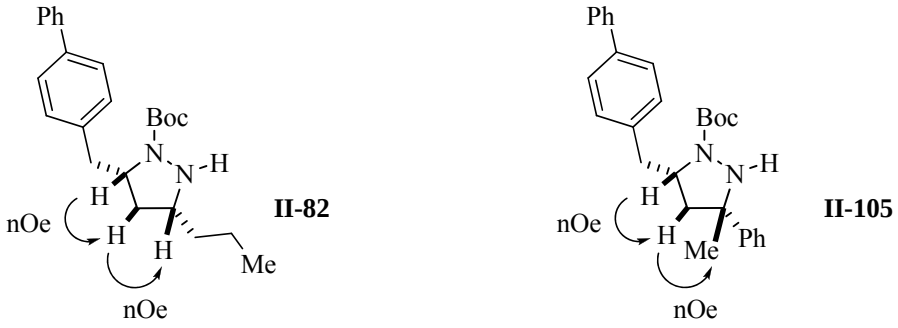


Entry	Hydrazine	ArBr	Product	Yield,[b] dr[c]
1	 **II-59**		 **II-98**	70%, >20:1 (7:1)
2	**II-59**		 **II-99**	54%, 5:1 (5:1)
3	 **II-60**		 **II-100**	66%, 13:1 (10:1)
4	**II-60**		 **II-101**	55%, >20:1 (>20:1)
5	**II-60**		 **II-102**	63%, 11:1 (8:1)
6	 **II-61**		 **II-103**	80%
7	 **II-62**		 **II-104**	56%
8	 **II-63**		 **II-105**	83%, 6:1 (6:1)
9	 **II-64**		 **II-106**	73%, >20:1 (12:1)

[a] Conditions: 1.0 equiv hydrazine, 1.2 equiv ArBr, 1.2 equiv NaO*t*-Bu, 2 mol % $Pd(OAc)_2$, 2 mol % Dpe-phos, toluene (0.25 M), 70 °C, 4–12 h. [b] Isolated yield, average of two or more experiments. [c] Diastereomeric ratios are reported for the isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures.

The stereochemistry of 3,5-*cis*-di- and tri-substituted pyrazolidines was also established through NMR analysis. The 3,5-*cis* stereochemistry of disubstituted pyrazolidines **II-82** was determined based on the nOe signals depicted in Figure II-6. Similarly, the 3,5-*cis* stereochemistry of tri-substituted pyrzolidine (**II-105**) was determined based on the depicted nOe signals (Figure II-5). The stereochemistry of the other *cis*-3,5-pyrazolidine products was assigned based on **II-82** and **II-105**.

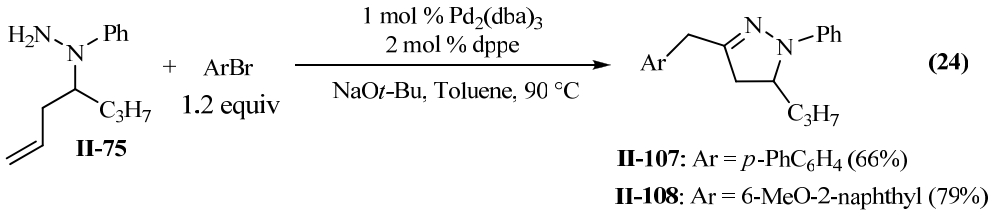
Figure II-5. Assignment of Stereochemistry of 3,5-*cis*-Disubstituted Pyrazolidines



II.7 Carboamination Reactions of Substrates Lacking N^1 Substituents

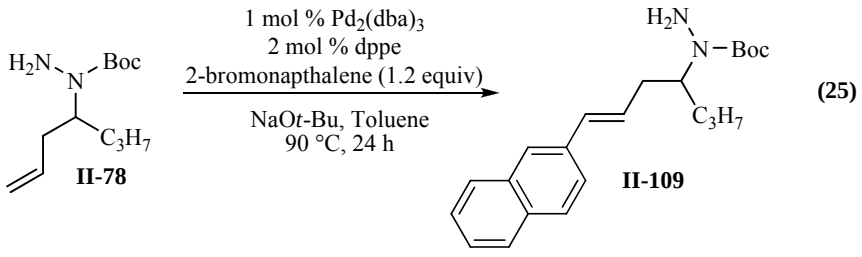
In order to further explore the scope of the pyrazolidine-forming carboamination reactions, we sought to examine the reactivity of substrates with an unprotected N^1-atom. Efforts to carry out Pd-catalyzed carboamination reactions of **II-75** did not generate pyrazolidines but instead afforded pyrazolines **II-107**–**II-108** in synthetically useful yields (eq 24). It is not clear if the oxidation to the pyrazoline product is Pd-catalyzed, or

if oxidation occurs upon workup. However, air-oxidation of NH-pyrazolidines that lack electron-withdrawing substituents on the second nitrogen atom appears to be very facile.

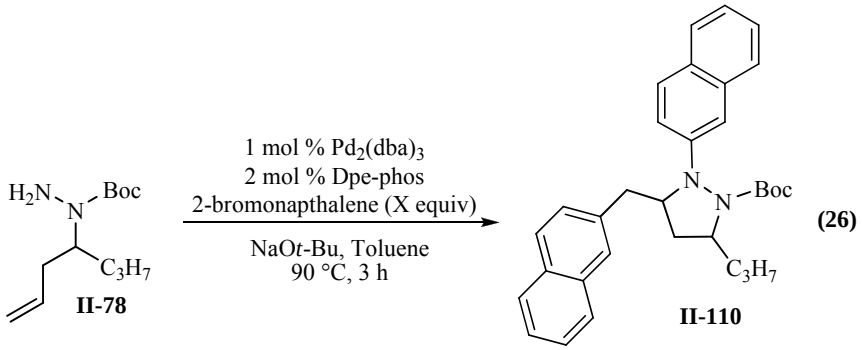


(24)

A substrate **II-78** with no N^1-substituent but bearing a Boc group on the internal nitrogen atom was examined under the same reaction conditions as outlined in Equation 24. However, Heck-arylation product **II-109** was observed via crude ^{1}H NMR analysis (eq 25). Interestingly, when instead a catalyst composed of $Pd_2(dba)_3$ and Dpe-phos was used, incomplete conversion to *N*-arylated pyrazolidine **II-110** was observed (eq 26). Increasing the amount of aryl bromide coupling partner from 1.2 to 2.1 equivalents allowed for sole formation of *N*-arylated pyrazolidine **II-110**. However, when a similar substrate **II-111** lacking a C3 substituent was examined under carboamination reaction conditions, only *N*-arylated product **II-112** was observed (eq 27).

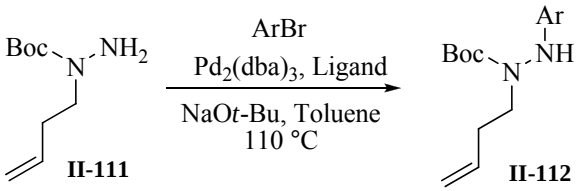


(25)



II-78 **II-110** **(26)**

X= 1.2 equiv, incomplete conversion
X= 2.1 equiv, 60% isolate yield **II-110**

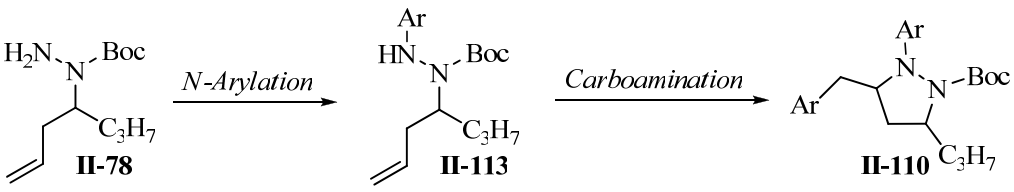


II-111 **II-112** **(27)**

Ligand= dppe, Dpe-phos

Although the mechanism for formation of **II-110** was not probed, it may involve initial *N*-arylation of **II-78** to afford **II-113**, followed by a carboamination reaction to afford **II-110** (Scheme II-5).

Scheme II-5. Proposed *N*-Arylation/Carboamination Pathway

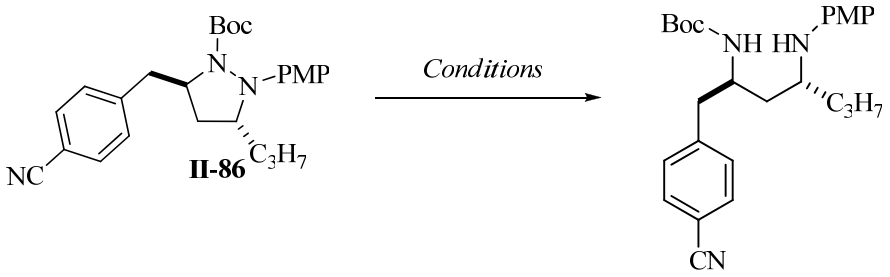


II-78 **II-113** **II-110**

II.8 Transformations of Pyrazolidine Products

In order to further illustrate the synthetic utility of the pyrazolidine-forming reactions described above, we briefly examined the conversion of pyrazolidine products into other useful compounds such as 1,3-diamines and pyrazolines. Our initial attempts to cleave the N–N bond of the pyrazolidine **II-86** using a number of different conditions were unsuccessful (Table II-8). Attempted hydrogenation of **II-86** led to cleavage of the protecting groups or over-reduction (Entries 1-3). Use of dissolving metal reduction conditions led to similar results (Entries 4-5). Lastly, **II-86** was inactive towards N-N bond cleavage via single electron reduction conditions (Entry 6).

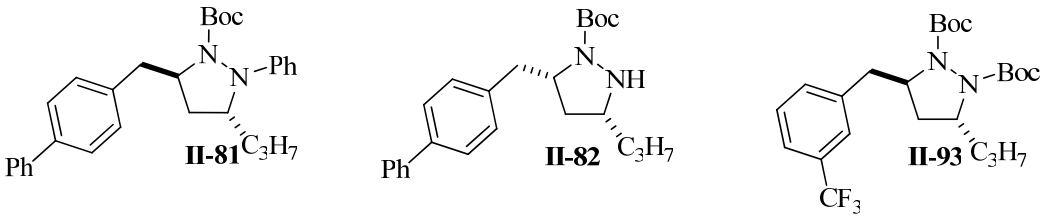
Table II-8. Attempted N-N Bond Reduction Conditions



Entry	Conditions	Result
1	PtO_2, 5 atm H_2, 1.6 M HCl in MeOH	Cleaves both Boc and PMP
2	PtO_2, 1 atm H_2, MeOH	Over-reduction
3	Raney Ni, 1 atm H_2, EtOH	Over-reduction
4	Na, NH_3 (l), THF, -78 °C → -40 °C	Complex Mixture
5	Li, NH_3 (l), THF, -78 °C	Over-reduction/loss of PMP
6	SmI_2 (0.1 M in THF), MeOH, HMPA	No Reaction

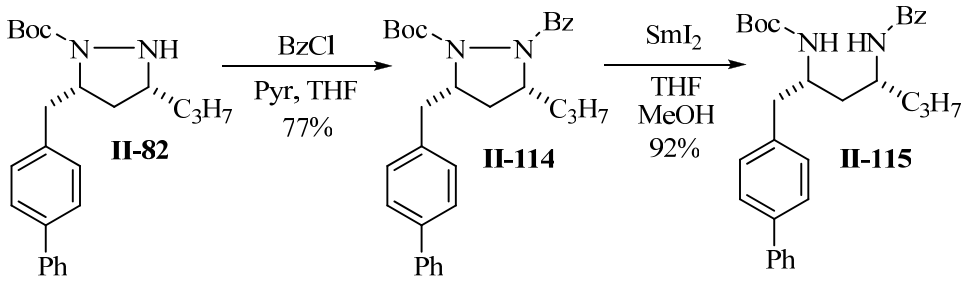
From these results, it appeared that the N-N bond of **II-86** was not sufficiently reactive to undergo reduction with Boc and PMP protecting groups on the nitrogen atoms. We examined substrates bearing alternative protecting groups under the conditions outlined in Table II-8 as well (Figure II-6). Unfortunately, similar results were obtained upon examination of substrates **II-81–II-82** and **II-93** under the hydrogenation, dissolving metal reduction, and single electron reduction conditions examined.

Figure II-6. Additional Substrates Examined Under N-N Bond Reduction Conditions

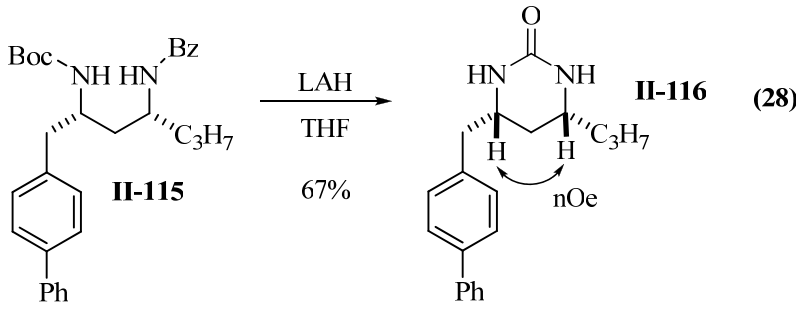


However, we were gratified to find that N–N bond cleavage of *cis*-3,5-disubstituted pyrazolidine **II-82** could be achieved after benzoylation of the unprotected nitrogen atom. As shown in Scheme II-6, treatment of **II-82** with benzoyl chloride and pyridine provided **II-114** in 77% yield. The doubly protected pyrazolidine was then converted to *syn*-1,3-diamine **II-115** in 92% yield by treatment with SmI_2.[29]

Scheme II-6. *Syn*-1,3-Diamine Synthesis

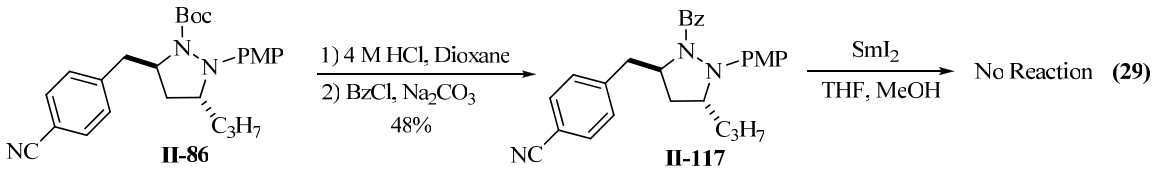


The stereochemistry of *syn*-1,3-diamine **II-115** was established by conversion to cyclic urea **II-116** through treatment with $LiAlH_4$ (eq 28). The 4,6-*cis* stereochemistry of **II-116** was then assigned on the basis of nOe signals between the C4 and C6 hydrogens.



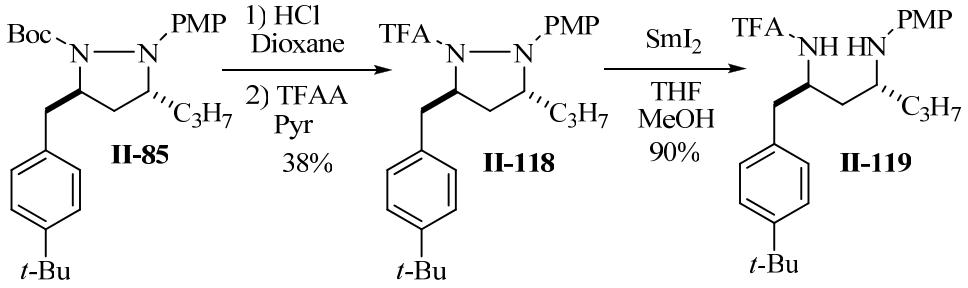
On the basis of our successful N-N bond cleavage of **II-114**, we sought to replace the Boc protecting group on *trans*-disubstituted pyrazolidine **II-86** with a more electron-withdrawing protecting group. Standard conditions for cleavage of *N*-Boc groups (TFA/CH_2Cl_2) led to complex mixtures of products and competing oxidation of the deprotected pyrazolidine. Unfortuantely, treatment of **II-86** with 4 M HCl in dioxane, followed by protection with benzoyl chloride afforded **II-117** in moderate yield (eq 29).

However, upon subjection of **II-117** to SmI_2 no N-N bond reduction was observed and **II-117** was recovered.

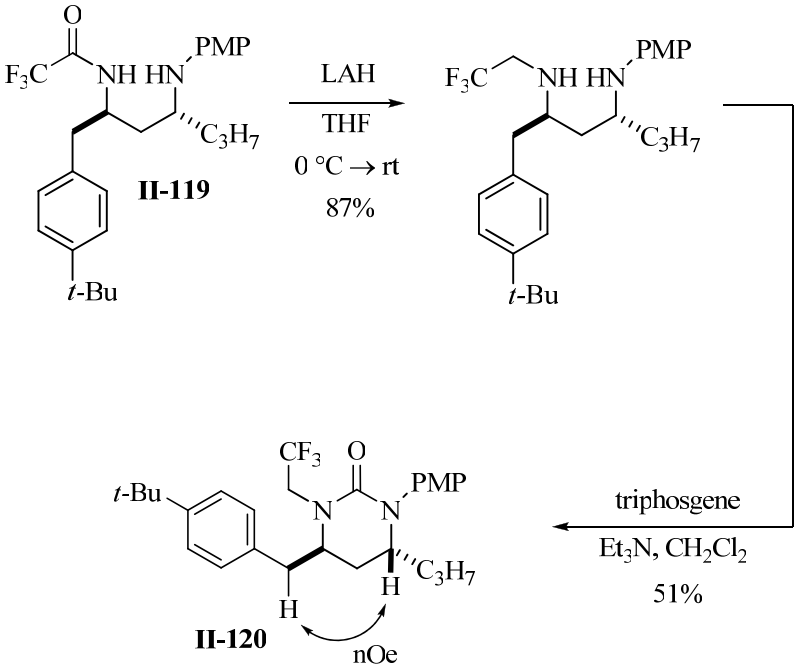


Conversion of *trans*-1,3-disubstituted pyrazolidine **II-85** to a 1,3-diamine required exchange of the *N*-Boc substituent for a trifluoroacyl group. Treatment of **II-85** with HCl/dioxane followed by addition of pyridine and trifluoroacetic anhydride generated **II-118** in a modest 38% yield (Scheme II-7). Fortunately, the N–N bond cleavage of **II-118** proceeded smoothly using conditions identical to those employed for the conversion of **II-114** to **II-115**, and the *anti*-1,3-diamine **II-119** was obtained in 90% yield. The stereochemistry of *anti*-1,3-diamine **II-119** was established by conversion to cyclic urea **II-120** via treatment with $LiAlH_4$ followed by triphosgene (Scheme II-8). The 4,6-*trans* stereochemistry of **II-120** was assigned on the basis of nOe signals between the hydrogens depicted.

Scheme II-7. *Anti*-1,3-Diamine Synthesis



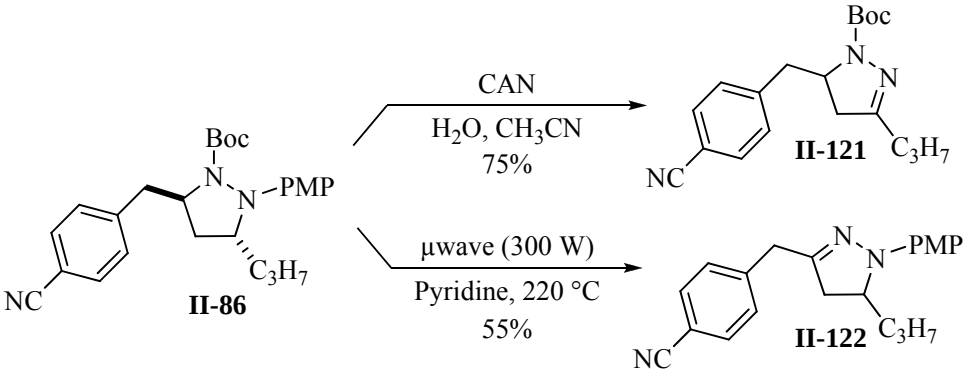
Scheme II-8. Assignment of Stereochemistry of *Anti*-1,3-Diamine



The selective conversion of *trans*-3,5-disubstituted pyrazolidine **II-86** to 3,5-disubstituted pyrazolines **II-121** and **II-122** was easily accomplished as shown in Scheme II-9. Treatment of **II-86** with CAN led to cleavage of the *N*-PMP group with concomitant

oxidation to pyrazoline **II-121** in 75% yield. Alternatively, use of microwave irradiation to remove the *N*-Boc group from **II-86** also led to facile oxidation and provided **II-122** in 55% yield.

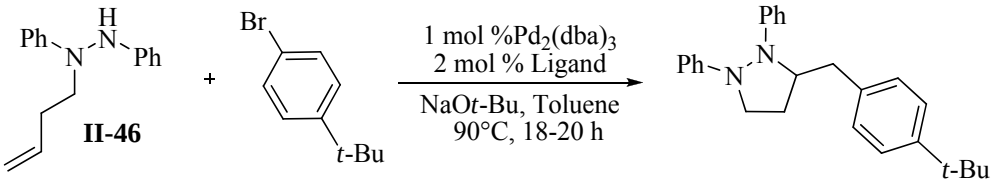
Scheme II-9. Synthesis of 3,5-Disubstituted Pyrazolines via Pyrazolidine Deprotection



II.9 Towards Asymmetric Pyrazolidine Synthesis

Future work in this area may involve development of an asymmetric carboamination reaction in order to access enantiopure pyrazolidine products. A brief examination of chiral ligands was completed with diphenyl hydrazine substrate **II-46** as shown in Table II-9. Incomplete conversion to product was observed in many reactions, and low levels of asymmetric induction were seen in reactions that did result in desired product formation. Based on these preliminary results, further optimization of this process is merited.

Table II-9. Chiral Ligands in *N*-Butenyl Hydrazine Carboamination



Ligand	% Conv.[a]	Yield[b]	%ee[c]
(±)-BINAP	----	64%	NA
(*R*)-BINAP	----	48%	0%
(*R*,*R*)-DIOP	(<10%)	----	----
(*S*)-Tol-BINAP	(<20%)	----	----
(*R*,*R*)-NORPHOS	(50%)	----	0%
(*R*)-MOP	(50%)	----	20%
(*S*)-PHANEPHOS	(75%)	----	20%
CTH-(*R*)-3,5-xylyl-PHANEPHOS	(75%)	----	20%
(*S*,*S*)-BDPP	(75%)	----	0%
(*R*)-(*S*)-JOSIPHOS	0%	----	----
(*S*,*S*)-CHIRAPHOS	0%	----	----
(*R*,*R*)-Me-DUPHOS	0%	----	----
(*R*)-MONOPHOS	0%	----	----
(*S*)-(+)-1-[(*R*)-2(Di-2-furylphosphino) ferrocenyl]ethyldi-3,5-xylyl-phosphine	0%	----	----

[a](% Conv.) refers to conversion of hydrazine substrate to pyrazolidine after 18-20 h. 0% conversion refers to no reaction. [b]Isolated yield. [c]Enantiopurity determined by chiral HPLC analysis.

II.10 Summary and Conclusions

In summary, we have developed a new stereoselective synthesis of *cis*- and *trans*-disubstituted pyrazolidines from *N*-butenyl hydrazine derivatives. The products are generated with good to excellent diastereoselectivity and chemical yield and can be transformed to synthetically useful pyrazolines or 1,3-diamines via oxidation or

reduction. These are the first examples of the use of hydrazine-derived substrates in Pd-catalyzed alkene carboamination reactions with aryl/alkenyl halides and represent a significant extension of carboamination methodology. Importantly, these experiments also demonstrate that allylic strain interactions can be manipulated through a simple substrate modification (N^2-protection vs. no N^2-protection) to allow for control of relative stereochemistry in Pd-catalyzed reactions.

II.11 Experimental Section

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. and used without further purification. All aryl bromides and *tert*-butyl-2-phenylhydrazinecarboxylate were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. *tert*-butyl 2-(4-methoxyphenyl)hydrazinecarboxylate was prepared via treatment of 4-methoxyphenylhydrazine hydrochloride with sodium hydroxide and di-*tert*-butyl dicarbonate. (±)-1-(hept-1-en-4-yl)-1,2-diphenylhydrazine (**I-35**) was prepared according to Katritzky's procedure.[25] Toluene, diethyl ether, and THF were purified using a GlassContour solvent purification system. Microwave heating was carried out using a CEM Discovery microwave reactor. The microwave reactions were run in closed reaction vessels with magnetic stirring and with the temperature controlled via IR detection. 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. Thus, the yields reported in the supporting information may differ from those shown in this Chapter.

Preparation of Substrates

General Procedure 1: Synthesis of N^1-Boc-N^2-aryl-N^2-butenylhydrazine derivatives. All N^1-Boc-N^2-aryl-N^2-butenylhydrazine derivatives were prepared via the following modified version of Katrizky's procedure for the synthesis of *N*,*N*'-diaryl-*N*-butenylhydrazines.[1] A flame-dried flask equipped with a Dean-Stark trap and a reflux condenser was cooled under a stream of nitrogen and charged with the substituted hydrazine (1 equiv), benzotriazole (1.1 equiv), the appropriate aldehyde (1.1 equiv), and benzene (0.25 M). The solution was heated to reflux with azeotropic removal of water until the starting aldehyde had been consumed as judged by TLC analysis (24–72 h). The reaction mixture was cooled to room temperature, aqueous NaOH (2 M, 1:1 by volume with reaction mixture) was added, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford N^2-(1-benzotriazolylalkyl)-N^1-boc-N^2-aryl hydrazines, which were used without further purification.

A flame-dried flask was cooled under a stream of nitrogen and charged with the N^2-(1-benzotriazolylalkyl)-N^1-boc-N^2-aryl-hydrazine derivative (1 equiv) in THF (0.1 M), and cooled to 0 °C. Allylmagnesium bromide (1 M in Et_2O, 2 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h, then warmed to rt and stirred until the starting material was consumed as judged by TLC analysis. The mixture was then cooled to 0 °C and quenched with aqueous NaOH (2 M, 1:1 by volume with reaction mixture). The mixture was transferred to a separatory funnel, the layers were

separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude *N*-butenylhydrazine product was purified by flash chromatography on silica gel.

(±)-*tert*-Butyl-2-(hept-1-en-4-yl)-2-phenylhydrazinecarboxylate (II-49). The reaction of butyraldehyde (5.5 g, 77.0 mmol), *tert*-butyl-2-phenylhydrazinecarboxylate (8.0 g, 38.4 mmol), benzotriazole (0.92 g, 77.0 mmol) and allylmagnesium bromide (38.0 mL, 1.0 M in THF) was conducted according to general procedure 1. This procedure afforded 5.82 g (50%) of the title compound as a yellow oil. This compound was observed as a 0.62:0.38 mixture of rotamers by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2 H), 6.80–6.78 (m, 3 H), 6.03 (s, br, 1 H), 5.90–5.81 (m, 1 H), 5.15–5.00 (m, 2 H), 3.88–3.78 (m, 1 H), 2.49–2.12 (m, 2 H), 1.69–1.58 (m, 2 H), 1.53–1.31 (m, 10 H), 1.29–1.15 (m, 1 H), 1.01–0.78 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 155.3, 149.9, 149.3, 137.1, 135.9 129.1, 118.7, 116.9, 115.6, 112.6, 80.9, 80.3, 60.5, 59.9, 36.9, 36.1, 34.2, 33.3, 28.2, 28.0, 20.0, 14.1; IR (film) 3240, 1749, 1698 cm^{-1}. Anal calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.08; H, 9.07; N, 9.18.

(±)-*tert*-Butyl-2-phenyl-2-(1-phenylbut-3-enyl)hydrazinecarboxylate (II-50). A flame-dried flask was cooled under a stream of nitrogen and charged with 1-phenylbut-3-en-1-ol (4.8 g, 32.2 mmol), Et_3N (9.15 mL, 65.8 mmol) and CH_2Cl_2 (33 mL, 1 M). The reaction mixture was cooled to 0 °C and stirred for 10 min, MsCl (2.8 mL, 36.2 mmol) was added dropwise, and the resulting solution was stirred at 0 °C until consumption of

the starting material was complete as judged by TLC analysis (ca. 30 min). The reaction mixture was quenched with saturated aqueous ammonium chloride (15 mL), transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ether (3 x 15 mL). The organic layers were combined and washed with water until pH = 7 (ca. 3 x 50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 1-phenylbut-3-enyl methanesulfonate (7.2 g, 99%). This product was judged to be >95% pure by ^{1}H NMR analysis, and was used without further purification.

A flame-dried flask was cooled under a stream of nitrogen and charged with *tert*-butyl-2-phenylhydrazinecarboxylate (2.0 g, 9.6 mmol) and THF (48 mL, 0.2 M). The resulting solution was cooled to –78 °C, nBuLi (12 mL, 19.2 mmol, 1.6 M in hexanes) was added dropwise, and the reaction mixture was stirred at –78 °C for 15 min. Neat 1-phenylbut-3-enyl methanesulfonate (2.8 g, 9.6 mmol) was then added to the reaction mixture dropwise, and the resulting mixture was stirred for 1.5 h at –78 °C. The reaction mixture was warmed to rt and stirred until consumption of the starting material was complete as judged by TLC analysis (ca. 5 h). The reaction mixture was diluted with water (20 mL) and ether (20 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ether (3 x 20 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography to afford 2.1 g (64%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.20 (m, 7 H), 6.87–6.81 (m, 3 H), 5.97 (s, br, 1 H), 5.15–5.12 (m, 1 H), 5.06–5.04 (m, 1 H), 4.96 (s, br, 1 H), 2.92 (m, 1 H), 2.70 (m, 1 H), 1.47 (s, 9 H), 1.25–1.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 155.2, 148.9, 137.1, 135.9, 129.1, 128.4, 127.8, 119.7, 116.9, 114.1, 80.5, 65.3,

36.2, 28.2; IR (film) 3256, 2978, 1699 cm^{-1}. MS (ESI) 361.1880 (361.1892 calcd for $C_{21}H_{26}N_2O_2$, M + Na^+).

(±)-*tert*-Butyl-2-(hept-1-en-4-yl)-2-(4-methoxyphenyl)hydrazinecarboxylate (II-53). The reaction of butyraldehyde (1.65 g, 22.9 mmol), *tert*-butyl 2-(4-methoxyphenyl)hydrazinecarboxylate (4.95 g, 20.8 mmol), benzotriazole (2.73 g, 22.9 mmol), and allylmagnesium bromide (37.5 mL, 37.5 mmol, 1.0 M in THF) was conducted according to general procedure 1. This procedure afforded 3.54 g (51%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82–6.74 (m, 4 H), 5.87 (s, br, 2 H), 5.08–5.04 (m, 1 H), 5.00–4.98 (m, 1 H), 3.75 (s, 3 H), 3.72–3.71 (m, 1 H), 2.38–2.35 (m, 1 H), 2.23–2.16 (m, 1 H), 1.62–1.60 (m, 2 H), 1.45 (s, 10 H), 1.37–1.27 (m, 1 H), 0.92–0.89 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 153.0, 143.6, 136.5, 116.5, 115.7, 114.6, 80.2, 60.9, 55.6, 35.7, 33.5, 28.3, 20.0, 14.2; IR (film) 2959, 1697, 1161 cm^{-1}. MS (ESI) 357.2158 (357.2154 calcd for $C_{19}H_{30}N_2O_4$, M + Na^+).

(±)-*tert*-Butyl-2-(9,9-dimethoxynon-1-en-4-yl)-2-phenylhydrazinecarboxylate (II-51). The reaction of 6,6-dimethoxyhexanal[2] (3.1 g, 19.2 mmol), *tert*-butyl 2-phenylhydrazinecarboxylate (2.0 g, 9.6 mmol), benzotriazole (2.28 g, 19.2 mmol) and allylmagnesium bromide (24.4 mL, 24.4 mmol, 1.0 M in THF) was conducted according to general procedure 1 except two equiv aldehyde and 2.5 equiv of Grignard reagent were employed. This procedure afforded 2.03 g (54%) of the title compound as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.19 (m, 2 H), 6.79–6.76 (m, 3 H), 6.08–5.81 (m, br, 2 H), 5.09–5.05 (m, 1 H), 5.00–4.98 (m, 1 H), 4.34–4.31 (m, 1 H), 3.85 (s, br, 1 H), 3.31–3.25 (m, 6 H), 2.38 (s, br, 1 H), 2.24–2.21 (m, 1 H), 1.65–1.54 (m, 3 H), 1.48–1.42 (m, 10 H), 1.37–1.26 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 149.2, 135.8, 129.1, 118.7, 116.9, 112.6, 104.3, 80.3, 60.0, 52.5, 52.4, 36.0, 32.1, 28.2, 26.4, 24.5; IR (film) 3273, 2943, 1698, 1160 cm^{-1}. MS (ESI) 415.2564 (415.2573 calcd for $C_{22}H_{36}N_2O_4$, M + Na^+).

(±)-1-(hept-1-en-4-yl)-1-phenylhydrazine (II-75). A solution of **II-49** (1.48 g, 4.86 mmol) in dichloromethane (12.0 mL) was cooled to 0 °C and trifluoroacetic anhydride (12.0 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to rt and stirred until the starting material had been consumed as determined by TLC analysis. The crude reaction mixture was concentrated *in vacuo*, the resulting material was dissolved in CH_2Cl_2 (10 mL), and solid potassium carbonate was added in one portion. The reaction mixture was stirred at rt until evolution of gas had ceased, and was then filtered. The organic solution was then dried over sodium sulfate and concentrated *in vacuo* to afford in 0.88 g (88%) of the title compound as a yellow oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2 H), 6.95–6.93 (m, 2 H), 6.74–6.70 (m, 1 H), 5.83–5.73 (m, 1 H), 5.09–5.04 (m, 1 H), 4.98–4.95 (m, 1 H), 3.87–3.80 (m, 1 H), 3.11 (s, br, 2 H), 2.46–2.39 (m, 1 H), 2.28–2.21 (m, 1 H), 1.76–1.67 (m, 1 H), 1.52–1.43 (m, 1 H), 1.37–1.23 (m, 2 H), 0.90 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 129.4, 121.0, 117.2, 115.3, 62.4, 35.3, 32.6, 19.7, 14.0 (one carbon signal is absent due to incidental equivalence); IR

(film) 3340, 2957, 1596 cm^{-1}. MS (ESI) 205.1696 (205.1705 calcd for $C_{13}H_{20}N_2$ M + H^+).

General Procedure 2: Synthesis of *N*^{1}-Boc-*N*^{2}-Butenyl Hydrazines. A flame-dried flask equipped with a reflux condenser was cooled under a stream of nitrogen and charged with *tert*-butyl carbazate (1 equiv), the appropriate aldehyde or ketone (1.5 equiv), and hexanes (0.82 M). The resulting solution was heated to reflux until the *tert*-butyl carbazate was completely consumed as judged by TLC analysis (0.5–12 h). The reaction mixture was cooled to room temperature and a precipitate formed. The precipitate was collected by vacuum filtration and washed with cold hexanes to afford the title compound as a crystalline solid. The crystalline *N*-boc hydrazone product was used without further purification.

A flame-dried flask was cooled under a stream of nitrogen and charged with the crude *N*-boc hydrazone (1 equiv) and THF (0.1 M). The resulting solution was cooled to 0 °C and allylmagnesium bromide (2 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, then warmed to rt and stirred until consumption of the starting material was complete as judged by TLC analysis (ca. 1 h). The reaction mixture was then cooled to 0 °C, quenched with aqueous NaOH (2 M, 1:1 by volume with reaction mixture), and transferred to a separatory funnel. The layers were separated and the organic layer was washed with aqueous NaOH (2 M, 2 x 10 mL), water (2 x 10 mL), and brine (2 x 5 mL), and then was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(±)-*tert*-Butyl-2-(hept-1-en-4-yl)hydrazinecarboxylate (II-59). The reaction of *tert*-butyl carbazate (2.7 g, 20.7 mmol) and butyraldehyde (2.8 mL, 31 mmol) was conducted according to general procedure 2 to afford 3.8 g (97%) of *tert*-butyl-2-butylidenehydrazinecarboxylate as a white solid, m.p. 73–75 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, br, 1 H), 7.14 (s, br, 1 H), 2.30-2.25 (m, 2 H), 1.56-1.53 (m, 2 H), 1.50 (s, 9 H), 0.95 (t, *J* = 7.5 Hz, 3 H). A portion of the *tert*-butyl-2-butylidenehydrazinecarboxylate product (2.0 g, 10.9 mmol) was treated with allylmagnesium bromide (22.0 mL, 22.0 mmol, 1.0 M in THF) according to the general procedure to afford 1.8 g (74%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, br, 1 H), 5.89–5.79 (m, 1 H), 5.14–5.07 (m, 2 H), 4.05 (s, br, 1 H), 2.94 (s, br, 1 H), 2.56–2.18 (m, 1 H), 2.13-2.07 (m, 1 H), 1.46 (s, 9 H), 1.39-1.35 (m, 4 H), 0.93-0.90 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 135.4, 117.2, 80.3, 58.5, 37.1, 34.5, 28.6, 18.8, 14.3; IR (film) 3325, 2961, 1715 cm^{-1}. MS (ESI) 251.1736 (251.1735 calcd for $C_{12}H_{24}N_2O_2$, M + Na^+).

(±)-*tert*-Butyl-2-(1-phenylbut-3-enyl)hydrazinecarboxylate (II-60). The reaction of *tert*-butyl carbazate (5.0 g, 38 mmol) and benzaldehyde (5.8 mL, 38 mmol) was conducted according to general procedure 2 to afford 8.0 g (96%) of *tert*-butyl-2-benzylidenehydrazinecarboxylate as a white solid, m.p. 190–192 °C (lit.[3] m.p. 189–190 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, br, 1 H), 7.85 (s, br, 1 H), 7.68–7.66 (m, 2 H), 7.37–7.34 (m, 3 H), 1.54 (s, 9 H). A portion of the *tert*-butyl-2-benzylidenehydrazinecarboxylate product (2.01 g, 9.1 mmol) was treated with

allylmagnesium bromide (18.2 mL, 18.2 mmol, 1.0 M in THF) according to the general procedure to afford 1.8 g (75%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.29 (m, 4 H), 7.27–7.23 (m, 1 H), 6.02 (s, br, 1 H), 5.81–5.72 (m, 1 H), 5.13–5.05 (m, 2 H), 4.33 (s, br, 1 H), 4.11 (s, br, 1 H), 2.41–2.38 (m, 2 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 142.0, 134.8, 128.4, 127.8, 127.4, 117.4, 80.3, 63.9, 40.1, 28.4; IR (film) 3295, 2978, 1713 cm^{-1}. MS (ESI) 285.1576 (285.1579 calcd for $C_{15}H_{22}N_2O_2$, M + Na^+).

***tert*-Butyl-2-(2-methylpent-4-en-2-yl)hydrazinecarboxylate (II-61)**. The reaction of *tert*-butyl carbazate (2.7 g, 20.7 mmol), $MgSO_4$ (ca. 1 g), HOAc (2 drops), and acetone (38.0 mL, 1 M) was conducted according to general procedure 2 to afford 6.0 g (92%) of *tert*-butyl-2-(propan-2-ylidene)hydrazinecarboxylate as a white solid, m.p. 87–90 °C (lit.[4] m.p. 85–87 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, br, 1 H), 2.04 (s, 3 H), 1.81 (s, 3 H), 1.51 (s, 9 H). A portion of the *tert*-butyl-2-(propan-2-ylidene)hydrazinecarboxylate product (2.07 g, 12 mmol) was treated with allylmagnesium bromide (24.0 mL, 24.0 mmol, 1.0 M in THF) according to the general procedure to afford 1.3 g (51%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.83 (m, 1 H), 5.78 (s, br, 1 H), 5.10 (s, 1 H), 5.08–5.06 (m, 1 H), 3.83 (s, br, 1 H), 2.14 (d, *J* = 7.0 Hz, 2 H), 1.46 (s, 9 H), 1.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 134.6, 117.8, 80.3, 56.9, 44.5, 28.4, 24.9; IR (film) 3281, 2977, 1715 cm^{-1}. MS (ESI) 237.1572 (237.1597 calcd for $C_{11}H_{22}N_2O_2$ M + Na^+).

***tert*-Butyl-2-(1-allylcyclohexyl)hydrazinecarboxylate (II-62)**. The reaction of *tert*-butyl carbazate (5.0 g, 37.8 mmol) and cyclohexanone (3.7 g, 37.8 mmol) was conducted according to general procedure 2 to afford 7.4 g (93%) of *tert*-butyl-2-cyclohexylidenehydrazinecarboxylate as a white solid, m.p. 128–130 °C (lit.[5] m.p. 125–127 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, br, 1 H), 2.36 (t, *J* = 6.0 Hz, 2 H), 2.21 (t, *J* = 6.0 Hz, 2 H), 1.71-1.60 (m, 6 H), 1.51 (s, 9 H). A portion of the *tert*-butyl-2-cyclohexylidenehydrazinecarboxylate product (2.01 g, 9.5 mmol) was treated with allylmagnesium bromide (19.0 mL, 19.0 mmol, 1.0 M in THF) according to the general procedure to afford 1.7 g (71%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94–5.87 (m, 2 H), 5.10–5.07 (m, 2 H), 3.85 (s, br, 1 H), 2.17–2.16 (m, 2 H), 1.66–1.58 (m, 2 H), 1.46 (s, 9 H), 1.41–1.39 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 134.4, 117.4, 80.0, 57.9, 40.7, 33.2, 28.3, 25.8, 21.8; IR (film) 3304, 2931, 1715, 1455 cm^{-1}. MS (ESI) 277.1883 (277.1892 calcd for $C_{14}H_{26}N_2O_2$ M + Na^+).

(±)-*tert*-Butyl-2-(2-phenylpent-4-en-2-yl)hydrazinecarboxylate (II-63). The reaction of *tert*-butyl carbazate (5.0 g, 38 mmol) and acetophenone (6.6 mL, 57 mmol) was conducted according to general procedure 2 to afford 4.7 g (53%) of *tert*-butyl-2-(phenylethylidene)hydrazinecarboxylate as a white solid, m.p. 172–174 °C (lit.[4] m.p. 169–170 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.78 (m, 2 H), 7.69 (s, br, 1 H), 7.38–7.32 (m, 3 H), 2.19 (s, 3 H), 1.55 (s, 9 H). A portion of the *tert*-butyl-2-(phenylethylidene)hydrazinecarboxylate product (1.0 g, 4.3 mmol) was treated with allylmagnesium bromide (8.6 mL, 8.6 mmol, 1.0 M in THF) according to the general

procedure to afford 0.5 g (42%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 2 H), 7.36–7.32 (m, 2 H), 7.26–7.23 (m, 1 H), 5.68–5.57 (m, 2 H), 5.07–5.02 (m, 2 H), 4.19 (s, br, 1 H), 2.54–2.49 (m, 1 H), 2.45–2.40 (m, 1 H), 1.48 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 144.4, 133.7, 128.3, 126.8, 126.3, 118.3, 80.1, 61.9, 45.6, 28.2, 22.5; IR (film) 3299, 2978, 1722 cm^{-1}. MS (ESI) 299.1729 (299.1735 calcd for $C_{16}H_{24}N_2O_2$, M + Na^+).

(±)-*tert*-Butyl-2-(2,2,3-trimethylhex-5-en-3-yl)hydrazinecarboxylate (II-64). The reaction of *tert*-butyl carbazate (5.0 g, 38 mmol) and pinacolone (7.1 mL, 57 mmol) was conducted according to general procedure 2 to afford 7.3 g (90%) of *tert*-butyl-2-(3,3-dimethylbutan-2-ylidene)hydrazinecarboxylate as a white solid, m.p. 135–137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, br, 1 H), 1.76 (s, 3 H), 1.50 (s, 9 H), 1.15 (s, 9 H). A portion of the *tert*-butyl-2-(3,3-dimethylbutan-2-ylidene)hydrazinecarboxylate product (3.0 g, 14.0 mmol) was treated with allylmagnesium bromide (28.0 mL, 28.0 mmol, 1.0 M in THF) according to the general procedure to afford 1.7 g (47%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07–5.97 (m, 1 H), 5.76 (s, br, 1 H), 5.13–5.07 (m, 2 H), 3.97 (s, br, 1 H), 2.34–2.27 (m, 1 H), 2.24–2.19 (m, 1 H), 1.45 (s, 9 H), 1.02 (s, 3 H), 0.97 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 136.5, 117.1, 80.0, 62.9, 39.9, 37.5, 28.4, 26.0, 17.2; IR (film) 3342, 2977, 1716 cm^{-1}. MS (ESI) 279.2037 (279.2048 calcd for $C_{14}H_{28}N_2O_2$, M + Na^+).

Synthesis of N^1-boc-N^2-boc-N^2-butenylhydrazine derivatives.

(±)-Di-*tert*-butyl-1-(hept-1-en-4-yl)hydrazine-1,2-dicarboxylate (II-66). A solution of *tert*-butyl-2-(hept-1-en-4-yl)hydrazinecarboxylate (**II-59**) (0.6 g, 2.4 mmol) in CH_2Cl_2 (2.5 mL) was treated with di-*tert*-butyl dicarbonate (0.5 g, 2.4 mmol) and heated to reflux until the starting material had been consumed as determined by TLC analysis (ca. 2 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 0.7 g (96%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11–6.72 (m, 2 H), 5.10–5.00 (m, 2 H), 4.25–4.04 (m, 1 H), 2.38–2.10 (m, 2 H), 1.60–1.40 (m, 2 H), 1.48 (s, 18 H), 1.39–1.23 (m, 2 H), 0.93–0.90 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 136.1, 116.4, 81.2, 80.8, 58.1, 56.2, 37.5, 37.2, 34.5, 28.2, 19.6, 14.0; IR (film) 3362, 2977, 1702 cm^{-1}. MS (ESI) 351.2252 (351.2260 calcd for $C_{17}H_{32}N_2O_4$, M + Na^+).

(±)-Di-*tert*-Butyl-1-(1-phenylbut-3-enyl)hydrazine-1,2-dicarboxylate (II-65). A solution of *tert*-butyl-2-(1-phenylbut-3-enyl)hydrazinecarboxylate (**II-60**) (0.2 g, 0.8 mmol) in CH_2Cl_2 (1.0 mL) was treated with pyridine (0.2 mL, 2.3 mmol) and di-*tert*-butyl dicarbonate (0.2 g, 0.8 mmol) and heated to reflux until the starting material had been consumed as determined by TLC analysis. The reaction mixture was cooled to rt and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 0.2 g (66%) of the title compound as a white solid, m.p. 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5 H), 5.83–5.79 (m, 1 H), 5.45–5.36 (m, 1

H), 5.13–5.02 (m, 2 H), 2.82–2.80 (m, 1 H), 2.65–2.56 (m, 1 H), 1.46 (s, br, 18 H), 1.05 (s, br, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 139.1, 135.2, 128.3, 128.1, 127.7, 127.6, 117.0, 81.4, 80.8, 59.4, 35.3, 28.2, 27.4; IR (film) 3271, 2979, 1703 cm^{-1}. MS (ESI) 385.2095 (385.2103 calcd for $C_{20}H_{30}N_2O_4$, M + Na^+).

Synthesis of Pyrazolidines via Pd-Catalyzed Carboamination

Pd-Catalyzed Synthesis of 3,5-*trans*-Disubstituted Pyrazolidines: General Procedure. A flame-dried Schlenk tube equipped with a magnetic stirbar 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 % complex, 2 mol % Pd), dppe (2 mol %), sodium *tert*-butoxide (1.7 equiv), and the aryl bromide (1.7 equiv). The Schlenk tube was purged with nitrogen and the hydrazine substrate (1.0 equiv) was added as a solution in toluene (4 mL solvent/ mmol substrate). The resulting mixture was heated to 90 °C until the starting material was consumed as judged by ^{1}H 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 extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(±)-(3*R*,5*R*)-*tert*-Butyl-5-(biphenyl-4-ylmethyl)-2-phenyl-3-propylpyrazolidine-1-carboxylate (II-81). The reaction of 50 mg (0.16 mmol) of **II-49** with 4-bromobiphenyl (65 mg, 0.28 mmol) was conducted for 18 h at 90 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (1.5 mg, 0.002 mmol, 1 mol %) and dppe (1.3 mg, 0.003 mmol, 2 mol %). This procedure afforded 59 mg (79%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 9:1 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 7.57–7.56 (d, *J* = 8.0 Hz, 2 H), 7.51–7.49 (d, *J* = 8.0 Hz, 2 H), 7.44–7.41 (t, *J* = 8.0 Hz, 2 H), 7.34–7.31 (t, *J* = 7.5 Hz, 1 H), 7.27–7.24 (m, 4 H), 6.97–6.96 (d, *J* = 8.0 Hz, 2 H), 6.91–6.88 (t, *J* = 7.0 Hz, 1 H), 4.41–4.36 (m, 1 H), 3.93–3.90 (m, 1 H), 3.44 (dd, *J* = 4.5, 12.5 Hz, 1 H), 2.56–2.51 (m, 1 H), 1.92–1.88 (m, 1 H), 1.84–1.81 (m, 1 H), 1.60–1.58 (m, 1 H), 1.47–1.42 (s, 9 H), 1.33–1.27 (m, 1 H), 1.27–1.25 (s, 2 H), 0.97–0.94 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 141.2, 139.5, 138.2, 129.7, 129.0, 128.8, 127.4, 127.2, 127.0, 120.5, 114.7, 80.7, 64.9, 60.5, 42.4, 37.3, 36.2, 28.6, 20.2, 14.3 (one carbon signal is absent due to incidental equivalence); IR (film) 2963, 1696 cm^{-1}. MS (ESI) 457.2855 (457.2855 calcd for $C_{30}H_{36}N_2O_2$, $M + H^+$).

(±)-(3*R*,5*R*)-*tert*-Butyl-5-(4-benzoylbenzyl)-2,3-diphenylpyrazolidine-1-carboxylate (II-83). The reaction of 26 mg (0.07 mmol) of **II-50** with 4-bromobenzophenone (34 mg, 0.13 mmol) was conducted for 5 h at 90 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.5 mg, 0.002 mmol, 2 mol %) and dppe (0.8 mg, 0.002

mmol, 2 mol %). This procedure afforded 30 mg (81%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as an 11:1 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 7.79 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.50–7.47 (m, 4 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.37–7.21 (m, 5 H), 6.91–6.85 (m, 3 H), 5.01 (t, *J* = 6.5 Hz, 1 H), 4.58–4.53 (m, 1 H), 3.22 (dd, *J* = 6.5, 13.5 Hz, 1 H), 2.68 (dd, *J* = 8.5, 13.5 Hz, 1 H), 2.45–2.40 (m, 1 H), 2.23–2.18 (m, 1 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 150.8, 143.4, 141.9, 137.7, 135.8, 132.3, 130.4, 129.9, 129.0, 128.7, 128.3, 127.3, 125.8, 120.2, 113.8, 81.2, 67.8, 59.7, 40.7, 40.2, 28.3 (one carbon signal is absent due to incidental equivalence); IR (film) 2977, 1703, 1658 cm^{-1}. MS (ESI) 541.2471 (541.2467 calcd for $C_{34}H_{34}N_2O_3$, M + Na^+).

(±)-(3*R*,5*R*)-*tert*-Butyl-2-(4-methoxyphenyl)-5-(2-methylbenzyl)-3-propylpyrazolidine-1-carboxylate (II-84). The reaction of 57 mg (0.17 mmol) of **II-53** with 2-bromotoluene (50 mg, 0.29 mmol) was conducted for 3 h at 90 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (1.6 mg, 0.002 mmol, 1 mol %) and dppe (1.6 mg, 0.004 mmol, 2 mol %). This procedure afforded 45 mg (63%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 10:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr upon purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.08 (m, 2 H), 7.08–7.05 (m, 2H), 6.96–6.91 (m, 2 H), 6.84–6.80 (m, 2 H), 4.38–4.30 (m, 1 H), 3.83–3.76 (m, 1 H), 3.79 (s, 3 H), 3.45 (dd, *J* =

4.0, 12.8 Hz, 1 H), 2.52 (dd, *J* = 10.0, 12.8 Hz, 1 H), 2.39 (s, 3 H), 1.94–1.87 (m, 1 H), 1.74–1.68 (m, 1 H), 1.59–1.53 (m, 3 H), 1.53–1.38 (m, 9 H), 1.45-1.38 (m, 4 H), 1.29–1.22 (m, 2 H), 0.94 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 137.0, 130.3, 130.0, 129.9, 126.5, 125.7, 115.9, 114.1, 65.2, 58.5, 55.6, 40.7, 39.9, 36.6, 35.8, 28.4, 19.9, 19.7, 13.9 (two carbon signals are absent due to incidental equivalence); IR (film) 2957, 1692 cm^{-1}. Anal calcd for $C_{26}H_{36}N_2O_2$: C, 73.55; H, 8.55; N, 6.60. Found: C, 73.53; H, 8.43; N, 6.55.

(±)-(3*R*,5*R*)-*tert*-Butyl-5-(4-*tert*-butylbenzyl)-2-(4-methoxyphenyl)-3-propylpyrazolidine-1-carboxylate (II-85). The reaction of 48 mg (0.14 mmol) of **II-53** with 1-bromo-4-*tert*-butylbenzene (49 mg, 40 μL, 0.23 mmol) was conducted for 4 h at 90 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.6 mg, 0.003 mmol, 2 mol %) and dppe (1.1 mg, 0.003 mmol, 2 mol %). This procedure afforded 38 mg (57%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 8:1 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 7.29–7.28 (m, 2 H), 7.11–7.10 (m, 2 H), 6.92–6.90 (m, 2 H), 6.83–6.81 (m, 2 H), 4.31–4.26 (m, 1 H), 3.80–3.74 (m, 1 H), 3.78 (s, 3 H), 3.38 (dd, *J* = 3.5, 12.5 Hz, 1 H), 2.48 (dd, *J* = 10.5, 12.0 Hz 1 H), 1.89–1.84 (m, 1 H), 1.80–1.76 (m, 1 H), 1.55 (s, 3 H), 1.46 (s, 9 H), 1.44-1.38 (m, 1 H), 1.29 (s, 9 H), 0.95–0.92 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 149.1, 145.5, 135.8, 128.7, 125.3, 116.0, 114.1, 80.2, 65.5, 60.5, 55.6, 42.2, 36.7, 35.7, 34.4, 31.4, 28.3, 20.0, 14.0 (one carbon signal is absent due to incidental equivalence); IR

(film) 2961, 2360, 1693 cm^{-1}. Anal calcd for $C_{29}H_{42}N_2O_3$: C, 74.64; H, 9.07; N, 6.00. Found: C, 74.61; H, 9.04; N, 5.94.

(±)-(3*R*,5*R*)-*tert*-Butyl-5-(4-cyanobenzyl)-2-(4-methoxyphenyl)-3-propylpyrazolidine-1-carboxylate (II-86). The reaction of 42 mg (0.13 mmol) of **II-53** with 4-bromobenzonitrile (42 mg, 0.23 mmol) was conducted for 4 h at 90 °C according to the general procedure using $Pd(OAc)_2$ (0.6 mg, 0.003 mmol, 2 mol %) and dppe (1.0 mg, 0.003 mmol, 2 mol %). This procedure afforded 39 mg (71%) 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 7.55 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 6.88–6.86 (m, 2 H), 6.82–6.80 (m, 2 H), 4.35–4.29 (m, 1 H), 3.83–3.80 (m, 1 H), 3.78 (s, 3 H), 3.40 (dd, *J* = 5.0, 13.0 Hz, 1 H), 2.60 (dd, *J* = 10.0, 13.5 Hz, 1 H), 1.86–1.81 (m, 1 H), 1.79–1.74 (m, 1 H), 1.59–1.58 (m, 2 H), 1.47–1.37 (m, 1 H), 1.44 (s, 9 H), 1.31–1.21 (m, 1 H), 0.97–0.93 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 145.2, 144.4, 132.3, 129.8, 118.9, 115.8, 114.1, 110.3, 105.0, 80.6, 65.0, 59.8, 55.6, 42.7, 36.8, 35.7, 28.3, 20.0, 14.0 (one carbon signal is absent due to incidental equivalence); IR (film) 2958, 2228, 1693 cm^{-1}. MS (ESI) 436.2596 (436.2600 calcd for $C_{26}H_{33}N_3O_3$, M + H^+).

(±)-(3*R*,5*R*)-*tert*-Butyl-3-(5,5-dimethoxypentyl)-2-phenyl-5-[(4-trifluoromethyl)benzyl]pyrazolidine-1-carboxylate (II-87). The reaction of 54 mg (0.14 mmol) of **II-51** with 4-bromobenzotrifluoride (52 mg, 33 μL, 0.23 mmol) was

conducted for 24 h at 90 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.0 mg, 0.003 mmol, 2 mol %) and P(2-furyl)$_3$ (1.4 mg, 0.006 mmol, 4 mol %). This procedure afforded 48 mg (65%) 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 7.53–7.51 (d, *J* = 8.0 Hz, 2 H), 7.29–7.23 (m, 4 H), 6.94–6.88 (m, 3 H), 4.39–4.34 (m, 2 H), 3.94–3.90 (m, 1 H), 3.40 (dd, *J* = 5.0, 13.0 Hz, 1 H), 3.32–3.26 (m, 1 H), 3.30 (s, 7 H), 2.57 (dd, *J* = 10.0, 13.5 Hz, 1 H), 1.89–1.83 (m, 1 H), 1.81–1.77 (m, 1 H), 1.63–1.54 (m, 4 H), 1.45 (s, 9 H), 1.43–1.35 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 142.8, 129.3, 129.1, 128.9 (q, *J* = 281.2 Hz), 128.8, 125.5, 125.4 (q, *J* = 14.8 Hz), 120.4, 114.3, 104.3, 80.7, 64.5, 59.9, 52.6, 52.6, 42.3, 37.0, 33.6, 32.5, 28.3, 26.6, 24.5; IR (film) 2938, 1695 cm^{-1}. MS (ESI) 559.2757 (559.2760 calcd for $C_{29}H_{39}F_3N_2O_4$, M + Na^+).

(±)-(3*R*,5*R*)-*tert*-Butyl-2-phenyl-5-(2-phenylallyl)-3-propylpyrazolidine-1-carboxylate (II-88). The reaction of 48 mg (0.16 mmol) of **II-49** with α–bromostyrene (23 μL, 34 mg, 0.19 mmol) was conducted for 12 h according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.7 mg, 0.003 mmol, 2 mol %) and dpe–phos (3.4 mg, 0.006 mmol, 4 mol %). This procedure afforded 50 mg (77%) 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 10:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2 H), 7.35–7.32 (m, 2 H), 7.29–7.21 (m, 3 H), 6.94–6.92

(d, *J* = 9.0 Hz, 2 H), 6.88–6.86 (t, *J* = 7.5 Hz, 1 H), 5.28 (s, 1 H), 5.02 (s, 1 H), 4.28–4.22 (m, 1 H), 3.89–3.85 (m, 1 H), 3.40 (dd, *J* = 3.5, 12.5 Hz, 1 H), 2.32 (dd, *J* = 10.5, 13.5 Hz, 1 H), 1.84–1.79 (m, 1 H), 1.76–1.72 (m, 1 H), 1.58–1.52 (m, 2 H), 1.43 (s, 9 H), 1.30–1.22 (m, 2 H), 0.93 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 145.2, 140.1, 128.7, 128.4, 127.6, 126.2, 120.0, 114.7, 114.2, 80.3, 64.4, 57.4, 57.2, 42.0, 36.7, 36.0, 28.4, 20.0, 14.0; IR (film) 2960, 2359, 1693 cm^{-1}. MS (ESI) 429.2502 (429.2518 calcd for $C_{26}H_{34}N_2O_2$ M + Na^+).

(±)-(3*R*,5*R*)-3-(4-*tert*-Butylbenzyl)-1,2-diphenyl-5-propylpyrazolidine (II-89). The reaction of 50 mg (0.18 mmol) of **II-47** with 1-bromo-4-*tert*-butylbenzene (48 mg, 32 μL, 0.30 mmol) was conducted for 18 h at 90 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.8 mg, 0.004 mmol, 2 mol %) and dppe (2.9 mg, 0.007 mmol, 4 mol%). This procedure afforded 48 mg (65%) 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 are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.30 (m, 2 H), 7.26–7.23, (m, 2 H), 7.19–7.15 (m, 3 H), 6.99–6.97 (m, 2 H), 6.88–6.85 (m, 3 H), 6.82–6.79 (m, 2 H), 4.15–4.10 (m, 1 H), 3.99–3.94 (m, 1 H), 3.11 (dd, *J* = 6.0, 13.5 Hz, 1 H), 2.56 (dd, *J* = 8.5, 14.0 Hz, 1 H), 2.15–2.10 (m, 1 H), 1.96–1.91 (m, 1 H), 1.70–1.60 (m, 1 H), 1.52–1.40 (m, 2 H), 1.39 (s, 9 H), 1.38–1.23 (m, 1 H), 0.92–0.89 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 149.1, 136.1, 128.9, 128.8, 128.7, 125.3, 119.3, 119.2, 113.6, 113.4, 65.4, 63.1, 41.3, 38.4, 37.3, 34.4, 31.3, 20.3, 14.0 (one

carbon signal is absent due to incidental equivalence); IR (film) 2959, 1595, 1494 cm^{-1}. MS (ESI) 413.2947 (413.2957 calcd for $C_{29}H_{36}N_2$ M + H^+).

(±)-3-(Biphenyl-4-ylmethyl)-1-phenyl-5-propyl-4,5-dihydro-*1H*-pyrazole (II-107). The reaction of 49 mg (0.24 mmol) of **II-75** with 4-bromobiphenyl (120 mg, 0.5 mmol) was conducted for 4 h according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 2 mol %) and dpe-phos (1.9 mg, 0.005 mmol, 2 mol %). This procedure afforded 45 mg (68%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.54 (m, 4 H), 7.44–7.41 (m, 2 H), 7.35–7.31 (m, 3 H), 7.28–7.23 (m, 2 H), 7.07–7.05 (m, 2 H), 6.82–6.79 (m, 1 H), 4.12–4.06 (m, 1 H), 3.75 (s, 2 H), 2.93 (dd, *J* = 6.0, 11.0 Hz, 1 H), 2.45 (dd, *J* = 6.0, 11.5 Hz, 1 H), 1.79–1.72 (m, 1 H), 1.47–1.39 (m, 1 H), 1.32–1.20 (m, 2 H), 0.89 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 145.5, 140.7, 139.6, 136.1, 129.3, 129.0, 128.8, 127.3, 127.2, 127.0, 118.5, 113.2, 59.9, 40.2, 36.7, 34.9, 18.3, 14.0; IR (film) 2957, 1599 cm^{-1}. MS (ESI) 377.1982 (377.1994 calcd for $C_{25}H_{26}N_2$ M + Na^+).

(±)-3-[(6-Methoxynaphthalen-2-yl)methyl]-1-phenyl-5-propyl-4,5-dihydro-*1H*-pyrazole (II-108). The reaction of 32 mg (0.16 mmol) of **II-75** with 2-bromo-6-methoxynaphthalene (63 mg, 0.27 mmol) was conducted for 3 h according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.7 mg, 0.003 mmol, 2 mol %) and dpe-phos (1.7 mg, 0.003 mmol, 2 mol %). This procedure afforded 47 mg (81%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (m, 2 H), 7.62 (s, 1 H), 7.36–7.33 (m, 1 H), 7.28–7.24 (m, 2 H), 7.16–7.12 (m, 2 H), 7.07–7.05 (m, 2 H),

6.82–6.78 (m, 1 H), 4.11–4.03 (m, 1 H), 3.91 (s, 3 H), 3.84 (s, 2 H), 2.89 (dd, *J* = 6.4, 11.2 Hz, 1 H), 2.41 (dd, *J* = 6.0, 17.2 Hz, 1 H), 1.78–1.69 (m, 1 H), 1.46–1.36 (m, 1 H), 1.31–1.16 (m, 2 H), 0.86 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 151.3, 145.6, 133.4, 132.2, 129.1, 129.0, 127.7, 127.2, 127.1, 119.0, 118.4, 113.2, 105.6, 59.9, 55.3, 40.2, 37.0, 34.9, 18.3, 13.9 (one carbon signal is absent due to incidental equivalence); IR (film) 2956, 1598 cm^{-1}. MS (ESI) 359.2125 (359.2123 calcd for $C_{24}H_{26}N_2O$ M + Na^+).

(±)-(3*R*,5*R*)-di-*tert*-Butyl-3-(biphenyl-4-ylmethyl)-5-propylpyrazolidine-1,2-dicarboxylate (II-91). The reaction of 41 mg (0.12 mmol) of **II-67** with 4-bromobiphenyl (49 mg, 0.21 mmol) was conducted for 14 h at 110 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.5 mg, 0.002 mmol, 2 mol %) and (**±**)-BINAP (1.5 mg, 0.002 mmol, 2 mol %). This procedure afforded 30 mg (52%) 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 (400 MHz, $CDCl_3$) δ 7.58–7.56 (m, 2 H), 7.52–7.50 (m, 2 H), 7.44–7.41 (t, *J* = 7.6 Hz, 2 H), 7.35–7.31 (m, 3 H), 4.48–4.40 (m, 1 H), 4.31–4.24 (m, 1 H), 3.05–2.96 (m, 1 H), 2.56 (dd, *J* = 7.6, 13.2 Hz, 1 H), 2.00–1.94 (m, 1 H), 1.84–1.80 (m, 1 H), 1.51 (s, 9 H), 1.49–1.41 (m, 2 H), 1.41 (s, 9 H), 1.29–1.26 (m, 2 H), 0.92 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 139.3, 137.4, 129.8, 128.7, 127.1, 127.0, 126.9, 80.7, 80.6, 59.9, 58.1, 40.7, 37.4, 36.7, 28.3, 28.1, 19.5, 13.8 (two carbon

signals are absent due to incidental equivalence); IR (film) 2975, 1697 cm^{-1}. MS (ESI) 503.2873 (503.2886 calcd for $C_{29}H_{40}N_2O_4$, M + Na^+).

(±)-(3*R*,5*R*)-di-*tert*-Butyl-3-(4-benzoylbenzyl)-5-propylpyrazolidine-1,2-dicarboxylate (II-92). The reaction of 83 mg (0.25 mmol) of **II-67** with 4-bromobenzophenone (112 mg, 0.43 mmol) was conducted for 14 h at 110 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 2 mol %) and **(±)**-BINAP (3.1 mg, 0.005 mmol, 2 mol %). This procedure afforded 103 mg (80%) of the title compound as a yellow oil. ^1H 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. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.72 (m, 4 H), 7.59–7.56 (m, 1 H), 7.48–7.39 (m, 4 H), 4.48–4.41 (m, 1 H), 4.30–4.24 (m, 1 H), 3.04–2.96 (m, 1 H), 2.64 (dd, *J* = 6.8, 13.6 Hz, 1 H), 1.99–1.92 (m, 1 H), 1.88–1.81 (m, 1 H), 1.50 (s, 9 H), 1.44–1.40 (m, 2 H), 1.40 (s, 9 H), 1.29–1.25 (m, 2 H), 0.92 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 143.4, 137.8, 135.7, 132.2, 130.2, 129.9, 129.8, 129.3, 128.2, 80.8, 80.7, 59.3, 58.0, 41.2, 37.5, 36.7, 28.3, 28.1, 19.5, 13.8 (one carbon signal is absent due to incidental equivalence); IR (film) 2976, 1698 cm^{-1}. MS (ESI) 531.2838 (531.2835 calcd for $C_{30}H_{40}N_2O_5$, M + Na^+).

(±)-(3*R*,5*R*)-di-*tert*-Butyl-3-propyl-5-[3-(trifluoromethyl)benzyl]pyrazolidine-1,2-dicarboxylate (II-93). The reaction of 98 mg (0.3 mmol) of **II-67** with 1-bromo-3-trifluoromethylbenzene (71 μL, 115 mg, 0.5 mmol) was conducted for 14 h at 110 °C

according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.4 mg, 0.006 mmol, 2 mol %) and **(±)-**BINAP (3.7 mg, 0.006 mmol, 2 mol %). This procedure afforded 124 mg (88%) 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 7.55–7.47 (m, 3 H), 7.41–7.38 (m, 1 H), 4.46–4.38 (m, 1 H), 4.32–4.24 (m, 1 H), 2.98–2.88 (m, 1 H), 2.61 (dd, *J* = 6.0, 13.5 Hz, 1 H), 1.97–1.92 (m, 1 H), 1.89–1.83 (m, 1 H), 1.45 (s, 9 H), 1.44–1.40 (m, 2 H), 1.37 (s, 9 H), 1.29–1.22 (m, 2 H), 0.92 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 132.8, 130.7, 128.6, 125.9, 125.8, 125.5, 123.2, 80.8, 80.7, 59.2, 58.0, 41.0, 37.7, 36.7, 28.2, 28.1, 28.0, 19.5, 13.7; IR (film) 2977, 1699 cm^{-1}. MS (ESI) 495.2448 (495.2447 calcd for $C_{24}H_{35}N_2O_4$, M + Na^+).

(±)-(3*R*,5*R*)-di-*tert*-Butyl-3-(naphthalene-2-ylmethyl)-5-phenylpyrazolidine-1,2-dicarboxylate (II-94). The reaction of 41 mg (0.11 mmol) of **II-66** with 2-bromonaphthalene (40 mg, 0.19 mmol) was conducted for 14 h at 110 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.5 mg, 0.002 mmol, 2 mol %) and **(±)-**BINAP (1.4 mg, 0.002 mmol, 2 mol %). This procedure afforded 31 mg (57%) 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 (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2 H), 7.72 (s, 1 H), 7.48–7.42 (m, 3 H), 7.36–7.19 (m, 6 H), 5.40–5.36 (m, 1 H), 4.60–4.52 (m, 1 H), 3.27–3.22 (m, 1

H), 2.77 (dd, *J* = 7.6, 13.2 Hz, 1 H), 2.43–2.36 (m, 1 H), 2.22–2.15 (m, 1 H), 1.50 (s, 9 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 135.6, 133.5, 132.3, 128.4, 128.0, 127.7, 127.6, 127.5, 127.1, 126.0, 125.8, 125.4, 81.2, 81.0, 61.7, 60.0, 40.2, 28.3, 28.2; IR (film) 2977, 1698 cm^{-1}. MS (ESI) 511.2555 (511.2573 calcd for $C_{30}H_{36}N_2O_4$, M + Na^+).

(±)-(3*R*,5*R*)-di-*tert*-Butyl-3-(3-methoxybenzyl)-5-phenylpyrazolidine-1,2-dicarboxylate (II-95). The reaction of 45 mg (0.12 mmol) of **II-66** with 3-bromoanisole (26 μL, 39 mg, 0.21 mmol) was conducted for 14 h at 110 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.5 mg, 0.002 mmol, 2 mol %) and **(±)**-BINAP (1.5 mg, 0.002 mmol, 2 mol %). This procedure afforded 30 mg (51%) 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 (400 MHz, $CDCl_3$) δ 7.35–7.34 (m, 2 H), 7.31–7.28 (m, 2 H), 7.23–7.20 (m, 2 H), 6.87–6.84 (m, 2 H), 6.79–6.76 (m, 1 H), 5.38–5.31 (m, 1 H), 4.50–4.42 (m, 1 H), 3.80 (s, 3 H), 3.08–3.04 (m, 1 H), 2.57 (dd, *J* = 8.0, 13.5 Hz, 1 H), 2.37–2.32 (m, 1 H), 2.19–2.13 (m, 1 H), 1.48 (s, 9 H), 1.43 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 141.3, 139.5, 129.3, 128.4, 127.1, 125.8, 121.7, 115.0, 111.8, 81.2, 81.0, 61.7, 59.8, 55.2, 40.0, 28.2, 28.1 (two carbon signals are absent due to incidental equivalence); IR (film) 2977, 1698 cm^{-1}. MS (ESI) 491.2513 (491.2522 calcd for $C_{27}H_{36}N_2O_5$, M + Na^+).

Pd-Catalyzed Synthesis of *cis*-3,5-Disubstituted Pyrazolidines: General Procedure. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol % complex, 2 mol % Pd), dpe-phos (2 mol %), sodium *tert*-butoxide (1.2 equiv), and the aryl bromide (1.2 equiv). The Schlenk tube was purged with nitrogen and the hydrazine substrate (1.0 equiv) was added as a solution in toluene (4 mL solvent/mmol substrate). The resulting mixture was heated to 70 °C until the starting material was consumed as judged by ^{1}H 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 extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(±)-(3*R*,5*S*)-*tert*-Butyl-5-(biphenyl-4-ylmethyl)-3-propylpyrazolidine-1-carboxylate (II-82). The reaction of 57 mg (0.25 mmol) of **II-59** with 4-bromobiphenyl (70 mg, 0.30 mmol) was conduced for 12 h at 70 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 2 mol %) and dpe-phos (2.7 mg, 0.005 mmol, 2 mol %). This procedure afforded 70 mg (74%) of the title compound as a yellow 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 10:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2 H), 7.53–7.52 (m, 2 H), 7.45 (m, 2 H), 7.35–7.32 (m, 1 H), 7.27–7.24 (m, 2H), 4.26–4.24 (m, 1 H), 3.42 (s, br, 1 H), 3.14 (dd, J = 4.0, 8.0 Hz, 1 H), 3.02–2.99

(m, 1 H), 2.79 (dd, *J* = 5.5, 8.0 Hz, 1 H), 2.32–2.27 (m, 1 H), 1.59–1.54 (m, 1 H), 1.51 (s, 9 H), 1.36–1.29 (m, 3 H), 1.23–1.17 (m, 1 H), 0.89 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 140.8, 139.2, 137.2, 130.0, 128.8, 127.1, 127.0, 126.9, 80.2, 60.4, 59.6, 40.6, 34.4, 32.2, 28.5, 20.0, 14.2; IR (film) 3234, 2963, 2360, 1714 cm^{-1}. MS (ESI) 403.2346 (403.2361 calcd for $C_{24}H_{32}N_2O_2$, M + Na^+).

(±)-(3*R*,5*S*)-*tert*-Butyl-5-(4-chlorobenzyl)-3-propylpyrazolidine-1-carboxylate (II-98). The reaction of 83 mg (0.36 mmol) of **II-59** with 1-bromo-4-chlorobenzene (83 mg, 0.44 mmol) was conducted for 12 h at 70 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.6 mg, 0.007 mmol, 2 mol %) and dpe-phos (3.9 mg, 0.007 mmol, 2 mol %). This procedure afforded 94 mg (77%) 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 >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.25 (m, 2 H), 7.11–7.10 (m, 2 H), 4.21-4.15 (m, 1 H), 3.40 (s, br, 1 H), 3.07 (dd, *J* = 4.0, 9.0 Hz, 1 H), 3.02–2.96 (m, 1 H), 2.74–2.70 (m, 1 H), 2.27–2.22 (m, 1 H), 1.62–1.53 (m, 1 H), 1.50 (s, 9 H), 1.38–1.29 (m, 2 H), 1.27–1.15 (m, 2 H), 0.89 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.6, 132.2, 130.8, 128.5, 80.3, 60.3, 59.5, 40.6, 40.2, 34.4, 28.4, 20.0, 14.1; IR (film) 3231, 2963, 1713 cm^{-1}. MS (ESI) 361.1672 (361.1659 calcd for $C_{18}H_{27}ClN_2O_2$, M + Na^+).

(±)-(3*R*,5*S*)-*tert*-Butyl-5-cinnamyl-3-propylpyrazolidine-1-carboxylate (II-99). The reaction of 50 mg (0.22 mmol) of **II-59** with β–bromostyrene (33 μL, 47 mg, 0.26 mmol)

was conducted for 2 h according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.0 mg, 0.004 mmol, 2 mol %) and dpe–phos (2.4 mg, 0.004 mmol, 4 mol %). This procedure afforded 40 mg (54%) of the title compound as a yellow oil. ^{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 (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 4 H), 7.23–7.21 (m, 1 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 6.18–6.11 (m, 1 H), 4.13–4.07 (m, 1 H), 3.70–3.59 (m, 1 H), 3.07–3.01 (m, 1 H), 2.69–2.63 (m, 1 H), 2.45–2.35 (m, 2 H), 1.68–1.61 (m, 1 H), 1.49 (s, 9 H), 1.37–1.28 (m, 2 H), 1.27–1.19 (m, 2 H), 0.93 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 137.3, 132.8, 128.5, 127.2, 126.0, 125.8, 80.1, 59.7, 59.1, 40.9, 38.6, 34.5, 28.4, 20.1, 14.1; IR (film) 2962, 1711, 1686 cm^{-1}. MS (ESI) 331.2385 (331.2386 calcd for $C_{20}H_{30}N_2O_2$ M + H$^+$).

(±)-(3*R*,5*S*)-*tert*-Butyl-5-(3-methylbenzyl)-3-phenylpyrazolidine-1-carboxylate (II-100). The reaction of 96 mg (0.37 mmol) of **II-60** with 3-bromotoluene (74 mg, 0.44 mmol) was conducted for 6 h at 70 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.7 mg, 0.007 mmol, 2 mol %) and dpe-phos (4.0 mg, 0.007 mmol, 2 mol %). This procedure afforded 86 mg (66%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 10:1 mixture of diastereomers; the isolated product was obtained with 13:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.23 (m, 3 H), 7.21–7.18 (m, 3 H), 7.06–7.00 (m, 3 H), 4.40–4.34 (m, 1 H), 4.13–4.09 (m, 1 H), 3.89–3.88 (m, 1 H), 3.15 (dd, *J* = 4.0, 9.0 Hz, 1 H), 2.82 (dd, *J* = 5.0, 8.0 Hz, 1

H), 2.56–2.51 (m, 1 H), 2.33 (s, 3 H), 1.91–1.85 (m, 1 H), 1.54 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 138.1, 138.0, 137.9, 130.4, 128.5, 128.4, 127.8, 127.2, 126.9, 126.6, 80.4, 62.5, 60.4, 41.3, 40.7, 28.5, 21.3; IR (film) 3244, 2975, 1712 cm^{-1}. MS (ESI) 375.2032 (375.2048 calcd for $C_{22}H_{28}N_2O_2$, M + Na^+).

(±)-(3*R*,5*S*)-*tert*-Butyl-5-[4-(*tert*-butoxycarbonyl)benzyl]-3-phenylpyrazolidine-1-carboxylate (II-101). The reaction of 57 mg (0.22 mmol) of **II-60** with *tert*-butyl-4-bromobenzoate (67 mg, 0.26 mmol) was conducted for 6 h at 70 °C following the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.0 mg, 0.004 mmol, 2 mol %) and dpe-phos (2.4 mg, 0.004 mmol, 2 mol %). This procedure afforded 58 mg (60%) of the title compound as a colorless 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 7.94–7.92 (m, 2 H), 7.30–7.21 (m, 7 H), 4.41–4.34 (m, 1 H), 4.17–4.11 (m, 1 H), 3.95–3.93 (m, 1 H), 3.26 (dd, *J* = 4.0, 8.8 Hz, 1 H), 2.89 (dd, *J* = 5.2, 8.0 Hz, 1 H), 2.55–2.49 (m, 1 H), 1.87–1.79 (m, 1 H), 1.59 (s, 9 H), 1.54 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 155.2, 142.8, 137.8, 130.4, 129.6, 129.4, 128.5, 127.9, 126.8, 80.9, 80.6, 62.4, 60.2, 41.2, 40.8, 28.4, 28.2; IR (film) 3246, 2976, 1711, 1611 cm^{-1}. MS (ESI) 461.2426 (461.2416 calcd for $C_{26}H_{34}N_2O_2$, M + Na^+).

(±)-(3*R*,5*S*)-*tert*-Butyl-3-phenyl-5-(2-phenylallyl)pyrazolidine-1-carboxylate (II-102). The reaction of 61 mg (0.23 mmol) of **II-60** with α–bromostyrene (37 μL, 52 mg, 0.28 mmol) was conducted for 12 h according to the general procedure using a catalyst

composed of $Pd(OAc)_2$ (1.0 mg, 0.005 mmol, 2 mol %) and dpe–phos (2.5 mg, 0.005 mmol, 2 mol %). This procedure afforded 55 mg (66%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 8:1 mixture of diastereomers; the isolated product was obtained with 11:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.46 (m, 2 H), 7.36–7.26 (m, 8 H), 5.35 (d, *J* = 1.2 Hz, 1 H), 5.14–5.13 (m, 1 H), 4.20–4.17 (m, 1 H), 4.10 (s, br, 1 H), 3.41 (dd, *J* = 3.2, 12.4 Hz, 1 H), 2.51 (dd, *J* = 3.6, 10.0 Hz, 1 H), 2.48–2.42 (m, 1 H), 1.87–1.79 (m, 1 H), 1.64–1.62 (m, 1 H), 1.54 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 145.0, 140.2, 138.1, 128.5, 128.4, 127.9, 127.7, 126.9, 126.2, 115.3, 80.5, 62.4, 57.9, 41.3, 41.1, 28.6 (one carbon signal is absent due to incidental equivalence); IR (film) 3235, 2976, 1712 cm^{-1}. MS (ESI) 365.2216 (365.2229 calcd for $C_{23}H_{28}N_2O_2$ M + H^+).

***tert*-Butyl-5-[4-(*tert*-butoxycarbonyl)benzyl]-3,3-dimethylpyrazolidine-1-carboxylate (II-103).** The reaction of 77 mg (0.36 mmol) of **II-61** with *tert*- butyl-4-bromobenzoate (111 mg, 0.43 mmol) was conducted for 12 h according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.6 mg, 0.007 mmol, 2 mol %) and dppe (2.9 mg, 0.007 mmol, 2 mol %). This procedure afforded 112 mg (80%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 4.32 (s, br, 1 H), 3.53 (s, br, 1 H), 3.15 (dd, *J* = 3.5, 13.0 Hz, 1 H), 2.78 (dd, *J* = 9.0, 13.0 Hz, 1 H), 1.95–1.91 (m, 1 H), 1.59 (s, 9 H), 1.52 (s, 9 H), 1.45–1.40 (m, 1 H), 1.15 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 165.6, 143.0, 130.3, 129.6,

129.3, 80.9, 80.2, 60.8, 46.9, 40.8, 36.6, 28.5, 28.2, 25.0, 24.6; IR (film) 2974, 1713 cm^{-1}. MS (ESI) 413.2410 (413.2416 calcd for $C_{22}H_{34}N_2O_4$ M + Na^+).

***tert*-Butyl-3-[(1-benzyl-1H-indol-5-yl)methyl]-1,2-diazaspiro[4.5]decane-2-carboxylate (II-104).** The reaction of 103 mg (0.4 mmol) of **II-62** with 1-benzyl-5-bromoindole (139 mg, 0.49 mmol) was conducted for 12 h according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.8 mg, 0.008 mmol, 2 mol %) and dppe (3.2 mg, 0.008 mmol, 2 mol %). This procedure afforded 103 mg (58%) of the title compound as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1 H), 7.31–7.25 (m, 2 H), 7.20–7.18 (d, *J* = 8.5 Hz, 2 H), 7.11–7.09 (m, 3 H), 7.01–6. 99 (m, 1 H), 6.48 (d, *J* = 3.5 Hz, 1 H), 5.30 (s, 2 H), 4.33 (s, br, 1 H), 3.38 (s, br, 1 H), 3.15 (dd, *J* = 4.0, 13.5 Hz, 1 H), 2.78 (dd, *J* = 8.5, 13.0 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.68–1.62 (m, 1 H), 1.59–1.57 (m, 1 H), 1.50 (s, 9 H), 1.38–1.19 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 137.5, 135.2, 129.2, 128.9, 128.7, 128.4, 127.6, 126.7, 123.5, 121.5, 109.6, 101.3, 79.7, 62.8, 60.7, 50.1, 44.1, 35.4, 33.4, 28.4, 25.9, 23.5, 22.6 (one carbon signal is absent due to incidental equivalence); IR (film) 2930, 1711, 1682, cm^{-1}. MS (ESI) 482.2781 (482.2783 calcd for $C_{29}H_{37}N_3O_2$ M + Na^+).

(±)-(3*R*,5*S*)-*tert*-Butyl-5-(biphenyl-4-ylmethyl)-3-methyl-3-phenylpyrazolidine-1-carboxylate (II-105). The reaction of 61 mg (0.22 mmol) of **II-63** with 4-bromobiphenyl (62 mg, 0.27 mmol) was conducted for 4 h at 70 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.0 mg, 0.004 mmol, 2 mol %) and dpe-phos (2.4 mg, 0.004 mmol, 2 mol %). This procedure afforded 80 mg (85%) of the title

compound as a white solid, m.p. 51–53 °C. ^{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. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.51 (m, 4 H), 7.45–7.41 (m, 3 H), 7.38–7.30 (m, 4 H), 7.26–7.25 (m, 3 H), 4.34 (s, br, 1 H), 4.10 (s, br, 1 H), 3.25–3.19 (m, 1 H), 2.69 (dd, *J* = 8.8, 13.2 Hz, 1 H), 2.46–2.41 (m, 1 H), 2.02–1.97 (m, 1 H), 1.56 (s, 9 H), 1.28 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 144.0, 140.9, 139.3, 137.3, 129.8, 128.7, 128.5, 128.2, 127.3, 127.1, 125.9, 125.5, 80.3, 65.7, 60.8, 45.9, 40.7, 28.5, 27.1; IR (film) 3250, 2974, 1713, cm^{-1}. MS (ESI) 451.2343 (451.2361 calcd for $C_{28}H_{32}N_2O_2$, M + Na^+).

(±)-(3*R*,5*S*)-*tert*-Butyl-3-*tert*-butyl-5-[(6-methoxynaphthalen-2-yl)methyl]-3-methylpyrazolidine-1-carboxylate (II-106). The reaction of 55 mg (0.21 mmol) of **II-64** with 2-bromo-6-methoxynapthalene (61 mg, 0.26 mmol) was conducted for 12 h at 70 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (0.9 mg, 0.004 mmol, 2 mol %) and dpe-phos (2.3 mg, 0.004 mmol, 2 mol %). This procedure afforded 65 mg (75%) of the title compound as a yellow oil. ^{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 >20:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.66 (m, 2 H), 7.55 (s, br, 1 H), 7.30–7.29 (m, 1 H), 7.14–7.10 (m, 2 H), 4.38 (s, br, 1 H), 3.92 (s, 3 H), 3.79 (s, br, 1 H), 3.12 (dd, *J* = 3.5, 10.0 Hz, 1 H), 2.93 (dd, *J* = 8.0, 5.5 Hz, 1 H), 1.81–1.74 (m, 1 H), 1.72-1.67 (m, 1 H), 1.50 (s, 9 H), 0.95 (s, 3 H), 0.82 (s, 9 H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 157.3, 133.2, 133.1, 128.9, 128.5, 127.9, 126.9, 118.7, 105.5, 79.9, 67.9, 59.9, 55.2, 40.5, 39.9, 34.2, 28.4, 25.6, 19.6 (two carbon signals are absent due to incidental equivalence); IR (film) 3276, 2971, 1713, 1682 cm^{-1}. MS (ESI) 435.2619 (435.2624 calcd for $C_{25}H_{36}N_2O_3$, M + Na^+).

Synthesis of 1,3-Diamines

(±)-(3*R*,5*S*)-*tert*-Butyl-2-benzoyl-5-(biphenyl-4-ylmethyl)-3-propylpyrazolidine-1-carboxylate (II-114). A solution of (±)-(3*R*,5*S*)-*tert*-butyl-5-(biphenyl-4-ylmethyl)-3-propylpyrazolidine-1-carboxylate (**II-82**) (0.16 g, 0.4 mmol) and pyridine (116 μL, 0.11 g, 1.4 mmol) in THF (4.1 mL) was cooled to 0 °C. Benzoyl chloride (48 μL, 0.4 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C until the starting material had been consumed as determined by TLC analysis (ca. 3 h). The reaction mixture was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1 M KH_2PO_4 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), then were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 0.16 g (82%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65–7.64 (m, 2 H), 7.57–7.52 (m, 4 H), 7.43–7.39 (m, 2 H), 7.32–7.29 (m, 3 H), 7.26–7.22 (m, 3 H), 4.66–4.52 (m, 1 H), 4.01–3.93 (m, 1 H), 3.48–3.34 (m, 1 H), 2.93 (dd, *J* = 8.5, 14 Hz, 1 H), 2.53–2.42 (m, 1 H), 2.27–2.22 (m, 1 H), 1.76–1.73 (m, 1 H), 1.57–1.52 (m, 1 H), 1.43–1.36 (m, 2 H), 1.21 (s, 9 H), 0.95 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 140.8, 139.5, 137.2, 135.4, 130.5, 129.5, 128.8, 128.4, 127.5, 127.2, 127.1, 127.0, 82.6, 59.7, 58.4, 39.4, 35.3, 27.7, 19.7, 14.1 (three carbon signals are absent due to incidental equivalence); IR (film) 2963, 1721, 1652 cm^{-1}. MS (ESI) 485.2812 (485.2804 calcd for $C_{31}H_{36}N_2O_3$, $M + H^+$).

(±)-(2*S*,4*R*)-*tert*-Butyl-4-benzamido-1-(biphenyl-4-yl)heptan-2-carbamate (II-115). A flame-dried flask was cooled under a stream of nitrogen and charged with samarium powder (0.39 g, 2.58 mmol). The flask was purged with nitrogen, and THF (8.6 mL, 0.3 M) was added followed by diiodomethane (0.1 mL, 0.33 g, 1.29 mmol). The reaction mixture was stirred at rt until a blue color persisted (ca. 1 h), and then a solution of (±)-(3*R*,5*S*)-*tert*-butyl-2-benzoyl-5-(biphenyl-4-ylmethyl)-3-propylpyrazolidine-1-carboxylate (**II-114**) (0.12 g, 0.3 mmol) in MeOH/THF (1.0 mL, 1:1 v:v) was added. The reaction mixture was stirred at rt until the starting material had been consumed as determined by TLC analysis. The reaction mixture was quenched with H_2O (5 mL), diluted with CH_2Cl_2 (10 mL), and filtered through celite. The filtrate was extracted with H_2O (2 x 5 mL), and the combined organic layers were washed with $NaHCO_3$ (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 0.11 g (94%) of the title compound as a white solid, m.p. 154–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.81 (m, 1 H), 7.57–7.54 (m, 2 H), 7.51–7.47 (m, 4 H), 7.45–7.40 (m, 4 H), 7.34–7.30 (m, 1 H), 7.26–7.22 (m, 2 H), 6.49–6.45 (m, 1 H), 4.78–4.74 (m, 1 H), 4.28–4.22 (m, 1 H), 3.99–3.92 (m, 1 H), 2.88–2.83 (m, 2 H), 1.76–1.70 (m, 2 H), 1.64–1.56 (m, 1 H), 1.53–1.45 (m, 1 H), 1.41 (s, 9 H), 1.37–1.24 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

167.2, 155.7, 141.0, 139.5, 137.1, 135.0, 131.3, 129.8, 128.7, 128.5, 127.2, 127.1, 127.0, 79.4, 49.5, 47.4, 41.2, 39.8, 37.3, 28.4, 19.3, 13.9 (one carbon signal is absent due to incidental equivalence); IR (film) 3352, 2955, 1683, 1633 cm^{-1}. MS (ESI) 509.2771 (509.2780 calcd for $C_{31}H_{38}N_2O_3$, M + Na^+).

(±)-1-(3*R*,5*R*)-5-(4-*tert*-Butylbenzyl)-2-(4-methoxyphenyl)-3-propylpyrazolidin-1-yl)-2,2,2-trifluoroethanone (II-118). A round-bottom flask was charged with a solution of 4 M HCl in dioxane (4.6 mL) and cooled to 0 °C. A solution of (±)-(3*R*,5*R*)-*tert*-butyl-5-(4-*tert*-butylbenzyl)-2-(4-methoxyphenyl)-3-propylpyrazolidine-1-carboxylate (**II-85**) (64 mg, 0.1 mmol) in dioxane (0.7 mL, 0.2 M) was added, the reaction mixture was stirred at 0 °C for 5 min, and then stirred at rt until consumption of the starting material was complete as determined by TLC analysis (ca. 3 h). The reaction mixture was concentrated *in vacuo*, and the crude product was dissolved in dichloromethane (1 mL, 0.1 M) and cooled to 0 °C. Pyridine (0.1 mL, 1.4 M) was added, followed by dropwise addition of trifluoroacetic anhydride (39 μL, 58 mg, 0.3 mmol). The reaction mixture was stirred at 0 °C for 5 min, and then stirred at rt until consumption of the starting material was complete as determined by TLC analysis. The reaction mixture was quenched with 2 M HCl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 24 mg (38%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.30 (m, 2 H), 7.17–7.15 (m, 2 H), 6.96–6.94 (m, 2 H), 6.87–6.84 (m, 2 H), 4.47–4.39 (m, 1 H), 3.80 (s, 3 H), 3.78–3.74 (m, 1 H), 3.70–3.66 (m, 1 H), 2.67–2.61 (m, 1 H), 1.96–1.89 (m, 1 H), 1.87–

1.81 (m, 1 H), 1.64–1.56 (m, 1 H), 1.48–1.40 (m, 1 H), 1.31 (s, 9 H), 1.20–1.15 (m, 2 H), 0.94 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2 (q, J_{CF} = 45.7 Hz), 155.4, 149.7, 144.8, 134.8, 128.6, 125.6, 117.7, 115.9 (q, J_{CF} = 357.1 Hz), 114.1, 69.6, 61.8, 55.5, 40.9, 35.1, 34.8, 34.4, 31.3, 20.1, 13.8; IR (film) 2961, 1698, 1202 cm^{-1}. MS (ESI) 485.2396 (485.2392 calcd for $C_{26}H_{33}F_3N_2O_2$, M + Na^+).

(±)-(2*R*,4*R*)-1-(4-*tert*-Butylphenyl)-4-(4-methoxyphenylamino)heptan-2-yl)-2,2,2-trifluoroacetamide (II-119). A flame-dried flask was cooled under a stream of nitrogen and charged with samarium powder (41 mg, 0.27 mmol). The flask was purged with nitrogen, and THF (0.9 mL, 0.3 M) was added followed by diiodomethane (11 μL, 37 mg, 0.14 mmol). The reaction mixture was stirred at rt until a blue color persisted (ca. 1 h), and then a solution of (±)-1-(3*R*,5*R*)-5-(4-*tert*-butylbenzyl)-2-(4-methoxyphenyl)-3-propylpyrazolidin-1-yl)-2,2,2-trifluoroethanone (**II-118**) (12.7 mg, 0.03 mmol) in MeOH/THF (1.0 mL, 1:1 v:v) was added. The reaction mixture was stirred at rt until the starting material had been consumed as determined by TLC analysis. The reaction mixture was quenched with H_2O (5 mL), diluted with CH_2Cl_2 (10 mL), and filtered through celite. The filtrate was extracted with H_2O (2 x 5 mL), and the combined organics were washed with $NaHCO_3$ (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 11 mg (90%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.08 (m, 1 H), 7.34–7.31 (m, 2 H), 7.14–7.12 (m, 2 H), 6.81–6.77 (m, 2 H), 6.63–6.59 (m, 2 H), 4.36–4.28 (m, 1 H), 3.76 (s, 3 H), 3.53–3.47 (m, 1 H), 3.05 (dd, J = 5.6, 14.0 Hz, 1 H), 2.98 (s, br, 1 H), 2.78 (dd, J = 8.8, 13.6 Hz, 1 H), 1.85–1.79 (m, 1

H), 1.59–1.45 (m, 2 H), 1.31 (s, 9 H), 1.29–1.16 (m, 3 H), 0.83 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5 (q, J_{CF} = 45.4 Hz), 153.2, 149.7, 140.4, 134.1, 128.9, 125.5, 116.4, 115.7 (q, J_{CF} = 348.8 Hz), 115.0, 55.7, 51.9, 50.2, 38.9, 37.4, 35.3, 34.5, 31.3, 29.7, 19.0, 14.0; IR (film) 3308, 2961, 1714 cm^{-1}. MS (ESI) 465.2728 (465.2729 calcd for $C_{26}H_{35}F_3N_2O_2$, M + H$^+$).

Conversion of II-86 to Disubstituted Pyrazolines

(±)-*tert*-Butyl-5-(4-cyanobenzyl)-3-propyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (II-121). A round bottom flask was charged with (3*R*,5*R*)-*tert*-butyl-5-(4-cyanobenzyl)-2-(4-methoxyphenyl)-3-propylpyrazolidine-1-carboxylate (**II-86**) (55.3 mg, 0.12 mmol) and CH_3CN (1.2 mL, 0.1 M) and cooled to 0 °C. A solution of ceric ammonium nitrate (0.2 g, 0.38 mmol) in H_2O (0.2 mL) was added dropwise over 3 min. The reaction mixture was stirred at 0 °C for 10 min, then warmed to rt and stirred until the starting material had been consumed as determined by TLC analysis (ca. 30 min). The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with aqueous Na_2SO_3 (10 mL), aqueous $NaHCO_3$ (10 mL), and brine (10 mL), then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 33 mg (78%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.57 (m, 2 H), 7.28–7.26 (m, 2 H), 4.56–4.48 (m, 1 H), 3.22–3.16 (m, 1 H), 2.87–2.76 (m, 2 H), 2.41 (dd, J = 4.5, 18 Hz, 1 H), 2.28–2.18 (m, 2 H), 1.57 (s, 9 H), 1.50–1.38 (m, 2 H), 0.88 (t, J = 7.5 Hz, 3 H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 156.6, 141.8, 134.6, 128.3, 127.7, 127.4, 117.8, 80.3, 63.2, 60.3, 40.2, 28.3, 28.2, 21.0, 14.1; IR (film) 2917, 2225, 1715, 1683 cm^{-1}. MS (ESI) 350.1832 (350.1844 calcd for $C_{19}H_{25}N_3O_2$, M + Na^+).

(±)-4-{[1-(4-methoxyphenyl)-5-propyl-4,5-dihydro-*1H*-pyrazol-3-yl]methyl}benzonitrile (II-122). Pyridine (0.5 mL, 0.3 M) and (±)-(3*R*,5*R*)-*tert*-butyl-5-(4-cyanobenzyl)-2-(4-methoxyphenyl)-3-propylpyrazolidine-1-carboxylate (**II-86**) (68 mg, 0.16 mmol) were combined in an 10 mL microwave reaction vessel equipped with a Teflon stirbar. The reaction mixture was heated in a benchtop microwave at 220 °C for 10 min (300 W, 220 °C, 5 min ramp), and then was cooled to rt, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 28 mg (55%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.61 (m, 2 H), 7.39–7.37 (m, 2 H), 7.01–6.99 (m, 2 H), 6.86–6.84 (m, 2 H), 3.97–3.91 (m, 1 H), 3.78 (s, 3 H), 3.75 (s, br, 2 H), 2.84 (dd, *J* = 11.0, 17.0 Hz, 1 H), 2.40 (dd, *J* = 7.5, 17.0 Hz, 1 H), 1.78–1.70 (m, 1 H), 1.44–1.37 (m, 1 H), 1.30–1.20 (m, 2 H), 0.89 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 149.2, 142.8, 140.1, 132.4, 129.7, 118.8, 116.3, 114.5, 110.7, 62.2, 55.6, 40.3, 37.1, 34.9, 18.7, 14.0; IR (film) 2930, 2227, 1508 cm^{-1}. MS (ESI) 334.1911 (334.1919 calcd for $C_{21}H_{23}N_3O$ M + Na^+).

(±)-(4*S*,6*R*)-4-(biphenyl-4-ylmethyl)-6-propyltetrahydropyrimidin-2(1*H*)-one (II-116). A flame-dried round bottom flask was cooled under a stream of nitrogen and charged with (±)-(2*S*,4*R*)-*tert*-butyl-4-benzamido-1-(biphenyl-4-yl)heptan-2-carbamate (**II-115**) (0.14 g, 0.3 mmol) and THF (1.0 mL, 0.3 M). The reaction mixture was cooled

to 0 °C, and a solution of $LiAlH_4$ (1.2 mL, 1.2 mmol, 1 M in THF) was added dropwise. The reaction mixture was warmed to rt and stirred until the starting material had been consumed as determined by TLC analysis. The reaction mixture was quenched with H_2O (0.1 mL) and diluted with CH_2Cl_2 (5 mL). Aqueous 3 M NaOH (0.2 mL), and H_2O (0.1 mL) were added, and the organic layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 60 mg (67%) of the title compound as a white solid, m.p. 59–61 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.53 (m, 3 H), 7.45–7.42 (m, 2 H), 7.35–7.32 (m, 1 H), 7.26–7.24 (m, 3 H), 5.17 (s, br, 1 H), 5.05 (s, br, 1 H), 3.68–3.62 (m, 1 H), 3.40–3.34 (m, 1 H), 2.86 (dd, *J* = 6.0, 13.5 Hz, 1 H), 2.70 (dd, *J* = 8.5, 13.5 Hz, 1 H), 1.97–1.94 (m, 1 H), 1.50–1.45 (m, 2 H), 1.44–1.29 (m, 3 H), 0.92 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 140.6, 139.9, 135.8, 129.6, 128.7, 127.5, 127.2, 127.0, 51.7, 50.2, 42.3, 38.2, 34.7, 18.4, 13.9; IR (film) 3233, 2957, 1672 cm^{-1}. MS (ESI) 309.1973 (309.1967 calcd for $C_{20}H_{24}N_2O$, $M + H^+$).

(±)-(4*R*,6*R*)-4-(4-*tert*-butylbenzyl)-1-(4-methoxyphenyl)-6-propyl-3-(2,2,2-trifluoroethyl)tetrahydropyrimidin-2-(*1H)*-one (II-120). A round bottom flask was charged with (±)-(2*R*,4*R*)-1-(4-*tert*-butylphenyl)-4-(4-methoxyphenylamino)heptan-2-yl)-2,2,2-trifluoroacetamide (**II-119**) (12.5 mg, 0.03 mmol) and THF (0.3 mL, 0.1 M). The solution was cooled to 0 °C and LAH (0.11 mL, 0.1 mmol, 1.0 M in THF) was added dropwise. The reaction mixture was stirred at 0 °C for 5 min, and then warmed to rt and stirred until the starting material had been consumed as determined by TLC analysis. The reaction mixture was quenched with H_2O (0.1 mL) and diluted with CH_2Cl_2 (2 mL).

Aqueous 3 M NaOH (0.2 mL), and H_2O (0.1 mL) were added, and the organic layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 10.6 mg (87%) of (±)-(2*R*,4*R*)-1-(4-*tert*-butylphenyl)-N^4-(4-methoxyphenyl)-N^2-(2,2,2-trifluoroethyl)heptane-2,4-diamine (**S1**) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.31 (m, 2 H), 7.07–7.05 (m, 2 H), 6.75–6.73 (m, 2 H), 6.53–6.51 (m, 2 H), 3.21 (s, 3 H), 3.52–3.48 (m, 1 H), 3.26–3.18 (m, 1 H), 3.11–2.98 (m, 2 H), 2.75 (dd, *J* = 6.0, 14.0 Hz, 1 H), 2.58 (dd, *J* = 7.0, 13.5 Hz, 1 H), 1.51–1.48 (m, 4 H), 1.31 (s, 9H), 1.29–1.23 (m, 4 H), 0.84 (t, *J* = 7.0 Hz, 3 H).

A round bottom flask was charged with triphosgene (6 mg, 0.02 mmol) and CH_2Cl_2 (0.1 mL). A solution of (±)-(2*R*,4*R*)-1-(4-*tert*-butylphenyl)-N^4-(4-methoxyphenyl)-N^2-(2,2,2-trifluoroethyl)heptane-2,4-diamine (**S1**) (8 mg, 0.02 mmol) and Et_3N (6 μL, 2.2 equiv) in CH_2Cl_2 (0.4 mL) was added, and the reaction mixture was stirred at rt until the starting material was consumed as determined by TLC analysis (ca. 1 h). The reaction mixture was concentrated *in vacuo* and the resulting crude product was dissolved in EtOAc (1.0 mL) and washed with $KHSO_4$ (0.5 mL), aqueous $NaHCO_3$ (0.5 mL), and brine (0.5 mL). The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 4.2 mg (51%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 7.36–7.34 (m, 2 H), 7.13–7.11 (m, 4 H), 6.91–6.89 (m, 2 H), 4.79–4.70 (m, 1 H), 3.90–3.80 (m, 1 H), 3.81 (s, 3 H), 3.79–3.72 (m, 2 H), 3.15–3.05 (m, 2 H), 2.84–2.78 (m, 1 H), 2.09–2.02 (m, 1 H), 1.96–1.88 (m, 1 H), 1.39–1.25 (m, 1 H), 1.32 (s, 9H), 1.00–0.92 (m, 1 H), 0.91–0.75 (m, 1 H), 0.77 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 155.2, 149.9, 134.3, 134.0, 129.4, 129.1 (q, *J* = 325.0 Hz), 128.8, 125.8, 114.1,

55.7, 55.5, 54.7, 46.4 (q, J = 38.1 Hz), 38.3, 36.3, 34.5, 31.3, 31.1, 18.0, 13.9; IR (film) 2960, 1654 cm^{-1}. MS (ESI) 499.2551 (499.2548 calcd for $C_{27}H_{35}N_2O_2$, M + Na^+).

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[18] Pyrazolidines may also be accessed via regio- and diastereoselective reduction of 2-pyrazolines. For examples, see: de los Santos, J. M.; Lopez, Y.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2008**, *73*, 550–557.

[19] For nucleophilic additions to pyrazolines with organocerium reagents, see: Kim, J. –H.; Denmark, S. E. *Synthesis* **1992**, 229–234.

[20] For nucleophilic additions to pyrazolines with Grignard reagents, see: Mangeney, P.; Tranchier, J. –P.; Lensen, N.; Alexakis, A. *J. Org. Chem.* **1992**, *57*, 4563–4565.

[21] For a recent review, see: Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571–582.

[22] a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621. b) Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099–3107. c) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605–3608. d) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459.

[23] a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860. b) Maloney, D. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7789–7792 and references cited therein.

[24] a) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859. b) Giese, B.; Bulliard, M.; Zeitz, H. –G. *Synlett* **1991**, 425–427. c) Garcia, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2005**, *70*, 10368–10374.

[25] Yang, B.; Qiu, G.; Katritzky, A. *J. Org. Chem*. **1997**, *62*, 8210-8214.

[26] Bredihhin, A.; Groth, U. M.; Maeorg, U. *Org. Lett*. **2007**, *9*, 1097-1099.

[27] Dppe = 1,2-bis(diphenylphosphino)ethane. Dpe-phos = bis(2-diphenylphosphino)phenyl ether.

[28] Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838–6852.

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Chapter III

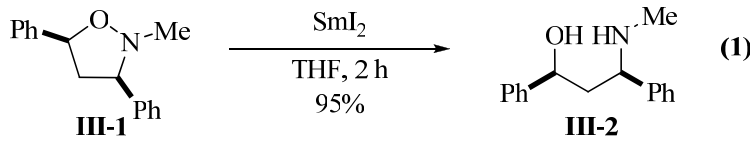
Mechanism and Stereocontrol in Isoxazolidine-Forming Reactions

The previous chapter described a new method of pyrazolidine synthesis via Pd-catalyzed carboamination using simple *N*-substituent manipulation to control product stereochemistry.[1] Upon completion of this work, we became interested in whether manipulation of allyic strain as a means to control product stereochemistry would be applicable in the synthesis of other heterocycles via our carboamination or carboetherification methodology. This chapter describes application of this concept in isoxazolidine synthesis[2], as well as the results of *N*-substituent and deuterium labeling studies used to probe the mechanism of isoxazolidine synthesis via both carboetherification and carboamination methodology.

III.1 Allylic Strain and Isoxazolidine Synthesis

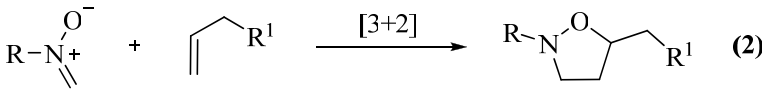
Structurally related to pyrazolidines, isoxazolidines[3] comprise another interesting class of heterocycles. These compounds are used as intermediates in the synthesis of complex molecules[4] and are found in several biologically active compounds.[5] Additionally, the N-O bond can easily be cleaved under reducing conditions to afford

1,3-amino alcohols which are also important synthetically.[6] As shown, subjection of isoxazolidine **III-1** to samarium diiodide in THF afforded the 1,3-diamine **III-2** in excellent yield (eq 1).



(1)

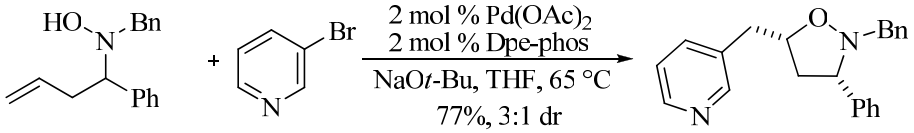
Isoxazolidines have most commonly been accessed via 1,3-dipolar cycloaddition strategies between nitrones and alkenes (eq 2). However, many of these reactions are prone to generating mixtures of regioisomers,[7] and typically the major stereoisomer forms as the result of *endo* addition on the less hindered face of the alkene. This can be considered a particular limitation, as a straightforward method for selective preparation of stereoisomers resulting from addition to the more substituted alkene face cannot be accomplished.



(2)

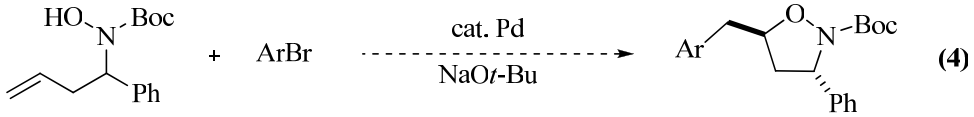
Studies on the synthesis of isoxazolidines via Pd-catalyzed carboetherification reactions of *N*-butenyl hydroxylamine derivatives with aryl bromides have been conducted in the Wolfe group.[3] In general, carboetherification reactions of *N*-benzyl-*N*-(but-3-enyl)hydroxylamines were shown to yield *cis*-3,5-disubstituted isoxazolidine products. For example, *N*-benzyl protected hydroxylamine **III-3** is transformed to 3,5-*cis*-

disubstituted isoxazolidine **III-4** in 77% yield and 3:1 dr (eq 3). This transformation is believed to proceed via transition state **III-6** in which the C1 phenyl substituent prefers to lie in a pseudoequatorial position, giving rise to the observed 3,5-*cis*-disubsituted isoxazolidine product stereochemistry (Figure III-1). The alternative transition state **III-5** suffers from an unfavorable 1,3-diaxial interaction between the C1 phenyl and C3 hydrogen atom.



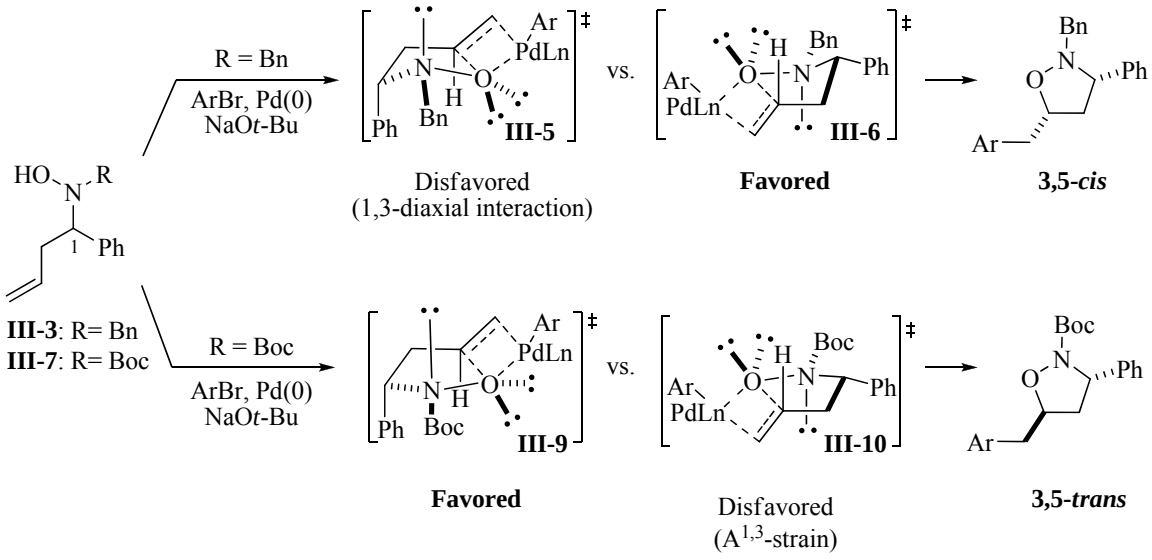
III-3 **III-4** **(3)**

Given our results on the stereoselective synthesis of pyrazolidines,[1] it seemed likely that the use of *N*-Boc-protected hydroxylamines **III-7** should lead to 3,5-*trans*-disubstituted isoxazolidine products **III-8** (eq 4). These reactions should proceed via transition state **III-9** in which the C1 phenyl group is oriented in a pseudoaxial position, which would minimize allylic strain interactions with the *N*-Boc group (Figure III-1). The alternative transition state **III-10** suffers from unfavorable $A^{1,3}$-strain between the *N*-Boc group and the C1 phenyl substituent.



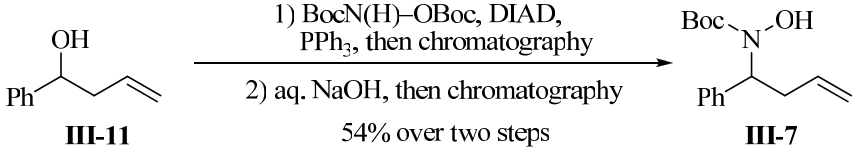
III-7 **III-8** **(4)**

Figure III-1. Stereochemical Hypothesis for Isoxazolidine Formation



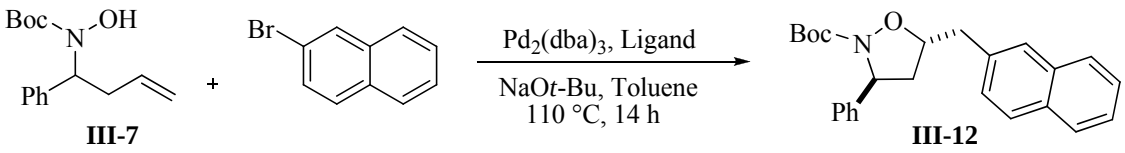
To probe our stereochemical hypothesis, hydroxylamine substrate **III-7** was synthesized (Scheme III-1). Mitsunobu reaction of 1-phenyl-3-buten-1-ol **III-11** and *N*,*O*-bis-(Boc)-hydroxylamine afforded an *N*,*O*-bis-(Boc)-*N*-butenylhydroxylamine derivative which could be subsequently deprotected to afford **III-7** in good yield.

Scheme III-1. Synthesis of *tert*-Butyl-*N*-hydroxy(1-phenylbut-3-enyl)carbamate



Although the original reaction conditions developed for the carboetherification reaction of *N*-benzyl hydroxylamine **III-3** were unsuitable for transformation of **III-7** to isoxazolidine product (Table III-1, Entry 3), a ligand screen was conducted that verified that the desired product could successfully be formed using a catalyst composed of 1 mol % $Pd_2(dba)_3$ and 4 mol % Xanthphos (Table III-1, Entry 9). We were pleased to observe upon purification of the crude reaction mixture, 3,5-*trans*-disubstituted isoxazolidine **III-12** was isolated in 49% yield with 11:1 dr. The 3,5-*trans*-isoxazolidine stereochemistry was confirmed by nOe analysis as illustrated in Figure III-3.

Table III-1. Ligand Optimization for 3,5-*trans*-Disubstituted Isoxazolidine Formation

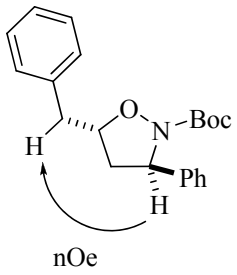


III-7 **III-12**

Entry	Ligand	Pd/L Ratio	Result
1	dppe	1:2	Heck + Isomerized SM
2	dppf	1:2	Heck / Mess
3	Dpe-phos	1:2	Heck + Isomerized SM
4	Xantphos	1:2	Heck + Isomerized SM + Isoxazolidine
5	NiXantphos	1:2	O-arylation + SM
6	BINAP	1:2	O-arylation + Heck + SM
7	$P(t\text{-Bu})_3 \bullet HBF_4$	1:4	Heck + SM
8	$P(o\text{-tol})_3$	1:4	SM
9	Xantphos	1:4	49% yield, 11:1 dr (crude dr: 7:1)

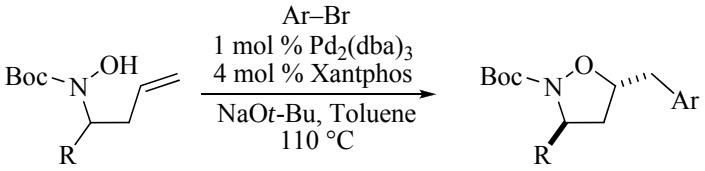
[a] Conditions: 1 equiv hydroxylamine, 1.2 equiv ArBr, 1.2 equiv NaO*t*-Bu, Toluene, 0.2 M.

Figure III-2. Assignment of Stereochemistry of 3,5-*trans*-Disubstituted Isoxazolidines



With optimized reaction conditions in hand, the scope of aryl bromide coupling partner was also examined (Table III-2). Modest levels of selectivity for *trans*-3,5-disubstituted isoxazolidine formation were observed as previously seen with **III-12**, and aryl bromides ranging from electron rich to electron poor participated in the reaction to give products **III-13**–**III-15**.

Table III-2. Scope of *N*-Boc Hydroxylamine Carboetherification[a]



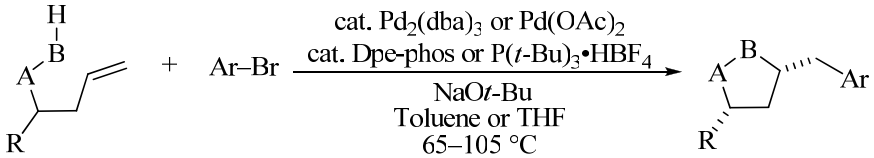
Entry	R	Ar	Product	Yield[b]	dr[c]
1	Ph	*p*-Ph-Ph	**III-13**	49%	11:1
2	Me	*p*-CN-Ph	**III-14**	59%	4:1
3	Me	*p*-CF_3-Ph	**III-15**	29%	6:1

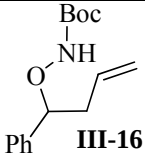
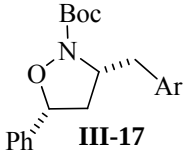
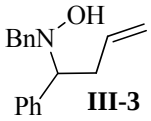
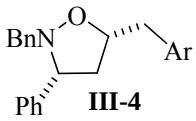
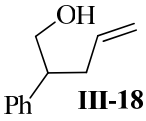
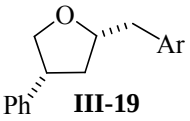
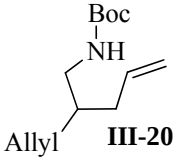
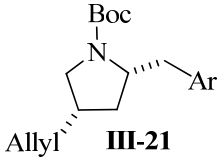
[a] Conditions: 1 equiv hydroxylamine, 1.2 equiv ArBr, 1.2 equiv NaO*t*-Bu, Toluene, 0.2 M. [b] Isolated yield (average of two or more experiments). [c] dr= diastereomeric ratio of isolated material.

III.2 Stereocontrol in Carboamination and Carboetherification Reactions of Substrates with a Substituent on C3

During the course of my experiments described above, another graduate student in the group (Georgia Lemen) demonstrated that carboamination reactions of *N*-Boc-*O*-(but-3-enyl)hydroxylamines that generate *cis*-3,5-disubstituted isoxazolidines proceed with excellent diastereoselectivity.[8] When hydroxylamine **III-16** was treated with a catalyst composed of Pd_2dba_3 and P(*t*-Bu)$_3$•HBF_4 in the presence of *tert*-butyl 4-bromobenzoate, **III-17** was generated in 78% yield and with >20:1 dr (Table III-3, Entry 1). The high stereoselectivity of this reaction was quite intriguing, as most related carboamination or carboetherification reactions of substrates with a substituent on C3 proceed with modest diastereoselectivity. For example, Hay and Wolfe demonstrated the coupling of **III-3** with 3-bromopyridine generated **III-4** in 77% yield, but with only 3:1 dr (Table III-3, Entry 2).[3] A similar limitation was observed in related tetrahydrofuran- and pyrrolidine-forming reactions of **III-18** and **III-20**, which generated **III-19** and **III-21** with 2–3:1 dr (Entries 3–4).[11,12] This notable difference in selectivity observed in the carboamination versus carboetherification process prompted our further experimentation in order to probe the origin of this effect.

Table III-3. Limitations of Stereocontrol



Entry	Substrate	Ar	Product	Yield (%)	dr
1	 **III-16**	*p*-CO_2*t*-BuPh	 **III-17**	78[b]	>20:1
2	 **III-3**	3-pyridyl	 **III-4**	77[a]	3:1
3	 **III-18**	*m*-OMePh	 **III-19**	84[a]	2:1
4	 **III-20**	*p*-CO_2*t*-BuPh	 **III-21**	72[a]	3:1

[a] Dpe-phos used as a ligand. [b] P(*t*-Bu)$_3$•HBF$_4$ used as a ligand.

III.3 *N*-Substituent Effects in Isoxazolidine Synthesis

In order to further probe the factors that influence diastereoselectivity in isoxazolidine-forming reactions that generate C–N vs C–O bonds, the carboamination and carboetherification of **III-3**, **III-7**, **III-16**, and **III-22**–**III-24** with simple aryl bromides was examined (Table III-4). This work was done in collaboration with Georgia Lemen; experiments that she performed are identified in the footnotes of Table III-4.

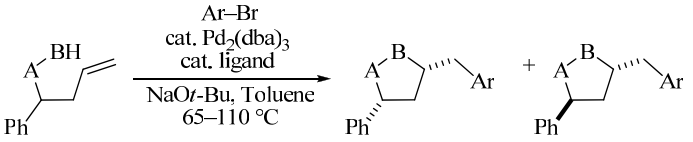
The ligand P(*t*-Bu)$_3$•HBF$_4$, which provided optimal results in reactions of **III-16**, was not effective for carboetherification reactions of **III-3**. As such, we elected to employ Dpe-phos and Xantphos as ligands for the experiments shown in Table III-4, as these ligands provided the desired products in most transformations of interest and had previously been used in the reactions of **III-3**, **III-16**, **III-18**, and **III-20** described in Table III-3. Use of Dpe-phos as a ligand for the reactions of substrates of **III-3**, **III-7**, **III-16**, and **III-22**–**III-24** provided slightly different results than were obtained with Xantphos. However, in most cases similar diastereoselectivities were observed with both catalyst systems.

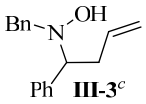
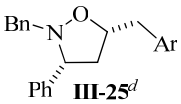
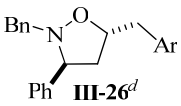
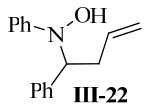
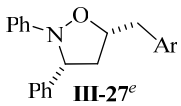
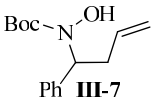
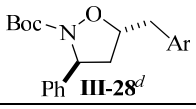
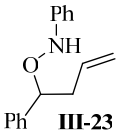
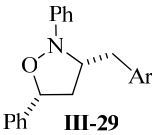
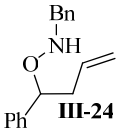
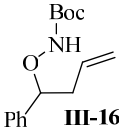
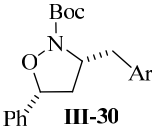
As shown in Table III-4, the selectivities and yields of these transformations were significantly influenced by the type of substituent on nitrogen. For example, Pd$_2$(dba)$_3$/Xantphos-catalyzed carboetherification reactions of *N*-benzyl- or *N*-phenyl substituted *N*-(but-3-enyl)hydroxylamines **III-3** and **III-22** proceeded with low diastereoselectivity (Entries 2 and 4, 1–2:1 dr). The analogous carboamination reaction of *N*-phenyl-*O*-(but-3-enyl)hydroxylamine **III-23** also proceeded with low selectivity (Entry 8**,** 2:1 dr)[9] whereas the reaction of the *N*-benzyl-protected derivative **III-24** failed to generate an isoxazolidine product. In contrast, the Pd-catalyzed carboetherification of *N*-

Boc-*N*-(but-3-enyl)hydroxylamine derivative **III-7** with 2-bromonaphthalene afforded *trans*-disubstituted product **III-28** with relatively high selectivity (Entry 6, 7:1 dr),[10] The conditions originally developed for Pd-catalyzed carboetherification of *N*-benzyl-*N*-(but-3-enyl)hydroxylamines were not effective with *N*-Boc-*N*-(but-3-enyl)hydroxylamine substrates (reference 3). However, use of Xantphos as ligand with a reaction temperature of 110 °C led to the successful conversion of **III-7** to **III-28**.

The $Pd_2(dba)_3$/Xantphos-catalyzed carboamination of *N*-Boc-*O*-(but-3-enyl)hydroxylamine **III-16** proceeded with good selectivity for formation of *cis*-disubstituted product **III-30** (Entry 12, 8:1 dr). Thus, the presence of the *N*-Boc protecting group appears to have a large influence on stereoselectivity in both the carboetherification and the carboamination reactions.

Table III-4. Diastereoselectivity in Carboetherification versus Carboamination Reactions



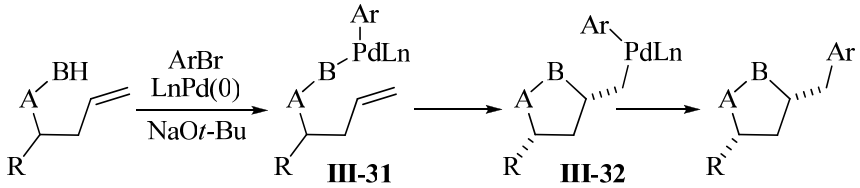
Entry	Ligand	Substrate	Major Product	dr[b]	Yield (%)[c]
1[j]	Dpe-phos	 **III-3**[c]	 **III-25**[d]	4:1	83
2[j]	Xantphos	**III-3**[c]	 **III-26**[d]	1:2	69[f]
3[j]	Dpe-phos	 **III-22**	 **III-27**[e]	3:1	79
4[j]	Xantphos	**III-22**	**III-27**[e]	1:1	75
5	Dpe-phos	 **III-7**	—	—	0[g]
6	Xantphos	**III-7**	 **III-28**[d]	1:7	33[g]
7	Dpe-phos	 **III-23**	 **III-29**	1:1	22–46[h]
8	Xantphos	**III-23**	**III-29**	2:1	38[h]
9[j]	Dpe-phos	 **III-24**	—	—	0[l]
10[j]	Xantphos	**III-24**	—	—	0[l]
11[j]	Dpe-phos	 **III-16**	 **III-30**	12:1	66
12[j]	Xantphos	**III-16**	**III-30**	8:1	71

[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 (average of two experiments). [d] Ar = Ph. [e] Ar = 2-naphthyl. [f] From reference 13b; we have obtained nearly identical results. [g] A mixture of products resulting from either Heck arylation or isomerization of the starting alkene was obtained. [h] Significant amounts of products derived from substrate N–O bond cleavage were also formed. [i] The major product was benzaldehyde *O*-1-phenylbut-3-enyl oxime. [j]Experiment conducted by Georgia Lemen.

III.4 Mechanism of Heterocycle Formation

As outlined in Chapter I, palladium-catalyzed carboetherification and carboamination reactions of γ-hydroxyalkenes[11] (e.g. **III-18**) and γ-aminoalkenes[12] (e.g. **III-20**) that provide tetrahydrofuran or pyrrolidine products are believed to proceed through the mechanism outlined in Scheme III-2.[13] In these transformations, formation of the carbon-heteroatom bond occurs via intramolecular alkene *syn*-heteropalladation from intermediate **III-31** (A = CH_2, B = O or NR^2) to generate **III-32**. This complex can then undergo C–C bond-forming reductive elimination to afford the observed products. The conversion of *N*-benzyl-*N*-(but-3-enyl)hydroxylamine substrates (e.g. **III-3**) to isoxazolidine products **(**e.g. **III-4**) is believed to occur via a similar mechanism. This hypothesis is supported by the observation that transformations of a substrate bearing a cyclic internal alkene proceed with net *syn*-addition of the oxygen atom and the aryl group to the alkene. Moreover, the fact that reactions involving **III-3**, **III-18**, or **III-20** all provided *cis*-disubstituted products with similar diastereoselectivity (Table III-3, ca. 2–3:1) is also suggestive of mechanistic similarities between the three processes.

Scheme III-2. Mechanism of Heterocycle Formation



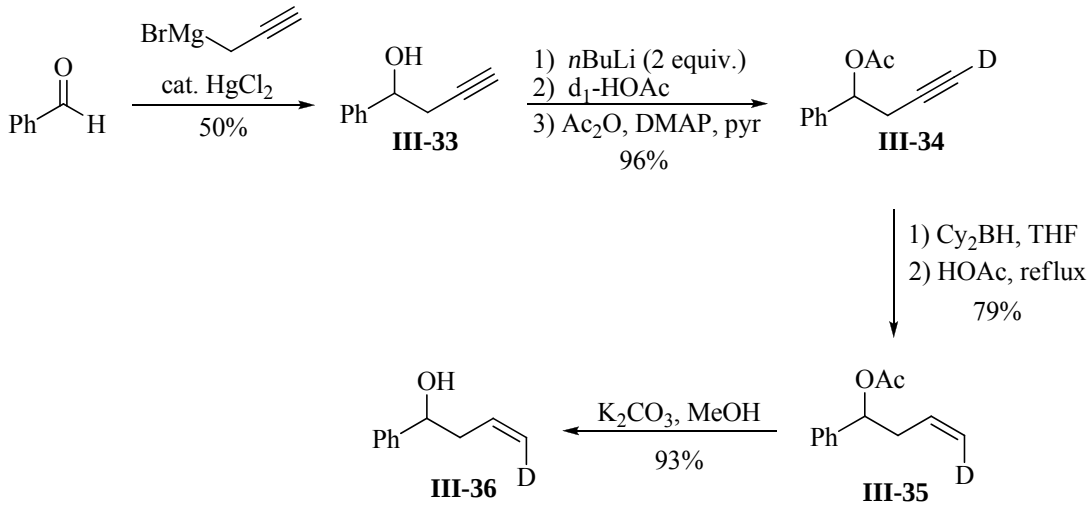
III-18: A = CH_2, B = O
III-20: A = CH_2, B = N-Boc
III-3: A = N-Bn, B = O
III-16: A = O, B = N-Boc

III-19: A = CH_2, B = O
III-21: A = CH_2, B = N-Boc
III-4: A = N-Bn, B = O
III-17: A = O, B = N-Boc

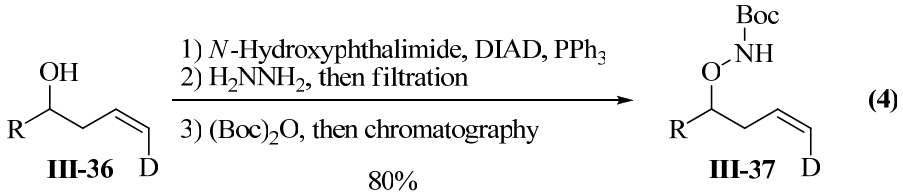
As described above, Pd-catalyzed carboamination reactions of **III-16** also provide *cis*-disubstituted products. However, the diastereoselectivity of these transformations is quite high (up to >20:1) relative to the reactions of **III-3**, **III-18**, and **III-20** shown in Table III-3. In order to rule out the possibility that the differences in diastereoselectivity observed in reactions of **III-16** were due to a change in mechanism, we conducted deuterium labeling experiments to determine the stereochemistry of alkene addition in both the carboamination and carboetherification processes. This work was done in collaboration with Mike Hay; experiments which he performed are identified in the endnotes of Chapter III.

Substrates for these studies were prepared from (*Z*)-4-deuterio-1-phenylbut-3-en-1-ol[14] **III-36** which was prepared in five steps from 1-phenylbut-3-yn-1-ol **III-33** (Scheme III-3). Addition of propargylmagnesium bromide to benzaldehyde afforded alcohol **III-33**.[15] Metalation with two equivalents of *n*-BuLi followed by quenching with D_2O and acetic anhydride provided **III-34**. Reduction of the alkyne to *Z*-alkene **III-35** was accomplished by hydroboration/protonolysis, and subsequent removal of the acetyl protecting group afforded the desired deuterated alcohol **III-36**.

Scheme III-3. Preparation of (*Z*)-4-Deuterio-1-phenylbut-3-en-1-ol

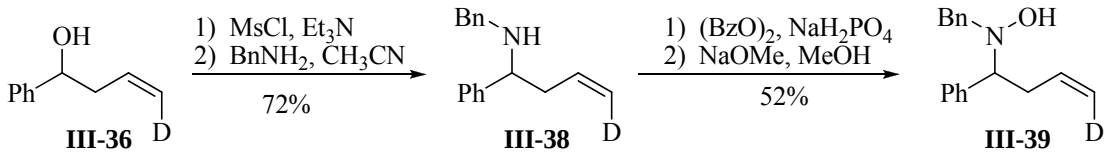


Alcohol **III-36** was converted to the desired *N*-Boc hydroxylamine **III-37** via conditions similar to those used to construct the all-proteo derivative **III-16**. Mitsunobu reaction of **III-36** with *N*-hydroxyphthalimide, followed by phthalimide cleavage and Boc protection of the intermediate afforded **III-37** in 80% yield and with 92% deuterium incorporation (eq 4).[15]



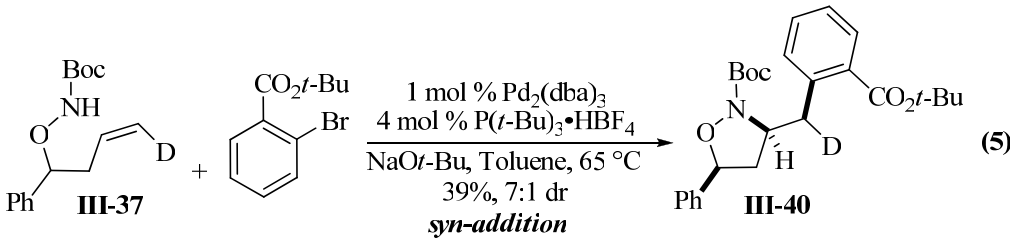
Preparation of **III-39** was accomplished in four steps from (*Z*)-4-deuterio-1-phenylbut-3-en-1-ol **III-36** (Scheme III-4). Mesylation of alcohol **III-36** and nucleophilic displacement of the mesylate with benzylamine afforded **III-38** in good yield. Subsequent treatment of **III-38** with benzoyl peroxide followed by sodium methoxide yielded the desired *N*-benzyl hydroxylamie **III-39**.

Scheme III-4. Preparation of (*Z*)-*N*-Benzyl-*N*-(4-deuterio-1-phenylbut-3-enyl)hydroxylamine

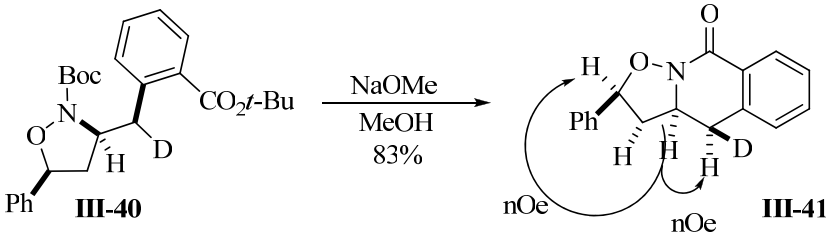


We then proceeded to examine the carboamination and carboetherification reactions of deuterated substrates **III-37** and **III-39**. The aryl bromide *tert*-Butyl-2-bromobenzoate was employed as the aryl halide coupling partner in both sets of experiments in order to facilitate assignment of stereochemistry through subsequent derivatization. However, use of this aryl bromide led to the formation of relatively large amounts of side products resulting from competing Heck-arylation of the substrates. As shown in Equation 5, treatment of **III-37** with *tert*-butyl-2-bromobenzoate under our optimized conditions afforded **III-40** in 39% yield as a 7:1 mixture of 3,5-*cis*:*trans* diastereomers.[15] In order to assay the stereochemistry of the product, isoxazolidine **III-40** was converted to derivative **III-41** via treatment with sodium methoxide in methanol

(Scheme III-5). The relative stereochemistry of **III-41** was assigned based on the nOe signals depicted in Scheme III-5. This result confirmed that palladium-catalyzed carboamination reactions of *N*-Boc-hydroxylamine substrates occur via a *syn*-aminopalladation process.

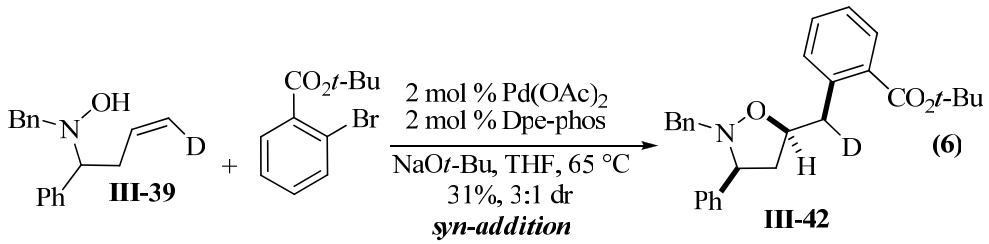


Scheme III-5. Assignment of Stereochemistry from Isoxazolidine-Forming Carboamination Reaction

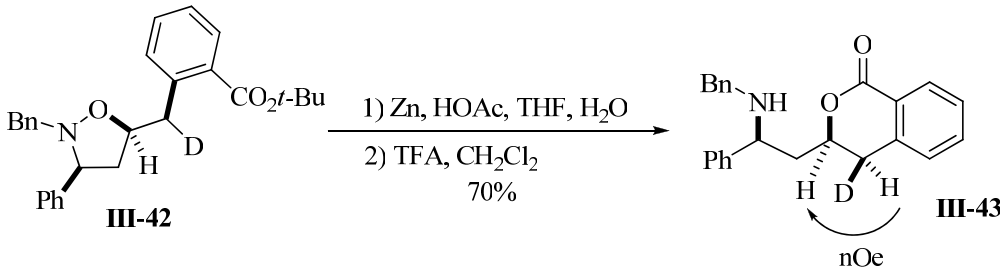


Similarly, the coupling of **III-39** with *tert*-butyl-2-bromobenzoate (eq 6) provided **III-42** in a modest 31% yield with 3:1 dr (3,5-*cis*:*trans*). To assay stereochemistry, isoxazolidine **III-42** was converted to derivative **III-43** via reduction of the N-O isoxazolidine bond followed by subsequent ring closure (Scheme III-6). The relative stereochemistry of **III-43** was assigned based on the nOe signals depicted in Scheme III-

6. This result confirmed that the palladium-catalyzed carboetherification reactions proceed via a *syn*-oxypalladation process.



Scheme III-6. Assignment of Stereochemistry of Isoxazolidine Formed via Palladium-Catalyzed Carboetherification Reaction

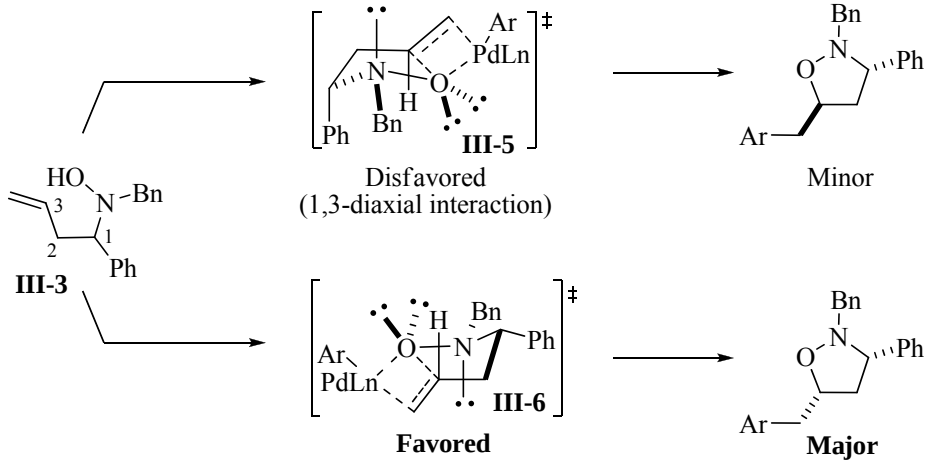


III.5 Selectivity Differences in Carboetherification vs. Carboamination Reactions

In light of these results, it seems likely that the differences observed in diastereoselectivity of isoxazolidine-forming carboetherification vs. carboamination reactions derive from conformational differences in the transition states for the heteropalladation step. In carboetherification reactions of **III-3**, the most favorable

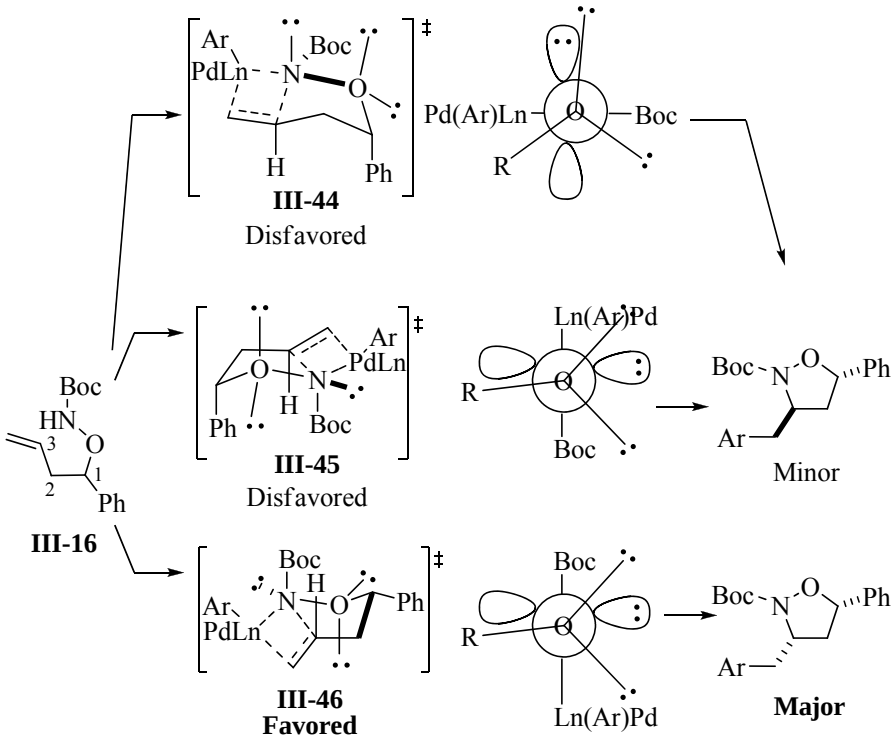
transition state **III-6** (Scheme III-7) would contain pseudoequatorial C1-phenyl and *N*-benzyl groups, and the nonbonded electrons on each heteroatom would be eclipsed with the substituents on the adjacent heteroatom. Hydroxylamines prefer to adopt a conformation in which the substituents on the nitrogen atom are eclipsed with the nonbonding electrons on the oxygen group in order to minimize repulsion between nonbonding electron pairs on the adjacent heteroatoms.[16] An alternative transition state (**III-5**), which leads to the *trans*-disubstituted product, should be higher in energy due to axial orientation of the phenyl group. However, the difference in energy between transition states **III-5** and **III-6** should be relatively small, as **III-5** is destabilized by only a single 1,3-diaxial interaction (between the C1 phenyl group and the alkene C3 hydrogen atom). This small energy difference is consistent with the modest diastereoselectivity (ca. 2–4:1 dr favoring *cis*-disubstitution) that is observed in reactions of these substrates.

Scheme III-7. Transition State for Oxypalladation of *N*-Benzyl Hydroxylamine **III-3**



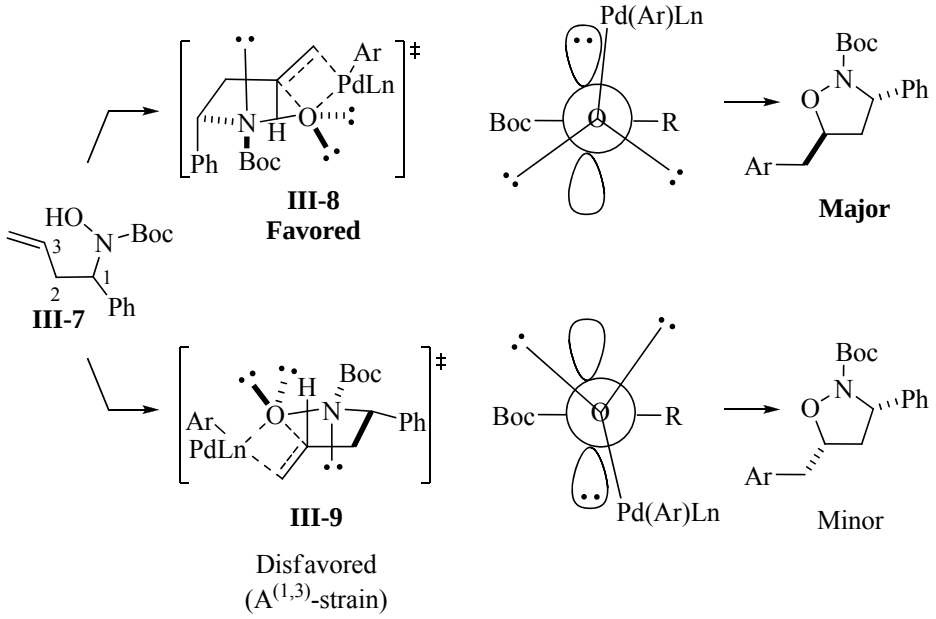
The relatively high diastereoselectivity obtained in carboamination reactions of **III-16** and related *N*-Boc protected substrates may be due to the fact that *O*-alkyl hydroxylamines bearing *N*-carbonyl groups prefer to assume conformations in which the *O*-alkyl substituent is oriented orthogonally to the Boc-group.[17] Thus, cyclization of **III-16** via transition state **III-46** (Scheme III-8) would minimize unfavorable eclipsing interactions between the nonbonded electrons on the oxygen and nitrogen atoms as well as 1,3-diaxial interactions, and would generate the observed major (*cis*-disubstituted) stereoisomer. Two transition states that would lead to the formation of the *trans*-disubstituted minor product are disfavored due to a combination of steric and stereoelectronic effects. Transition state **III-44** appears to be particularly unfavorable as it contains a 1,3-diaxial interaction between the phenyl group and the alkene C3 H-atom, *and* also suffers from electron-repulsion between the eclipsed nonbonding electrons on the adjacent N and O atoms. An alternative transition state **III-45**, which leads to the minor (*trans*) stereoisomer, minimizes this electron-repulsion. However, **III-45** is destabilized by two 1,3-diaxial interactions, Ph–H and Ph–Boc, that are not present in the more favorable transition state **III-46**. Thus, the difference in energy between transition states **III-44**, **III-45** and **III-46** is expected to be greater than that between **III-5** and **III-6**, which leads to the observed higher diastereoselectivity in the reactions of **III-3** relative to **III-16**. The low diastereoselectivity observed in carboamination reactions of *N*-phenyl substituted substrate **III-23** may result from twisting of the *N*-aryl group out of conjugation with the nonbonding electrons on nitrogen, which leads to pyramidalization of the nitrogen atom and cyclization via a transition state similar to **III-6**.

Scheme III-8. Transition States for Aminopalladation of *N*-Boc Hydroxylamine **III-16**



The stereochemical outcome of the Pd-catalyzed carboetherification of *N*-Boc-protected *N*-(but-3-enyl)hydroxylamine **III-7**, which provides *trans*-disubstituted isoxazolidine **III-28**, may also be due to the preferred conformation of the *N*-Boc-hydroxylamine moiety. As shown in Scheme III-9, cyclization through transition state **III-8** in which the C1-phenyl group is oriented in a pseudoaxial position would minimize allylic strain interactions with the *N*-Boc group, which would be oriented parallel to the forming ring.[18] In contrast, transition state **III-9** would suffer from significant $A^{(1,3)}$-strain.

Scheme III-9. Transition States for Oxypalladation of *N*-Boc Hydroxylamine **III-7**



III.6 Summary and Conclusions

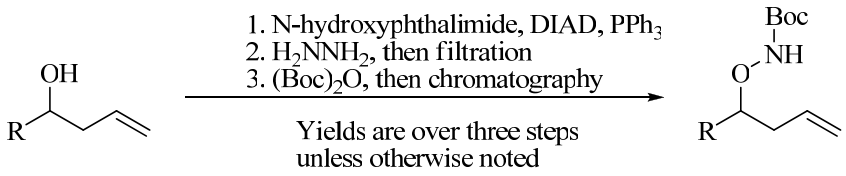
In conclusion, In order to probe factors that affect selectivity in isoxazolidine forming reactions, a combination of deuterium labeling studies coupled with systematic variation of *N*-substituents were conducted. Two significant mechanistic details have resulted: (a) despite differences in stereoselectivity, carboamination and carboetherification reactions that generate tetrahydrofurans, pyrrolidines, and isoxazolidines appear to proceed via very similar mechanisms; and (b) the effect of hydroxylamine *N*-substituent on conformation has a large effect on stereocontrol. This latter observation may be relevant to previously reported cyclization reactions of similar

substrates,[19] and will likely be of use in the future design and planning of other stereocontrolled transformations.

III.7 Experimental

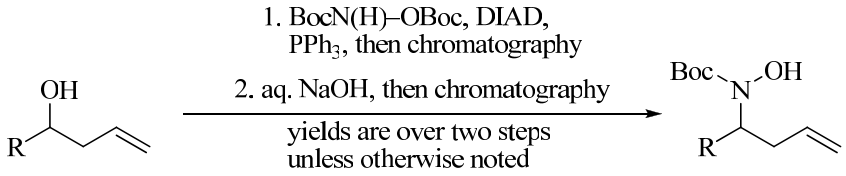
General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. $Pd(OAc)_2$, $Pd_2(dba)_3$, phosphine ligands, aryl bromides, and common reagents were obtained from commercial sources and used as obtained. *N*-phenyl hydroxylamine,[20] *N*-Boc-hydroxylamine,[21] *N,O*-bis-(Boc)-hydroxylamine,[22] 1-phenylbut-3-en-1-ol,[23] 1-(4-methoxyphenyl)-3-buten-1-ol,[24] and *N*-benzyl-*N*-(1-phenylbut-3-enyl)hydroxylamine (**II-5**)[25] were prepared according to literature procedures. 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.

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.

(±)-*tert*-Butyl 1-phenylbut-3-enyloxycarbamate (III-16).[26] The conversion of 1-phenyl-3-buten-1-ol[23] **(**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, m.p. 30.5–33.0 ºC (m.p. 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^+).

(±)-*N*-phenyl-*N*-(1-phenylbut-3-enyl)hydroxylamine (III-22).[27] A flame dried flask was evacuated and backfilled with nitrogen then charged with *N*-benzylideneaniline *N*-oxide[20] (200 mg, 1.0 mmol) and THF (2 mL). The mixture was cooled to 0 °C and a solution of allylmagnesium bromide in diethyl ether (2.0 mL, 1 M, 2.0 mmol) 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, m.p. 88.5–91.5 ºC (m.p. 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 (III-7). The conversion of 1-phenylbut-3-en-1-ol[23] (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 (III-23). 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. ^1H 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).

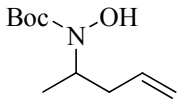
A flame-dried flask was cooled under a stream of nitrogen and charged with 1-phenylbut-3-en-1-ol (150 mg, 1.01 mmol), *N*-Boc-*N*-phenyl hydroxylamine (339 mg, 1.62 mmol), and triphenylphosphine (425 mg, 1.62 mmol). The flask was purged with nitrogen, THF (8.0 mL) was added, and the reaction mixture 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 treated with 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 (III-24). A flame dried flask was charged with *O*-(1-phenylbut-3-enyl)hydroxylamine (**S1**) (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 4h. 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$^+$).



(±)-*tert*-Butyl-hydroxy(pent-4-en-2-yl)carbamate (S1). The reaction of pent-4-en-2-ol (2.0 mL, 1.7 g, 19.4 mmol), triphenylphosphine (6.1 g, 23.3 mmol), DIAD (4.7 mL, 4.8 g, 23.7 mmol) and *tert*-butyl-*tert*-butoxycarbonyloxycarbonate (5.4 g, 23.3 mmol) was conducted according to general procedure 1. This procedure afforded 5.5 g (94%) of the *N*-boc-*O*-boc-*N*-butenylhydroxylamine as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88–5.70 (m, 1 H), 5.13–5.03 (m, 2 H), 4.33–4.19 (m, 1 H), 2.49–2.36 (m, 1 H), 2.23–2.11 (m, 1 H), 1.53 (s, 9 H), 1.48 (s, 9 H), 1.19–1.16 (m, 3 H).

A portion of the *N*-Boc-*O*-Boc-*N*-butenylhydroxylamine product (4.0 g, 13.4 mmol) was treated with 1 M aqueous sodium hydroxide (34.0 mL, 33.5 mmol) in methanol (134 mL) according to the general procedure to afford 2.6 g (97%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, br, 1 H), 5.83–5.74 (m, 1 H), 5.13–5.00 (m, 2 H), 4.12–4.06 (m, 1 H), 2.48–2.42 (m, 1 H), 2.21–2.15 (m, 1 H), 1.47 (s, 9 H), 1.20 (d, *J* = 6.5 Hz, 3 H), 0.93–0.90 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 135.4, 116.9, 81.5, 54.5, 37.9, 28.3, 17.1; IR (film) 3219, 2979, 1693 cm^{-1}. MS (ESI) 224.1264 (224.1263 calcd for $C_{10}H_{19}NO_3$, M + Na^+).

Synthesis of Isoxazolidines via Pd-Catalyzed Carboamination

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 stirbar 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*)-3-Napthalen-2-ylmethyl-5-phenylisoxazolidine-2-carboxylic acid *tert*-butyl ester (III-17, Table III-3, Entry 1). The reaction of **III-16** (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^+).

General Procedure 4: Pd-catalyzed Synthesis of Isoxazolidines via Carboetherification vs Carboamination as Shown in Table III-2 and III-4. A flame- or oven- dried Schlenk tube equipped with a magnetic stirbar 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.

(±)-(3S,5R)-*tert*-Butyl-5-(biphenyl-4-ylmethyl)-3-phenylisoxazolidine-2-carboxylate (III-13, Table III-2, Entry 1). The reaction of 58.1 mg (0.2 mmol) of **III-7** with 2-bromobiphenyl (61 mg, 0.3 mmol) was conducted according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (2.0 mg, 0.002 mmol, 1 mol %) and Xantphos (5.1 mg, 0.009 mmol, 4 mol %). This procedure afforded 44.5 mg (49%) 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 11:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.52 (m, 4 H), 7.44–7.41 (m, 2 H), 7.37–7.30 (m, 6 H), 7.25–7.24 (m, 2 H), 5.31–5.28 (m, 1 H), 4.59–4.54 (m, 1 H), 3.17–3.13 (m, 1 H), 2.79–2.75 (m, 1 H), 2.56–2.51 (m, 1 H), 2.39–2.34 (m, 1 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.6, 141.8, 140.9, 139.7, 136.5, 129.7, 128.7, 128.5, 127.3, 127.2, 127.2, 127.0, 126.0,

81.9, 80.8, 61.9, 42.6, 39.4, 28.2; IR (film) 2978, 1699 cm^{-1}. MS (ESI) 438.2048 (438.2045 calcd for $C_{27}H_{29}NO_3$, M + Na^+).

(±)-(3*R*,5*R*)-*tert*-Butyl-5-(4-cyanobenzyl)-3-methylisoxazolidine-2-carboxylate (III-14, Table III-2, Entry 2). The reaction of 51 mg (0.25 mmol) of **S1** with 4-bromobenzonitrile (55 mg, 0.3 mmol) was conducted according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.003 mmol, 1 mol %) and Xantphos (5.8 mg, 0.010 mmol, 4 mol %). This procedure afforded 45.5 mg (59%) 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 4:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.59 (m, 2 H), 7.46–7.41 (m, 2 H), 4.45–4.40 (m, 1 H), 4.34–4.29 (m, 1 H), 3.03–2.98 (m, 1 H), 2.72 (dd, *J* = 14.0, 5.0 Hz, 1 H), 2.18–2.12 (m, 1 H), 2.06–2.02 (m, 1 H), 1.50 (s, 9 H), 1.28 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.4, 143.4, 132.2, 130.1, 118.9, 110.5, 81.7, 79.8, 54.5, 40.9, 40.0, 28.2, 20.8; IR (film) 2919, 1682 cm^{-1}. MS (ESI) 325.1529 (325.1528 calcd for $C_{17}H_{22}N_2O_3$, M + Na^+).

(±)-(3*R*,5*R*)-*tert*-Butyl-3-methyl-5-(4-(trifluoromethyl)benzyl)isoxazolidine-2-carboxylate (III-15, Table III-2, Entry 3). The reaction of 72.8 mg (0.36 mmol) of **S1** with 4-bromobenzotrifluoride (60 μL, 96 mg, 0.43 mmol) was conducted for 12 h at 65 °C according to the general procedure using $Pd_2(dba)_3$ (3.3 mg, 0.004 mmol, 1 mol %) and Xantphos (8.3 mg, 0.014 mmol, 4 mol %). This procedure afforded 35.9 mg (29%) 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 6:1 dr following purification. Data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2 H), 7.44–7.40 (m, 2 H), 4.46–4.41 (m, 1 H), 4.32–4.29 (m, 1 H), 3.04 (dd, *J* = 14.0, 7.5 Hz, 1 H), 2.71 (dd, *J* = 14.5, 6.0 Hz, 1 H), 2.18–2.13 (m, 1 H), 2.03–1.98 (m, 1 H), 1.51 (s, 9 H), 1.29 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.5, 141.9, 129.6, 125.4 (q, *J* = 17.6 Hz), 81.6, 80.1, 54.5, 40.8, 39.7, 28.3, 28.2, 20.9 (one carbon signal is absent due to incidental equivalence); IR (film) 2979, 1699 cm^{-1}. MS (ESI) 368.1438 (368.1449 calcd for $C_{17}H_{22}F_3NO_3$, M + Na^+).

(±)-(3*S*,5*S*)-2,5-Dibenzyl-3-phenylisoxazolidine (III-25, Table III-4, Entry 1). The reaction of **III-3** (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) *m/z* 330.1850 (330.1858 calcd for $C_{23}H_{23}NO$, M + H^+).

(±)-(3*S*,5*S*)-5-(Naphthalen-2-ylmethyl)-2,3-diphenylisoxazolidine (III-27, Table III-4, Entry 3). The reaction of **III-22** (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, m.p. 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 missing 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$^+$).

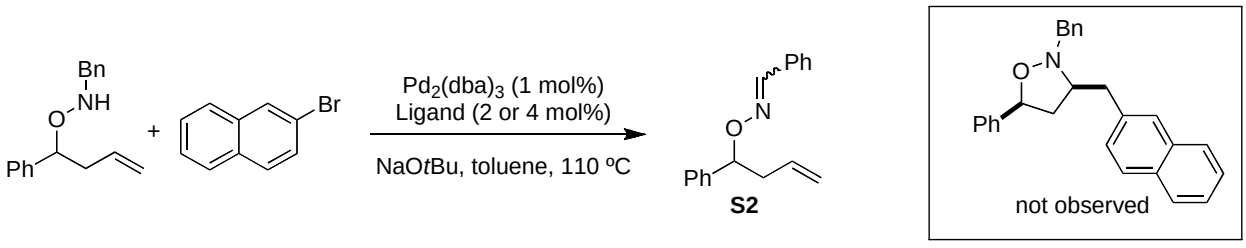
(±)-(3*S*,5*S*)-5-(Naphthalen-2-ylmethyl)-2,3-diphenylisoxazolidine (III-27, Table III-4, Entry 4). The reaction of **III-22** (47 mg, 0.20 mmol) with 2-bromonapthalene (49.7 mg, 0.24 mmol) was conducted at 110 ºC according to general procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.0020 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 (III-28, Table III-4, Entry 6). The reaction of **III-7** (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 (III-29, Table III-4, Entry 7). The reaction of **III-23** (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 missing 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 (III-29, Table III-4, Entry 8). The reaction of **III-23** (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 III-4, Entry 9). The reaction of **III-24** (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 (**S2**) 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 III-4, Entry 10). The reaction of **III-24** (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 **S2** 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 (**III-24**) was recovered in 90 % purity (as determined by ^{1}H NMR analysis).

(±)-(3*S*,5*S*)-3-Napthalen-2-ylmethyl-5-phenylisoxazolidine-2-carboxylic acid *tert*-butyl ester (III-30, Table III-4, Entry 11). The reaction of **III-16** (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 (III-30, Table III-4, Entry 12). The reaction of **III-16** (66 mg, 0.25 mmol) with 2-bromonapthalene (62 mg, 0.30 mmol) was conducted at 110 ºC for 2 h according to general procedure 4 using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.025 mmol) and Xantphos (5.8 mg, 0.010 mmol). This procedure afforded 69 mg (71%) of the title compound as a white solid. ^{1}H NMR analysis of the crude reaction mixture indicated the product was formed as a 8:1 mixture of diastereomers; the isolated product was obtained with 7:1 dr following purification. Data were identical to those provided above.

Assignment of Stereochemistry

Deuterium Labeling Studies

(±)-(*Z*)-*O*-(4-Deuterio-1-phenylbut-3-enyl)-hydroxylamine carbamic acid *tert*-butyl ester (III-37). The conversion of (*Z*)-4-deuterio-1-phenylbut-3-en-1-ol[28] to the title compound was accomplished using general procedure 1. This procedure afforded 0.89 g (80%) of the title compound as a colorless oil. The material contained ca. 92% deuterium incorporation at the 4-position as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2 H), 7.34–7.30 (m, 3 H), 6.91 (s, br, 1 H), 5.83–5.76 (m, 1 H), 5.05–5.01 (m, 1 H), 4.80 (t, J = 7.0 Hz, 1 H), 2.76–2.69 (m, 1 H), 2.52–2.45 (m, 1 H), 1.45 (s, 9 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 5.17 (s, 1 D); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 139.7, 133.6, 128.4, 128.1, 127.1, 117.0 (t, J_{CD} = 23.5 Hz), 86.9, 81.4, 39.5, 28.1; IR (film) 3305, 1721 cm^{-1}; MS (ESI) 287.1474 (287.1482 calcd for $C_{15}H_{20}DNO_3$, M + Na^+).

(±)-(*Z*)-*N*-Benzyl-4-deuterio-1-phenylbut-3-en-1-ylamine (III-38). A flame-dried flask was cooled under a stream of nitrogen and charged with (*Z*)-4-deuterio-1-phenylbut-3-en-1-ol (0.53 g, 3.56 mmol), Et_3N (1.0 mL, 7.12 mmol) and CH_2Cl_2 (4 mL). The reaction mixture was cooled to 0 °C and stirred for 10 min, MsCl (0.33 mL, 4.27 mmol) was added dropwise, and the resulting solution was stirred at 0 °C until consumption of the starting material was complete as judged by TLC analysis (ca. 30 min). The reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL), transferred to

a separatory funnel, the layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The organic layers were combined and washed with water until pH = 7 (ca. 2 x 20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford (*Z*)-4-deuterio-1-phenylbut-3-enyl methanesulfonate (0.70 g, 89%). This product was judged to be >95% pure by ^{1}H NMR analysis, and was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5 H), 5.73–5.68 (m, 1 H), 5.56–5.53 (m, 1 H), 5.13–5.11 (m, 1 H), 2.87–2.80 (m, 1 H), 2.69–2.62 (m, 1 H), 2.68 (s, 3 H).

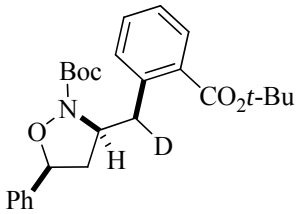
A flame-dried flask was cooled under a stream of nitrogen and charged with (*Z*)-4-deuterio-1-phenylbut-3-enyl methanesulfonate (0.70 g, 3.1 mmol), benzylamine (0.68 mL, 6.22 mmol) and acetonitrile (6 mL). The resulting solution was stirred at room temperature until consumption of the starting material was complete as judged by TLC analysis (ca. 24 h). The reaction mixture was diluted with ether (10 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ether (3 x 20 mL). The organic extracts were combined, washed with aqueous sodium chloride (2 x 20 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 0.61 g (82%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 4 H), 7.33–7.29 (m, 2 H), 7.28–7.22 (m, 4 H), 5.73–5.67 (m, 1 H), 5.03–5.01 (d, J = 6.0 Hz, 1 H), 3.70–3.66 (m, 2 H), 3.54–3.51 (d, J = 13.5 Hz, 1 H), 2.46–2.36 (m, 2 H), 1.73 (s, br, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 140.6, 135.4, 128.4, 128.3, 128.1, 127.3, 127.0, 126.8, 117.3 (t, J_{CD} = 23.4 Hz), 61.6, 51.4, 43.1; IR (film) 3326, 1454 cm^{-1}. MS (ESI) 239.1661 (239.1658 calcd for $C_{17}H_{18}DN$, M + H$^+$).

(±)-(*Z*)-*N*-Benzyl-*N*-(4-deuterio-1-phenylbut-3-enyl)hydroxylamine (III-39). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-38** (0.34 g, 1.44 mmol), sodium phosphate (1.02 g, 7.2 mmol), dibenzoyl peroxide (0.38 g, 1.58 mmol) and ether (3 mL). The resulting mixture was heated to reflux until consumption of the starting material was complete as judged by TLC analysis (ca. 15 h). The reaction mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. The crude residue was dissolved in CH_2Cl_2 and washed with aqueous sodium carbonate. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined and washed with water (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography on silica gel to afford 0.43 g (82%) of (*Z*)-*O*-benzoyl-*N*-benzyl-*N*-(4-deuterio-1-phenylbut-3-enyl)hydroxylamine as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–8.08 (m, 1 H), 7.90–7.88 (m, 2 H), 7.55–7.50 (m, 2 H), 7.46–7.44 (m, 2 H), 7.41–7.38 (m, 4 H), 7.35–7.31 (m, 3 H), 7.25–7.22 (m, 1H), 5.64–5.60 (m, 1 H), 4.89–4.87 (d, *J* = 10.0 Hz, 1 H), 4.10–4.07 (m, 2 H), 3.91–3.88 (d, *J* = 14.0 Hz, 1 H), 2.85–2.80 (m, 1 H), 2.68–2.62 (m, 1 H).

A flame-dried flask was cooled under a stream of nitrogen and charged with (*Z*)-*O*-benzoyl-*N*-benzyl-*N*-(4-deuterio-1-phenylbut-3-enyl)hydroxylamine (110 mg, 0.32 mmol) and methanol (3 mL). Sodium methoxide (0.1 mL, 0.45 mmol, 25 wt%) was added dropwise, and the reaction mixture was stirred at room until consumption of the starting material was complete as judged by TLC analysis (ca. 30 min). The reaction mixture was concentrated *in vacuo,* and the residue was dissolved in CH_2Cl_2 (10 mL).

Aqueous hydrochloric acid (10 mL, 1.6 M) was added and the biphasic mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was basified with aqueous sodium carbonate until pH = 10, and was then extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 40 mg (52%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.34 (m, 4 H), 7.31–7.28 (m, 5 H), 7.27–7.23 (m, 1 H), 5.67–5.63 (m, 1 H), 4.94–4.91 (d, J = 10.4 Hz, 1 H), 4.76 (s, br, 1 H), 3.79–3.71 (m, 2 H), 3.59–3.56 (d, J = 12.8 Hz, 1 H), 2.95–2.88 (m, 1 H), 2.64–2.57 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 135.3, 129.3, 128.8, 128.4, 128.2, 127.6, 127.2, 116.4 (t, J_{CD} = 29.3 Hz), 71.9, 61.5, 38.3 (one carbon signal is absent due to incidental equivalence); IR (film) 3315, 1494 cm^{-1}. MS (ESI) 255.1601 (255.1608 calcd for $C_{17}H_{18}DNO$, M + H$^+$).

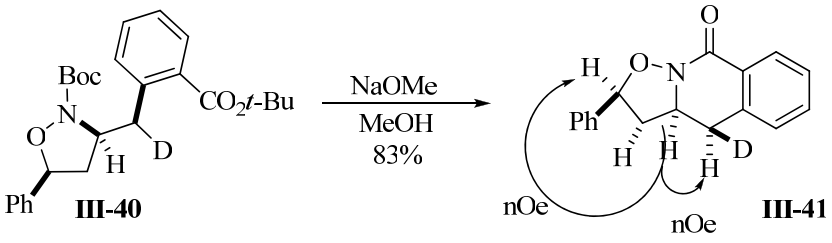
Pd-Catalyzed Reaction of (*Z*)-*O*-(4-Deuterio-1-phenylbut-3-enyl)-hydroxylamine carbamic acid *tert*-butyl ester (III-39) with *tert*-Butyl 2-Bromobenzoate.



(±)-(3*S,3'*S**,5*S**)-*tert*-butyl 3-[2-(*tert*-butoxycarbonyl)benzyl]-5-phenylisoxazolidine-2-carboxylate-3'D (III-40).** The reaction of **III-37** (140 mg, 0.53 mmol) with *tert*-butyl 2-bromobenzoate (161 mg, 0.63 mmol) was conducted for 2 h at 65 °C according to general procedure 3. This procedure afforded 91 mg (39%) of the title

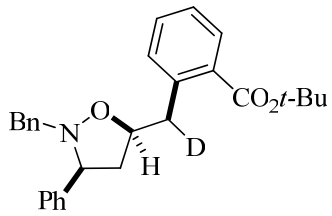
compound as a pale yellow oil. The material was isolated as a 7:1 mixture of diastereomers with ca. 80% deuterium incorporation as judged by ^{1}H NMR analysis. All isomers contained one or zero deuterium atoms as judged by MS analysis. Data are for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 1 H), 7.42–7.35 (m, 5 H), 7.34–7.31 (m, 2 H), 7.29–7.25 (m, 1 H), 4.88 (dd, J = 6.8, 10.4 Hz, 1 H), 4.68–4.64 (m, 1 H), 3.44 (d, J = 4.4 Hz, 1 H), 2.87 (ddd, J = 7.2, 8.4, 12.4 Hz, 1 H), 2.03 (ddd, J = 6.0, 10.2, 12.4 Hz, 1 H), 1.59 (s, 9 H), 1.23 (s, 9 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 3.10 (s, 1 D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 157.1, 139.7, 137.6, 132.6, 131.6, 131.1, 130.3, 128.3, 128.2, 126.6, 126.2, 83.0, 81.2, 80.9, 61.6, 43.3, 40.4 (t, J_{CD} = 21.1 Hz), 28.1, 27.8; IR (film) 2977, 1714 cm^{-1}. MS (ESI) 463.2324 (463.2319 calcd for $C_{26}H_{32}DNO_5Na$, M + Na^+).

Stereochemical Analysis of III-40. Isoxazolidine **III-40** was converted to derivative **III-41** using the sequence described below.



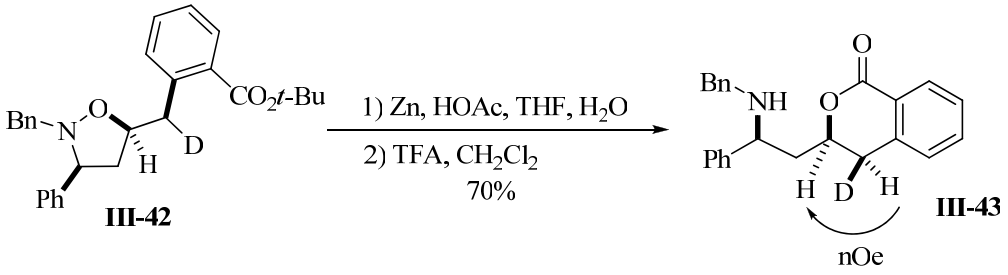
(±)-(2*S,3a*S**,4*S**)-2-phenyl-3a,4-dihydro-2*H*-isoxazolo[2,3-*b*]isoquinolin-9(3*H*)-one-4D (III-41).** A flame-dried flask equipped with a reflux condenser was cooled under a stream of nitrogen and charged with freshly prepared sodium methoxide (6 mL, 2.2 M in methanol, 13.2 mmol). Deuterated isoxazolidine **III-40** (46 mg, 0.10 mmol) was added as a solution in methanol (2 mL), and the resulting mixture was heated to reflux for 1 h. The reaction mixture was cooled to rt, quenched with saturated aqueous ammonium chloride (10 mL), and diluted with ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, decanted, and concentrated *in vacuo* to provide 22 mg (83%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.5 Hz, 1 H), 7.48–7.46 (m, 2 H), 7.44–7.42 (m, 1 H), 7.41–7.38 (m, 3 H), 7.35–7.32 (m, 1 H), 7.20 (d, *J* = 7.5 Hz, 1 H), 5.40 (dd, *J* = 5.5, 9.0 Hz, 1 H), 4.44–4.40 (m, 1 H), 3.23–3.21 (m, 1 H), 3.04 (td, *J* = 6.0, 12.5 Hz, 1 H), 2.38 (td, *J* = 9.5, 12.5 Hz, 1 H); ^{2}H NMR (83 MHz, $CHCl_3$) δ 3.10 (s, 1 D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 138.1, 135.5, 131.6, 129.4, 128.6, 128.5, 128.4, 127.7, 127.4, 126.9, 80.8, 57.6, 43.5, 34.7 (J_{CD} = 19.6 Hz); IR (film) 1668 cm^{-1}. MS (ESI) 289.1058 (289.1063 calcd for $C_{17}H_{14}DNO_2$, M + Na^+).

Pd-Catalyzed Reaction of (*Z*)-*N*-benzyl-*N*-(4-deuterio-1-phenylbut-3-enyl)hydroxylamine (III-39) with *tert*-Butyl 2-Bromobenzoate.



(±)-(3*S,3'*S**,5*S**)-*tert*-Butyl-2-[(2-benzyl-3-phenylisoxazolidin-5-yl)methyl]benzoate-3'D (III-42).** The reaction of 22 mg (0.09 mmol) of **III-39** with *tert*-butyl 2-bromobenzoate (26 mg, 0.1 mmol) was conducted for 14 h at 65 °C according to general procedure 4 using a catalyst composed of $Pd(OAc)_2$ (0.4 mg, 0.001 mmol) and Dpe-phos (1.0 mg, 0.001 mmol) in THF solvent at 65 °C. This procedure afforded 14 mg (36%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.75 (dd, *J* = 1.0, 7.5 Hz, 1 H), 7.47–7.46 (d, *J* = 7.0 Hz, 2 H), 7.39–7.32 (m, 4 H), 7.31–7.23 (m, 4 H), 7.19–7.11 (m, 2 H), 6.98–6.96 (m, 1 H), 4.50–4.46 (m, 1 H), 3.95–3.93 (d, *J* = 13.5 Hz, 1 H), 3.86–3.82 (m, 1 H), 3.72–3.69 (d, *J* = 13.5 Hz, 1 H), 3.27–3.23 (m, 1 H), 2.86–2.81 (m, 1 H), 2.13–2.07 (m, 1 H), 1.56 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 140.3, 139.5, 138.2, 132.8, 132.4, 131.0, 130.2, 129.1, 128.6, 128.0, 127.6, 127.5, 126.9, 126.1, 81.2, 70.8, 59.9, 45.5, 39.9 (t, J_{CD} = 17.8 Hz), 28.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2976, 1709 cm^{-1}. MS (ESI) 431.2450 (431.2445 calcd for $C_{28}H_{30}DNO_3$, M + H$^+$).

Stereochemical Analysis of III-42. Isoxazolidine **III-42** was converted to derivative **III-43** using the sequence described below.



(2*S,3*S**,4*S**)-3-[2-(Benzylamino)-2-phenylethyl)isochroman-1-one-4-D (III-43).** To a solution of **III-42** (6.8 mg, 0.02 mmol) in THF (0.1 mL) was added Zn powder (3.0 mg, 0.05 mmol), acetic acid (0.2 mL), and H_2O (0.1 mL). The reaction mixture was stirred at 60 °C for 30 min, and then a second portion of Zn powder (3.0 mg, 0.05 mmol) was added. The reaction mixture was then stirred at 60 °C until consumption of the starting material was complete as judged by TLC analysis (ca. 2 h). The reaction mixture was cooled to rt, filtered, quenched with saturated aqueous sodium carbonate (1 mL), diluted with CH_2Cl_2 (5 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with H_2O (2 x 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.* The crude product was dissolved in CH_2Cl_2 (1 mL), and trifluoroacetic acid (1 mL) was added dropwise. The resulting solution was stirred at room temperature until consumption of the starting material was complete as judged by TLC analysis (ca. 15 min). The reaction mixture was quenched with aqueous sodium carbonate (10 mL), diluted with CH_2Cl_2 and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 4

mg (70%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.35 (m, 7 H), 7.34–7.26 (m, 7 H), 4.34–4.32 (m, 1 H), 4.08–4.05 (m, 1 H), 3.71–3.67 (m, 1 H), 3.66–3.51 (m, 2 H), 2.72 (s, 1 H), 2.43–2.33 (m, 1 H), 1.97–1.92 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 142.8, 140.4, 138.9, 133.6, 130.3, 128.7, 128.4, 128.2, 127.6, 127.5, 127.4, 127.3, 127.0, 125.0, 76.3, 58.8, 51.5, 43.6, 33.5 (t, J_{CD} = 20.1 Hz); IR (film) 3381, 2919, 1724 cm^{-1}. MS (ESI) 359.1860 (359.1870 calcd for $C_{22}H_{22}DNO_2$, $M + Na^+$).

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[8] For full scope of carboamination process, see Ref. 1.

[9] The Pd-catalyzed carboamination reactions of **III-23** also generated significant amounts of 1-phenylbut-3-en-1-ol and other side products resulting from substrate N–O bond cleavage. Control experiments indicated that the N–O bond cleavage occurred upon heating the substrate in the presence of NaO*t*-Bu with no palladium catalyst.

[10] For related results in the synthesis of pyrazolidines via Pd-catalyzed carboamination reactions of *N*-(but-3-enyl)hydrazine derivatives see Ref. 2.

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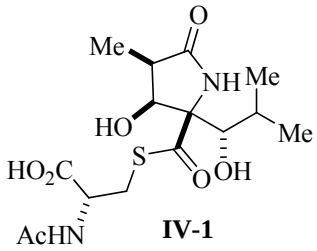
Chapter IV

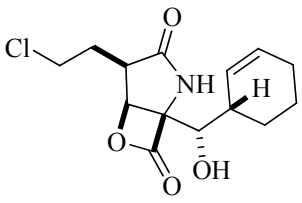
Development of Carboamination Methodology for the Synthesis of Pyrrolidinones

Pyrrolidinones are a class of heterocycle that we have had a long-standing interest in accessing via our carboamination methodology. The pyrrolidinone moiety is a prominent subunit of a wide variety of natural products and pharmaceutically important compounds.[1] Due to their interesting biological activity, pyrrolidinone-containing natural products have been targets of many total synthesis endeavors. For example, the 26S protease inhibitor (+)-Lactacystin **IV-1** has been subject of a large number of synthetic studies[2,3] given its potency and potential for use in the treatment of arthritis (Figure IV-1).[4] Other notable examples include bicyclic pyrrolidinone Salinosporamide A **IV-2**, which has displayed remarkable cytotoxicity in vitro (IC_{50} ~10 nM) directed at the inhibition of the 20S proteasome,[5] and Cytochalasin B **IV-3**, an interesting metabolite from the fungus *Helminthosporium dematioideum* known to inhibit a wide variety of cellular movements.[6]

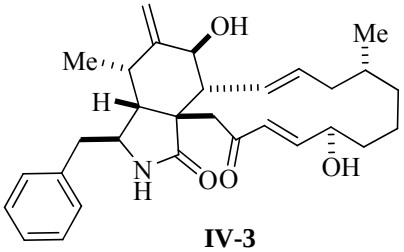
Figure IV-1. Biologically Active Natural Products with Pyrrolidinone Subunits



IV-1
(+)-*Lactacystin*

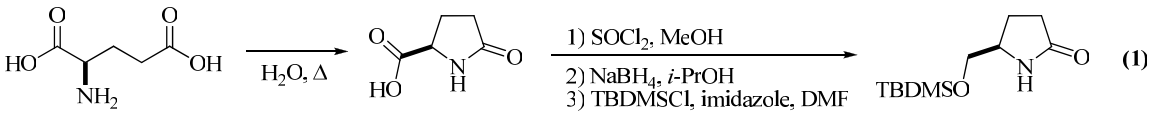


IV-2
Salinosporamide A



IV-3
Cytochalasin B

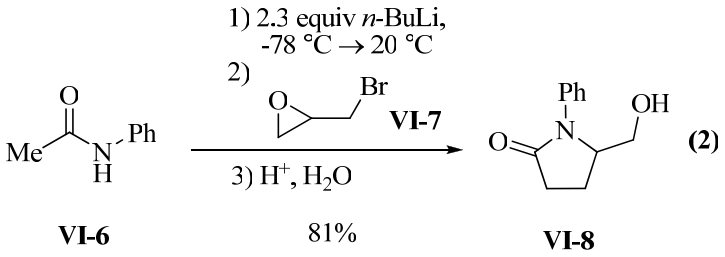
In examining a molecule such as Cytochalasin B (Figure IV-1, **IV-3**), many possible disconnections can be envisioned in order to construct the pyrrolidinone core. Amino acids are common and useful precursors to these types of molecules (eq 1). For example, D-glutamic acid can be heated in water in order to afford pyrrolidinone **IV-4**. Subsequent conversion to the methyl ester followed by reduction with sodium borohydride and protection yields **IV-5**: an intermediate en route to Cytochalasin B.[6b]



IV-4 **IV-5** **(1)**

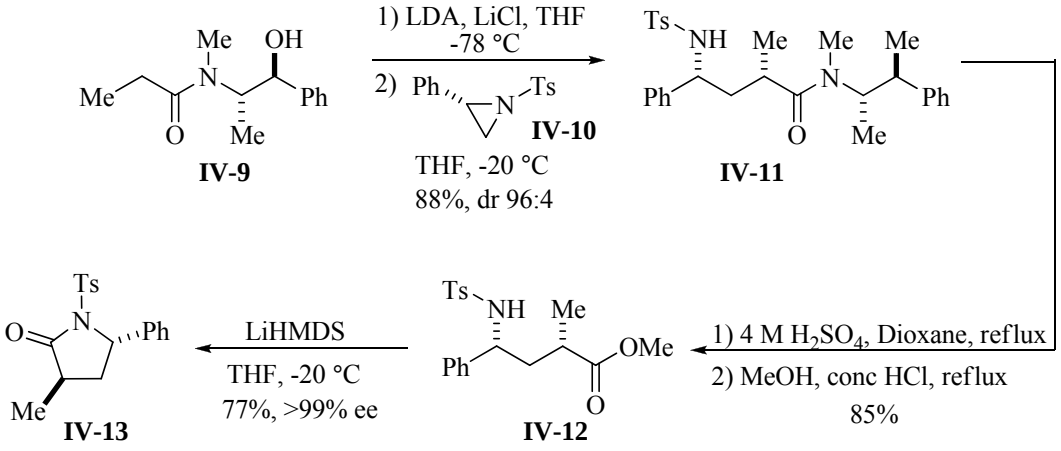
A number of other routes have also been employed for the synthesis of pyrrolidinones. Regioselective formation of 5-(hydroxymethyl)pyrrolidin-2-ones **IV-8** can be accomplished via generation of amide dianions from amides such as **VI-6** and

reaction with epibromohydrin **IV-7** (eq 2).[7] However, the reaction is not general; epibromohydrin **IV-7** was the only epoxide examined in the transformation.

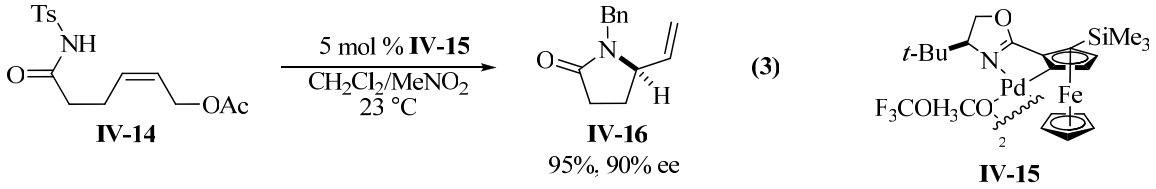


A method to generate enantioenriched pyrrolidinones involves generation of chiral enolates from **IV-9** and aziridine **IV-10** ring opening (Scheme IV-1).[8] The auxiliary is then cleaved from compounds **IV-11**, and methyl esters **IV-12** are generated for use in base-promoted cyclizations to afford pyrrolidinones such as **IV-13**. Although this method allows for pyrrolidinones to be formed in good yields and with excellent selectivity, the number of synthetic steps to reach the desired products is quite lengthy.

Scheme IV-1. Regioselective Aziridine Ring Opening

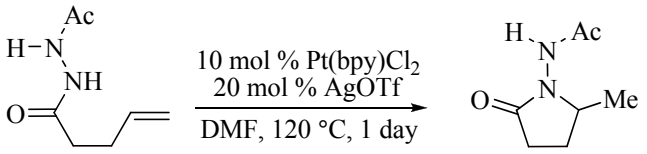


Catalytic, asymmetric cyclization reactions of homoallylic carbamates **IV-14** using palladium catalyst **IV-15** have also been developed. These reactions afford enantioenriched pyrrolidinones such as **IV-16** in good yield (eq 3).[9] A requirement of this methodology is the *Z*-configuration of the allylic *N*-arylsulfonylcarbamate substrate.[10]



IV-14 **IV-16** 95%, 90% ee **(3)** **IV-15**

A very recent report illustrated intramolecular hydrohydrazination reactions affording products **IV-18** (eq 4).[11] High platinum catalyst loading and high temperatures were necessary for successful conversion of derivative such as **IV-17** to **IV-18**.

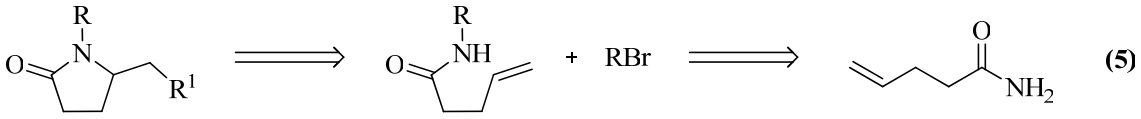


IV-17 **IV-18** **(4)**

IV.1 Synthesis of Amide Substrates for Carboamination Reactions

We envisioned that substrates for our investigations could be quite similar to those used in the carboamination process to construct pyrrolidines. Retrosynthetic analysis of the pyrrolidinone core reflected that the core heterocycle could be derived

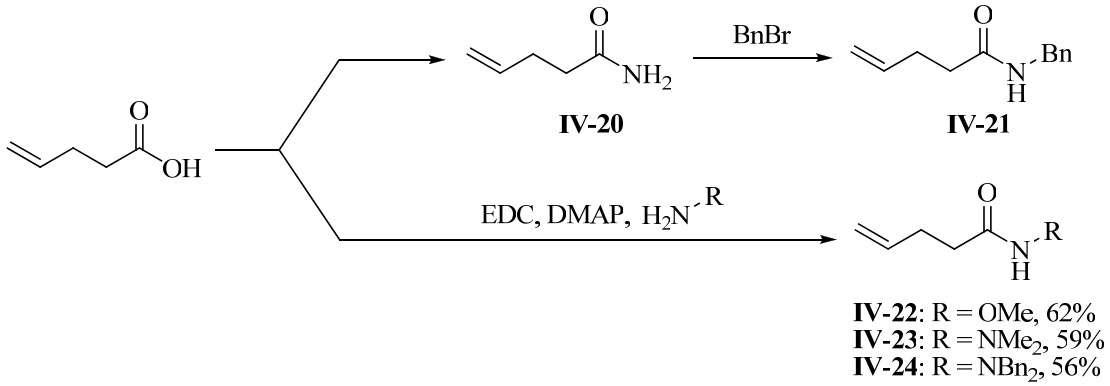
from γ,δ-unsaturated amides **IV-19** and aryl or alkenyl bromides (eq 5). We realized that the electron-withdrawing nature of the carbonyl adjacent to the cyclizing nitrogen atom had the propensity to render it a significantly weaker nucleophile than that of γ-amino alkene substrates used to construct pyrrolidines. However, variation of the R-group on the cyclizing nitrogen atom could be done easily, allowing for straightforward manipulation of the electronics of the nitrogen atom of the γ-amido alkene substrates.



IV-19 **IV-20** **(5)**

Since 4-pentenamide **IV-20** had been previously prepared from commercially available 4-pentenoic acid en route to γ-amino alkene substrates, the procedure for accessing the initial substrate for our studies (*N*-benzylpent-4-enamide **IV-21** was quite straightforward (Scheme IV-2). Other substrates designed for these studies include *N*-methoxypent-4-enamide **IV-22**, *N*',*N*'-Dimethylpent-4-enehydrazide **IV-23**, and *N*',*N*'-Dibenzylpent-4-enehydrazide **IV-24** which were prepared via reaction of the appropriate hydroxylamine or hydrazine with 4-pentenoic acid under peptide coupling conditions.

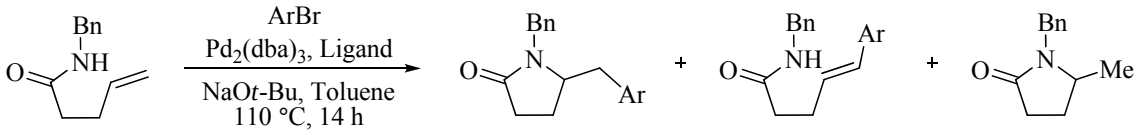
Scheme IV-2. Preparation of γ,δ-Unsaturated Amide Substrates



IV.2 *N*-Substituent Effects in Amide Carboamination

With the desired substrates in hand, a ligand screen was conducted for the coupling of γ,δ-unsaturated amide **IV-21** with 4-*tert*-butyl bromobenzoate (Table IV-1). Use of bidentate ligands such as Xantphos and BINAP, which have been useful in other carboamination processes, led to complex mixtures of the desired pyrrolidinone and Heck arylation product **IV-26** (Table IV-1, Entries 1-6). As expected, the decreased nucleophilicity of the cyclizing nitrogen atom appeared to either disfavor Pd-N bond formation or slow the rate of aminopalladation.

Table IV-1. Ligand Optimization[a]



IV-21 | **IV-25** ***Pyrrolidinone*** | **IV-26** ***Heck*** | **IV-27** ***Hydroamination***

Entry	Ligand	Ratio **IV-25 : IV-26 : IV-27**
1	NiXantphos	1 : 3.6 : 0
2	Xantphos	1 : 2.3 : 0
3	dppe	1 : 2.9 : 0
4	dppb	1 : 2.0 : 0
5	dppf	1 : 3.6 : 0
6	BINAP	1 : 3.1 : 0
7	$P(Cy)_3 \bullet HBF_4$	1 : 1.3 : 0
8	$P(2\text{-furyl})_3$	0 : 1 : 0
9	$P(o\text{-tol})_3$	0 : 0 : 1[c]
10	XPhos	0 : 0 : 1[c]
11	dpp-benzene	1[d] : 0 : 0

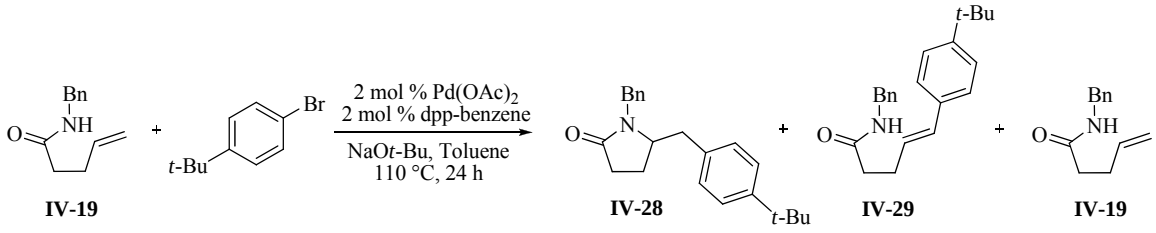
[a] Conditions: 1.0 equiv of amide, 1.2 equiv ArBr (ArBr= 4-*tert*-butyl bromobenzene), 1.2 equiv NaO*t*-Bu, 1 mol % $Pd_2(dba)_3$, 2 mol % Ligand (Entries 1-6, 11) or 4 mol % Ligand (Entries 7-10), Toluene (0.25 M), 110 °C. [b] Ratios of products are estimates bases on crude ^{1}H NMR analysis. [c] The reaction was incomplete at 14 h. [d] The reaction was incomplete at 41 h.

When sterically hindered, monodentate ligands such as P(*o*-tol)$_3$ and XPhos were examined, only the hydroamination product **IV-27** was observed, although conversion of substrate to this product appeared to be sluggish (Entries 9-10, Table IV-1). The ligand dpp-benzene gave only the desired pyrrolidinone product **IV-25** (Entry 11). However after 41 h, the reaction was still not complete as determined by ^{1}H NMR analysis.

In efforts to increase the reaction rate and facilitate desired product formation, several other reaction parameters were examined. Use of $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ in the reaction resulted in formation of the desired pyrrolidinone **IV-28** (Scheme IV-3). However, competing Heck-arylation **IV-29** was observed as well as incomplete substrate

consumption. The effect of excess ligand in the reaction was also examined (Scheme IV-4). However complete suppression of desired product formation was observed. Finally, use of xylenes as a solvent and a reaction temperature of 130 °C resulted in complete conversion of substrate **IV-19** to product **IV-28**, although an inseparable 2:1 mixture of desired product **IV-28** to Heck-arylation product **IV-9** was obtained (Scheme IV-5).

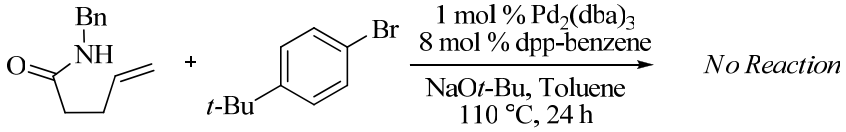
Scheme IV-3. Effect of Pd-Catalyst on Carboamination of γ,δ-Unsaturated Amide **IV-19**



IV-19 **IV-28** **IV-29** **IV-19**

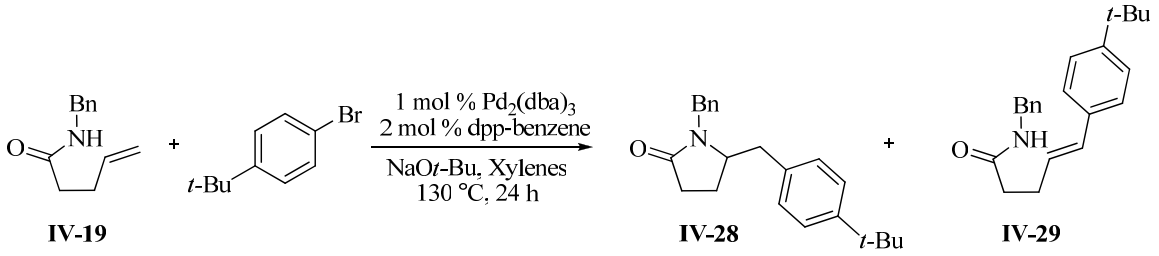
Ratio **IV-28:IV-29:IV-19= 1:1:2**

Scheme IV-4. Effect of Excess Ligand on Carboamination of **IV-19**



IV-19

Scheme IV-5. Effect of Increased Temperature on Carboamination of **IV-19**



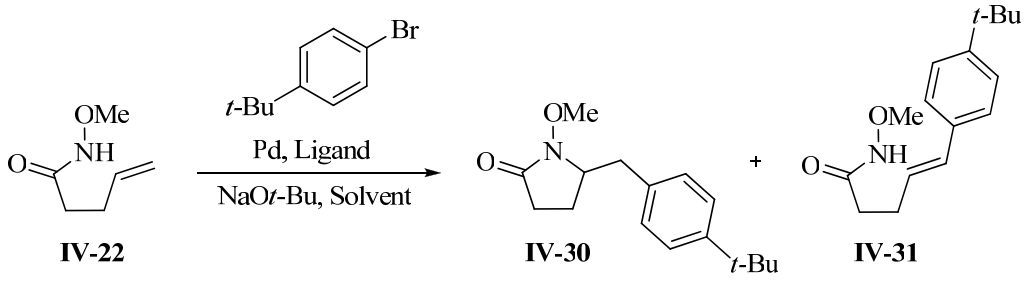
IV-19 **IV-28** **IV-29**

Ratio **IV-28:IV-29= 2:1**

Upon consideration of results obtained with *N*-benzyl γ,δ-unsaturated amide substrate **IV-19**, it appeared that the nucleophilicity of the cyclizing nitrogen atom was significantly decreased with respect to reactions involving γ-amino alkene substrates. We felt that installation of an electron donating group on nitrogen would render the nitrogen more nucleophilic, and therefore increase reactivity. Towards this end, a substrate **IV-22** derived from *O*-methylhydroxylamine hydrochloride was examined.

The results of studies involving *N*-methoxypent-4-enamide **IV-22** are outlined in Table IV-2. Complex mixtures of products were formed when bidentate phosphines were used, including Heck-arylation product **IV-31** formation (Entries 3, 4 and 6). Competing N-O bond cleavage of **IV-22** appeared to be problematic at temperatures above 110 °C (Entries 8 and 10). However, a reaction conducted at 65 °C gave no desired product (Entry 5).

Table IV-2. *N*-methoxypent-4-enamide in Pd-Catalyzed Carboamination



IV-22 **IV-30** **IV-31**

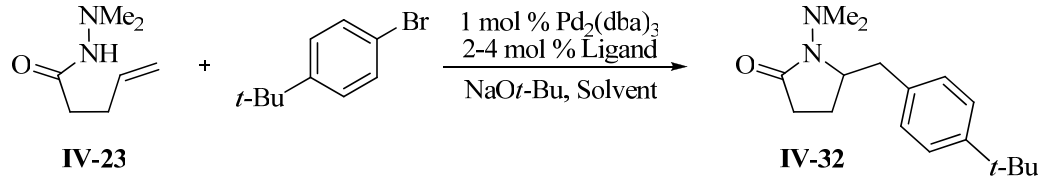
Entry	Pd	Ligand	Solvent/Temp	Ratio **IV-30:IV-31**
1	$Pd_2(dba)_3$[a]	dpp-benzene	Toluene/110 °C	0 : 1[c,d]
2	$Pd(OAc)_2$[b]	dpp-benzene	Toluene/110 °C	0 : 1
3		dppe	Toluene/110 °C	0 : 1[d]
4		Dpe-phos	Toluene/110 °C	0 : 1[d]
5			Toluene/65 °C	0 : 0[c]
6		Xantphos	Toluene/110 °C	0 : 1[d]
7		$P(o\text{-tol})_3$	Toluene/110 °C	0 : 0[c,d]
8			Xylenes/130 °C	0 : 0[c,d]
9		XPhos	Toluene/110 °C	0 : 0[c,d]
10			Xylenes/130 °C	0 : 0[c,d]

[a] Conditions: 1 mol % $Pd_2(dba)_3$, 2 mol % Ligand, 1.2 equiv NaO*t*-Bu. [b] Conditions: 2 mol % $Pd(OAc)_2$, 2-4 mol % Ligand, 1.2 equiv NaO*t*-Bu. [c] Reaction was incomplete at 12 h. [d]Products from N-O bond cleavage detected.

Following our unsuccessful attempts to effect carboamination of *N*-methoxy amide **IV-22**, substrate **IV-23** derived from 1,1-dimethylhydrazine was examined (Table IV-3). Dpp-benzene, Dpe-phos, and P(*o*-tol)$_3$ were chosen as ligands initially due to their success in previously attempted carboamination processes. As illustrated below, dpp-benzene was the only ligand of the three which formed an active Pd-catalyst for the successful carboamination of *N*',*N*'-dimethylpent-4-enehydrazide **IV-23**, although running the reaction in toluene at 110 °C for 12 hours resulted in incomplete conversion to product (Entry 3). However, after 12 hours at 130 °C in xylenes, the reaction was

complete as determined by ^{1}H NMR analysis, yielding 98% isolated yield of pyrrolidinone **IV-32** (Entry 4). These optimized reaction conditions were chosen for subsequent reactions involving substrates of this type.

Table IV-3. *N*',*N*'-Dimethylpent-4-enehydrazide Reaction Condition Optimization



IV-23 **IV-32**

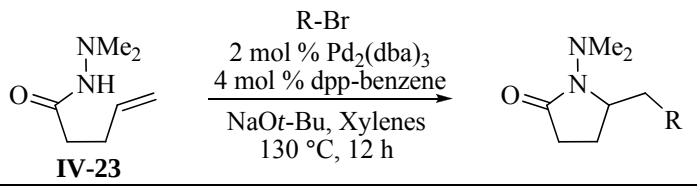
Entry	Ligand	Solvent/Temp	Yield[c]
1	P(o-tol)$_3$	Toluene/110 °C	—[a]
2	Dpe-phos	Toluene/110 °C	—[a]
3	dpp-benzene	Toluene/110 °C	—[a,b]
4		Xylenes/130 °C	98%

[a] No reaction after 12 h. [b] Pyrrolidinone detected by crude ^{1}H NMR analysis [c] Isolated yield.

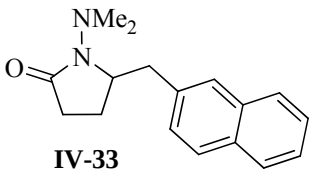
IV.3 Scope and Limitations

With optimized reaction conditions in hand, the scope of the Pd-catalyzed carboamination reaction of **IV-23** for the synthesis of pyrrolidinones was examined (Table IV-4). A variety of aryl bromides were suitable coupling partners ranging from electron-rich **IV-35** to electron–poor **IV-34**. Alkenyl bromides can also be utilized; an 86% isolated yield of pyrrolidinone **IV-36** was obtained using β-bromostyrene.

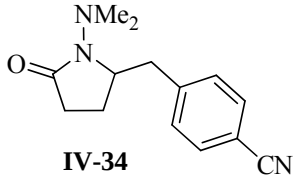
Table IV-4. Scope of *N*',*N*'-Dimethylpent-4-enehydrazide Carboamination[a]



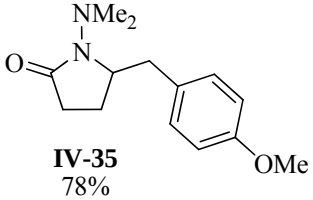
IV-23



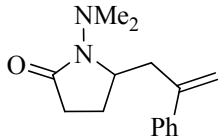
IV-33
85%



IV-34
83%



IV-35
78%

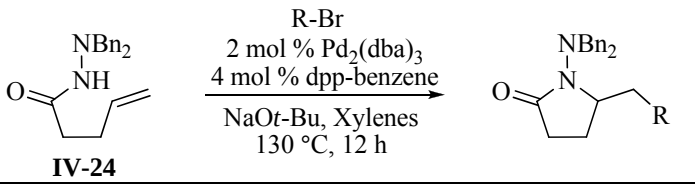


IV-36
86%

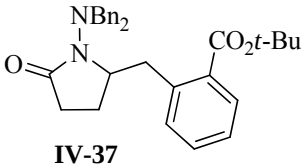
[a] Conditions: 1.0 equv amide, 1.2 equiv R-Br, 1.2 equiv NaO*t*-Bu, Xylenes, 0.4 M.

We next turned our attention to a substrate in which the pendant nitrogen atom possessed protecting groups that could be removed after formation of the pyrrolidinone products. As shown in Table IV-5, *N*',*N*'-dibenzylpent-4-enehydrazide **IV-24** undergoes the carboamination process with a variety of aryl and alkenyl bromide coupling partners in good to excellent yields. Yields of products **IV-37–IV-42** are slightly lower than expected due to the difficulty of removing Heck-arylation side-products during purification.

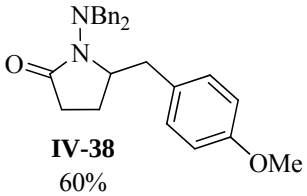
Table IV-5. Scope of *N*',*N*'-Dibenzylpent-4-enehydrazide Carboamination Reactions[a]



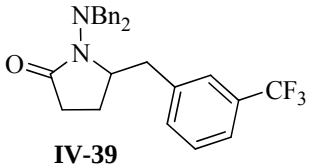
IV-24



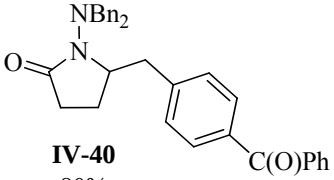
IV-37
85%



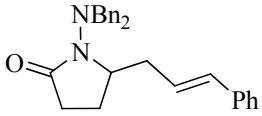
IV-38
60%



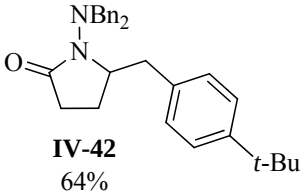
IV-39
52%



IV-40
80%



IV-41
57%

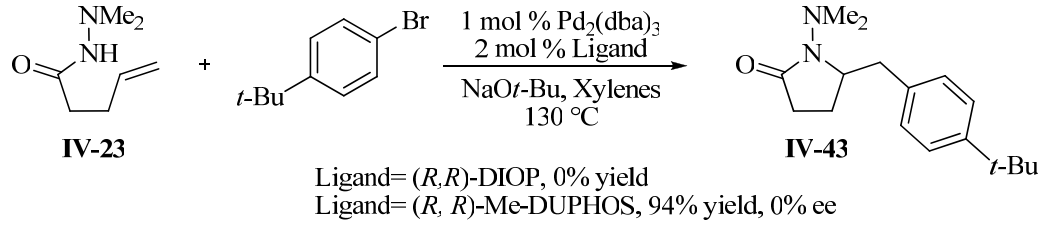


IV-42
64%

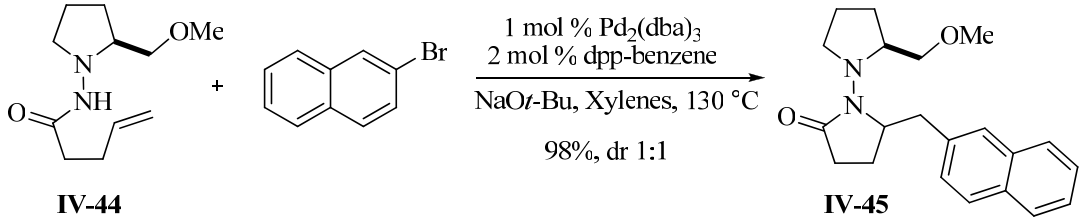
[a] Conditions: 1.0 equv amide, 1.2 equiv R-Br, 1.2 equiv NaO*t*-Bu, Xylenes, 0.4 M.

A few preliminary experiments towards and asymmetric version of the reaction were conducted with **IV-23** (Scheme IV-6). Use of (*R*,*R*)-DIOP as a ligand in the reaction showed no product formation after 12 hours. Although (*R*,*R*)-Me-Duphos provided a 94% isolated yield of pyrrolidinone **IV-43**, HPLC analysis revealed the product was formed as a 50:50 mixture of enantiomers.

Scheme IV-6. Chiral Ligand Screen in Pyrrolidinone Carboamination



Another attempt at the asymmetric synthesis of pyrrolidinones was made through the use of a chiral auxiliary (eq 6). Substrate **IV-44** was synthesized and subjected to the optimized carboamination reaction conditions which yielded 98% of the desired pyrrolidinone **IV-45** with 1:1 dr. Therefore, further optimization is necessary in order to develop an asymmetric variant of this reaction.



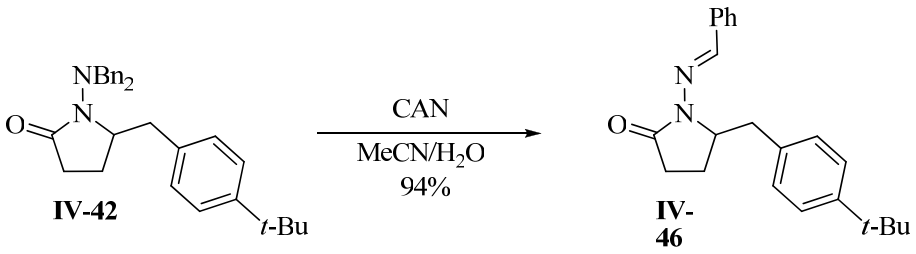
(6)

IV.4 Significant Transformations of *N*-Amino Pyrrolidinone Products

The pyrrolidinone products formed in the carboamination reactions are potentially useful precursors to a wide variety of synthetically interesting molecules. Stereoselective alkylations of lactam enolates are known,[12] and methods exist for benzyl deprotection of the *N*',*N*'-dibenzyl-pyrrolidinone products.[13] A preliminary investigation into benzyl

deprotection of these products has been conducted. For example, treatment of *N*',*N*'-dibenzyl-pyrrolidinone **IV-42** with cerium ammonium nitrate in a 50:50 mixture of acetonitrile and water cleaves selectively one of the benzyl protecting groups while oxidation of the remaining benzyl protecting group to the hydrazone **IV-46** occurs in 94% yield (Scheme IV-x). Attempts to cleave the resulting hydrazone have been unsuccessful.

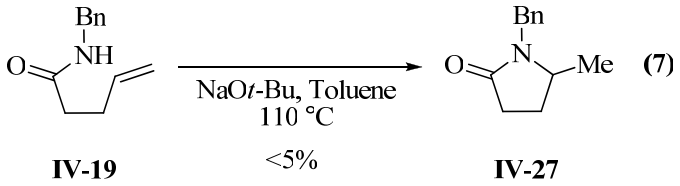
Scheme IV-7. Benzyl Protecting Group Cleavage



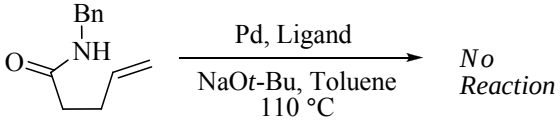
IV.5 Studies Involving Hydroamination Product Formation

As noted in Table IV-1, reaction of *N*-benzyl amide substrate **IV-19** in the presence of a catalyst composed of $Pd_2(dba)_3$ and XPhos resulted in formation of hydroamination product **IV-27** (Entry 10). Incomplete conversion to product was observed, and complex mixtures of products were formed when the reaction temperature was increased from 110 °C in toluene to 130 °C in xylenes.

Control experiments were conducted in order to probe the origin of the hydroamination product. Conducting the reaction in the absence of the Pd-catalyst and aryl bromide resulted in formation of trace amounts of the hydroamination product (eq 7). Therefore, it was determined that the hydroamination process was not base mediated. Attempting to run the reaction in the absence of the aryl bromide coupling partner resulted in no reaction (eq 8).



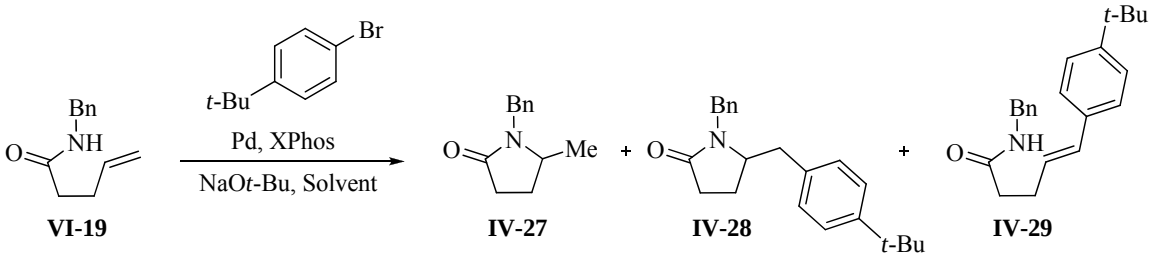
IV-19 **IV-27** **(7)**



IV-19 **(8)**

Alternative Pd-catalysts were also screened for the hydroamination reaction, including $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)_2$, and $Pd_2(p\text{-OMe-dba})_3$ (Table IV-6). The best results were obtained from a catalyst composed of $PdCl_2(CH_3CN)_2$ and XPhos, resulting in sole hydroamination product formation after 22 h (Entry 5). A combination of $Pd(OAc)_2$ and XPhos gave similar results, although the reaction was incomplete at 22 h (Entry 5). Interestingly, increasing the temperature from 130 °C in xylenes to 150 °C in diglyme using either catalyst system resulted in formation of the 5-benzyl pyrrolidinone **IV-28** (Entries 6 and 9).

Table IV-6. Optimization of Catalyst System for Hydroamination



Entry	Pd	Solvent/Temp	Ratio **IV-27**:**IV-28**:**IV-29**	Yield[g]
1	$Pd_2(dba)_3$[a]	Toluene/110 °C	1[c] : 0 : 0	N.D
2		Xylenes/130 °C	NA[c]	N.D
3	$Pd_2(p\text{-OMe-dba})_3$[a]	Toluene/110 °C	1[d] : 0 : 0	N.D
4	$Pd(OAc)_2$[b]	Toluene/110 °C	1[e] : 0 : 0	N.D
5		Xylenes/130 °C	1[d] : 0 : 0	N.D
6		Diglyme/150 °C	1 : 2 : 0	N.D
7	$PdCl_2(CH_3CN)_2$[b]	Toluene/110 °C	1[c] : 0 : 0	N.D
8		Xylenes/130 °C	1[f] : 0 : 0	50%
9		Diglyme/160 °C	1 : 2 : 0	N.D
10	$PdCl_2(PPh_3)_2$[b]	Xylenes/130 °C	0 : 0 : 1	N.D
11	$PdCl_2(dppf)_2$[b]	Xylenes/130 °C	0 : 0 : 1	N.D

[a] Conditions: 1 mol % Pd, 2 mol % XPhos, 1.2 equiv NaO*t*-Bu. [b] Conditions: 2 mol % Pd, 2 mol % Xphos, 1.2 equiv NaO*t*-Bu. [c] Reaction was incomplete at 40 h. [d] Reaction was incomplete at 22 h. [e] Reaction time= 45 h. [f] Reaction time= 22 h. [g] Isolated yield.

IV.6 Summary and Conclusions

We have developed a new method for pyrrolidinone synthesis via Pd-catalyzed carboamination of γ,δ-unsaturated amides with aryl or alkenyl bromides. The pyrrolidinone products are accessed in good to excellent yields, and have the potential to be useful precursors in a variety of other interesting transformations.

IV.7 Experimental

General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. $Pd(OAc)_2$, $Pd_2(dba)_3$, and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. *N*-benzylpent-4-enamide was prepared via protection of with benzyl bromide.[14] Toluene, diethyl ether, dichloromethane and THF were purified using a GlassContour solvent purification system. 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.

Preparation of Substrates

General Procedure A. A flame-dried flask was cooled under a stream of nitrogen and charged with the appropriate hydroxylamine or hydrazine (1 equiv) and EDC (1 equiv) in CH_2Cl_2 (0.5 M) at 0 °C. Triethylamine (1 equiv) was added, followed by 4-pentenoic acid (1 equiv). The reaction mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca 12 h). The mixture was then cooled to 0 °C, and quenched with 2 M HCl (1 mL/mmol substrate). The resulting mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (2 mL/mmol substrate). 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.

(±)-*N*-Methoxypent-4-enamide (IV-22). The reaction of *O*-methylhydroxylamine hydrochloride (1.1 g, 13.6 mmol) with 4-pentenoic acid (1.2 mL, 11.9 mmol) was conducted for 12 h according to General Procedure A. The crude product was purified by flash chromatography on silica gel to afford 0.9 g (62%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, br, 1 H), 5.84–5.80 (m, 1 H), 5.10–5.01 (m, 2 H), 3.75 (s, 3 H), 2.43–2.39 (m, 2 H), 2.19–2.15 (m, 2 H).

(±)-*N*',*N*'-Dimethylpent-4-enehydrazide (IV-23). The reaction of *N*',*N*'-dimethylhydrazine (1.1 mL, 14.6 mmol) with 4-pentenoic acid (1.5 mL, 14.6 mmol) was conducted for 12 h according to General Procedure A. The crude product was purified by flash chromatography on silica gel to afford 1.2 g (59%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (s, br, 0.43 H), 5.97 (s, br, 0.57 H), 5.91–5.77 (m, 1 H), 5.10–5.06 (m, 1 H), 5.03–4.99 (m, 1 H), 2.59 (s, 3 H), 2.57–2.56 (m, 1 H), 2.52 (s, 3 H), 2.43–2.36 (m, 2 H), 2.19–2.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 169.9, 137.5, 136.8, 115.7, 114.9, 48.5, 47.5, 34.3, 31.2, 29.6, 28.7; IR (film) 3209, 2954, 1662 cm^{-1}. MS (ESI) 165.0998 (165.1004 calcd for $C_7H_{14}N_2O$, M + Na^+).

(±)-*N*',*N*'-Dibenzylpent-4-enehydrazide (IV-24). The reaction of *N*',*N*'-dibenzylhydrazine (3.1 g, 14.6 mmol) with 4-pentenoic acid (1.5 mL, 14.6 mmol) was

conducted for 12 h according to General Procedure A. The crude product was purified by flash chromatography on silica gel to afford 2.4 g (56%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 5 H), 7.32–7.27 (m, 5 H), 6.06 (s, br, 1 H), 5.65–5.57 (m, 1 H), 4.92–4.85 (m, 2 H), 4.18 (s, 1 H), 3.94 (d, *J*= 13 Hz, 1 H), 3.67 (d, *J*= 13 Hz, 1 H), 2.21–2.15 (m, 0.5 H), 2.14–2.12 (m, 1 H), 1.99–1.94 (m, 2.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 137.6, 135.6, 129.8, 129.1, 128.5, 128.3, 127.8, 114.6, 62.7, 59.3, 34.0, 30.6, 29.2, 28.3; IR (film) 3322, 3030, 1667 cm^{-1}. MS (ESI) 317.1625 (317.1630 calcd for $C_{19}H_{22}N_2O$, M + Na^+).

(*S*)-*N*-[2-(methoxymethy)pyrrolidin-1-yl]pent-4-enamide (IV-44). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, br, 0.41 H), 5.96 (s, br, 0.45 H), 5.91–5.78 (m, 1 H), 5.10–5.02 (m, 1 H), 5.01–4.98 (m, 1 H), 3.48–3.40 (m, 0.50 H), 3.41–3.37 (m, 2 H), 3.34 (s, 3 H), 3.29–3.27 (m, 0.58 H), 3.22 (s, br, 0.67 H), 3.05–3.01 (m, 0.47 H), 2.82–2.77 (m, 0.52 H), 2.72 (s, br, 0.58 H), 2.64–2.51 (m, 2 H), 2.42–2.36 (m, 2 H), 2.20–2.17 (m, 1 H), 2.04–1.93 (m, 1 H), 1.88–1.77 (m, 1 H), 1.75–1.61 (m, 1 H).

Synthesis of Pyrrolidinones via Pd-Catalyzed Carboamination

Pd-Catalyzed Synthesis of Pyrrolidinones: General Procedure. A flame-dried Schlenk tube equipped with a magnetic stirbar 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 % complex, 2 mol % Pd), dpp-benzene (4 mol %), sodium *tert*-butoxide (1.7 equiv), and the

aryl bromide (1.7 equiv). The Schlenk tube was purged with nitrogen and the substrate (1.0 equiv) was added as a solution in xylenes (4 mL solvent/ mmol substrate). The resulting mixture was heated to 130 °C until the starting material was consumed as judged by ^{1}H 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 extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

(±)-5-[(4-*tert*-Butylbenzyl)-1-dimethylamino]pyrrolidin-2-one (IV-32). The reaction of 32 mg (0.23 mmol) of **IV-23** with 4-*tert*-butyl bromobenzene (43 μL, 0.27 mmol) was conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (4.2 mg, 0.005 mmol, 2 mol %) and dpp-benzene (4.1 mg, 0.009 mmol, 4 mol %). This procedure afforded 62 mg (98%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.31 (m, 2 H), 7.14–7.12 (m, 2 H), 3.72–3.65 (m, 1 H), 3.35 (dd, *J* = 3.6, 13.2 Hz, 1 H), 2.90 (s, 6 H), 2.45–2.39 (m, 1 H), 2.32–2.24 (m, 1 H), 2.20–2.12 (m, 1 H), 1.94–1.84 (m, 1 H), 1.73–1.64 (m, 1 H), 1.31 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 149.3, 134.5, 128.8, 125.4, 60.4, 43.6, 39.4, 34.4, 31.3, 29.3, 22.8; IR (film) 2954, 1699 cm^{-1}. MS (ESI) 297.1951 (297.1943 calcd for $C_{17}H_{26}N_2O$, M + Na^+).

(±)-1-Dimethylamino-5-[(naphthalen-2-yl)methyl]pyrrolidin-2-one (IV-33). The reaction of 49 mg (0.35 mmol) of **IV-23** with 2-bromonapthlene (86 mg, 0.41 mmol) was conducted for 20 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (6.3 mg, 0.007 mmol, 2 mol %) and dpp-benzene (6.2 mg, 0.014 mmol, 4 mol %). This procedure afforded 77 mg (85%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (m, 3 H), 7.65 (s, br, 1 H), 7.50–7.42 (m, 2 H), 7.35–7.34 (m, 1 H), 3.84–3.77 (m, 1 H), 3.57 (dd, *J* = 3.6, 13.2 Hz, 1 H), 2.94 (s, 6 H), 2.59 (dd, *J* = 2.4, 10.8 Hz, 1 H), 2.36–2.28 (m, 1 H), 2.22–2.14 (m, 1 H), 1.92–1.83 (m, 1 H), 1.77–1.68 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 135.3, 133.5, 132.2, 128.1, 127.6, 127.5, 127.4, 126.1, 125.5, 60.4, 43.7, 40.3, 29.3, 22.8 (one carbon signal is absent due to incidental equivalence); IR (film) 2947, 1695 cm^{-1}. MS (ESI) 291.1477 (291.1473 calcd for $C_{17}H_{20}N_2O$, M + Na^+).

(±)-5-[(4-Benzonitrile)-1-dimethylamino]pyrrolidin-2-one (IV-34). The reaction of 41 mg (0.29 mmol) of **IV-23** with 4-bromobenzonitrile (64 mg, 0.35 mmol) was conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (5.3 mg, 0.006 mmol, 2 mol %) and dpp-benzene (5.2 mg, 0.012 mmol, 4 mol %). This procedure afforded 65 mg (93%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.61 (m, 2 H), 7.33–7.32 (m, 2 H), 3.71–3.70 (m, 1 H), 3.45 (dd, *J* = 3.6, 9.5 Hz, 1 H), 2.88 (s, 6 H), 2.54–2.50 (m, 1 H), 2.36–2.27 (m, 1 H), 2.24–2.16 (m, 1 H), 1.74–1.87 (m, 1 H), 1.66–1.60 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 143.4, 132.2, 129.9, 118.7, 110.4, 59.8, 43.5, 40.4, 29.1, 22.8; IR (film) 2948, 1694 cm^{-1}. MS (ESI) 244.1459 (244.1450 calcd for $C_{14}H_{17}N_3O$, M + H^+).

(±)-1-Dimethylamino-5-(4-methoxybenzyl)pyrrolidin-2-one (IV-35). The reaction of 45 mg (0.31 mmol) of **IV-23** with 1-bromo-4-methoxybenzene (78 μL, 0.63 mmol) was conducted for 15 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (5.7 mg, 0.006 mmol, 2 mol %) and dpp-benzene (5.5 mg, 0.012 mmol, 4 mol %). This procedure afforded 60 mg (79%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.11 (m, 2 H), 6.86–6.84 (m, 2 H), 3.80 (s, 3 H), 3.68–3.64 (m, 1 H), 3.32 (dd, *J* = 3.6, 9.6 Hz, 1 H), 2.91 (s, 6 H), 2.42–2.36 (m, 1 H), 2.26–2.23 (m, 1 H), 2.20–2.12 (m, 1 H), 1.90–1.84 (m, 1 H), 1.71–1.64 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 158.3, 130.1, 129.6, 113.9, 60.6, 55.2, 43.6, 39.1, 29.3, 22.7; IR (film) 2948, 1696 cm^{-1}. MS (ESI) 271.1426 (271.1422 calcd for $C_{14}H_{20}N_2O_2$, M + Na^+).

(±)-1-Dimethylamino-5-(2-phenylallyl)pyrrolidin-2-one (IV-36). The reaction of 39 mg (0.27 mmol) of **IV-23** with α-bromostyrene (70 μL, 0.54 mmol) was conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (4.9 mg, 0.005 mmol, 2 mol %) and dpp-benzene (4.8 mg, 0.011 mmol, 4 mol %). This procedure afforded 57 mg (86%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2 H), 7.37–7.33 (m, 2 H), 7.31–7.26 (m, 1 H), 5.36 (s, 1 H), 5.12 (s, 1 H), 3.58–3.51 (m, 1 H), 3.46–3.41 (m, 1 H), 2.85 (s, 6 H), 2.32–2.23 (m, 2 H), 2.19–2.10 (m, 1 H), 1.95–1.86 (m, 1 H), 1.68–1.59 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 144.7, 140.3, 128.4, 127.7, 126.1, 114.8, 57.2, 43.5, 40.0, 29.3, 22.9; IR (film) 2945, 1695 cm^{-1}. MS (ESI) 267.1485 (267.1473 calcd for $C_{15}H_{20}N_2O$, M + Na^+).

(±)-*tert*-Butyl-2-[1-(dibenzylamino)-5-(oxopyrrolidin-2-yl)methyl]benzoate (IV-37). The reaction of 60 mg (0.24 mmol) of **IV-24** with *tert*-butyl 2-bromobenzoate (75 mg, 0.29 mmol) was conducted for 20 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (4.4 mg, 0.005 mmol, 2 mol %) and dpp-benzene (4.3 mg, 0.010 mmol, 4 mol %). This procedure afforded 92 mg (82%) of the title compound as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.72 (m, 1 H), 7.51–7.41 (m, 4 H), 7.36–7.30 (m, 5 H), 7.28–7.26 (m, 2 H), 7.22–7.18 (m, 1 H), 6.93–6.91 (m, 1 H), 4.53–4.45 (m, 3 H), 4.02–4.00 (m, 1 H), 3.52 (dd, *J* = 4.0, 12.5 Hz, 1 H), 3.08–3.03 (m, 1 H), 2.48–2.44 (m, 1 H), 2.33–2.27 (m, 1 H), 2.10–2.03 (m, 1 H), 1.59 (s, 9 H), 1.52–1.45 (m, 1 H), 1.42–1.35 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 166.6, 138.9, 132.3, 131.3, 131.1, 130.4, 129.9, 129.4, 128.3, 127.4, 126.1, 81.1, 62.1, 36.3, 29.4, 28.2, 22.7 (one carbon signal is absent due to incidental equivalence); IR (film) 2977, 1694 cm^{-1}. MS (ESI) 493.2459 (493.2467 calcd for $C_{30}H_{34}N_2O_3$, M + Na^+).

(±)-1-Dibenzylamino-5-(4-methoxybenzyl)pyrrolidin-2-one (IV-38). The reaction of 46 mg (0.14 mmol) of **IV-24** with 4-bromoanisole (21 μL, 0.17 mmol) was conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (2.6 mg, 0.003 mmol, 2 mol %) and dpp-benzene (2.5 mg, 0.006 mmol, 4 mol %). This procedure afforded 37 mg (64%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.38 (m, 4 H), 7.37–7.27 (m, 6 H), 6.80–6.78 (m, 1 H), 6.75–6.73 (m, 2 H), 4.55–4.48 (m, 3 H), 4.00–3.93 (m, 1 H), 3.75 (s, 3 H), 3.14 (dd, *J* = 3.6, 9.6 Hz, 1 H), 2.61–2.54 (m, 1 H), 2.24–2.17 (m, 1 H), 2.08–1.99 (m, 1 H), 1.64–1.58 (m, 1 H), 1.48–1.40 (m, 1 H), 1.33–1.23 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 158.1,

138.0, 129.7, 129.6, 128.3, 127.6, 113.8, 62.3, 60.0, 55.2, 38.5, 29.4, 23.6 (three carbon signals are absent due to incidental equivalence); IR (film) 2919, 1695 cm^{-1}. MS (ESI) 423.2036 (423.2036 calcd for $C_{26}H_{28}N_2O_2$, M + Na^+).

(±)-1-Dibenzylamino-5-[(3-trifluoromethyl)benzyl]pyrrolidin-2-one (IV-39). The reaction of 36 mg (0.12 mmol) of **IV-24** with 1-bromo-3-(trifluoromethyl)benzene (34 μL, 0.24 mmol) was conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (2.2 mg, 0.002 mmol, 2 mol %) and dpp-benzene (2.1 mg, 0.005 mmol, 4 mol %). This procedure afforded 30 mg (58%) of the title compound as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.34 (m, 8 H), 7.32–7.28 (m, 4 H), 7.06–7.03 (m, 1 H), 7.02–6.98 (m, 1 H), 4.61–4.48 (m, 3 H), 4.00–3.96 (m, 1 H), 3.17 (dd, *J* = 4.5, 12 Hz, 1 H), 2.51–2.44 (m, 1 H), 2.26–2.19 (m, 1 H), 2.10–2.01 (m, 1 H), 1.58–1.52 (m, 1 H), 1.47–1.39 (m, 1 H), 1.28–1.19 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 138.9, 138.0, 132.2, 129.8, 128.8, 128.4, 127.8, 125.4 (q, *J*= 17 Hz), 61.9, 39.2, 29.4, 24.0 (one carbon signal is absent due to incidental equivalence); IR (film) 2930, 1696 cm^{-1}. MS (ESI) 461.1818 (461.1817 calcd for $C_{26}H_{25}F_3N_2O$, M + Na^+).

(±)-5-[(4-Benzoylbenzyl)-1-dibenzylamino]pyrrolidin-2-one (IV-40). The reaction of 42 mg (0.13 mmol) of **IV-24** with 4-bromobenzophenone (68 mg, 0.26 mmol) was conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd(OAc)_2$ (1.0 mg, 0.003 mmol, 2 mol %) and dpp-benzene (1.2 mg, 0.003 mmol, 2 mol %). This procedure afforded 50 mg (81%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.73 (m, 2 H), 7.66–7.64 (m, 2 H), 7.60–

7.56 (m, 1 H), 7.48–7.28 (m, 12 H), 7.23–6.94 (m, 2 H), 4.60–4.42 (m, 3 H), 4.01–3.97 (m, 1 H), 3.22 (dd, *J* = 3.2, 9.6 Hz, 1 H), 2.65–2.57 (m, 1 H), 2.27–2.11 (m, 1 H), 2.09–2.02 (m, 1 H), 1.67–1.61 (m, 1 H), 1.50–1.42 (m, 1 H), 1.33–1.24 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 143.0, 138.1, 137.7, 135.7, 132.3, 130.3, 129.9, 129.8, 128.7, 128.4, 128.3, 127.7, 61.8, 39.5, 29.4, 24.0 (two carbon signals are absent due to incidental equivalence); IR (film) 2931, 1696 cm^{-1}. MS (ESI) 497.2215 (497.2205 calcd for $C_{32}H_{30}N_2O_2$, M + Na^+).

(±)-5-Cinnamyl-1-(dibenzylamino)pyrrolidin-2-one (IV-41). The reaction of 48 mg (0.16 mmol) of **IV-24** with β–bromostyrene (42 μL, 60 mg, 0.32 mmol) was conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (2.9 mg, 0.003 mmol, 2 mol %) and dpp-benzene (2.9 mg, 0.006 mmol, 4 mol %). This procedure afforded 63 mg (65%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.27 (m, 2 H), 7.25–7.18 (m, 8 H), 7.17–7.09 (m, 5 H), 6.23 (d, *J*= 16 Hz, 1 H), 5.84–5.76 (m, 1 H), 4.97–4.12 (m, 3 H), 3.95–3.86 (m, 1 H), 2.62–2.56 (m, 1 H), 2.53–2.47 (m, 1 H), 2.26–2.12 (m, 1 H), 2.10–1.96 (m, 1 H), 1.78–1.70 (m, 1 H), 1.69–1.56 (m, 1 H), 1.42–1.33 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 132.7, 128.8, 128.5, 128.4, 128.3, 127.6, 127.2, 125.9, 125.3, 60.5, 36.6, 29.5, 23.1 (one carbon signal is absent due to incidental equivalence); IR (film) 2916, 1695 cm^{-1}. MS (ESI) 419.2104 (419.2099 calcd for $C_{27}H_{28}NO_2$, M + Na^+).

(±)-5-[(4-*tert*-Butylbenzyl)-1-dibenzylamino]pyrrolidin-2-one (IV-42). The reaction of 43 mg (0.13 mmol) of **IV-24** with 4-*tert*-butyl-bromobenzene (28 μL, 0.16 mmol) was

conducted for 18 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (2.4 mg, 0.003 mmol, 2 mol %) and dpp-benzene (2.4 mg, 0.005 mmol, 4 mol %). This procedure afforded 40 mg (71%) of the title compound as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.39 (m, 4 H), 7.36–7.33 (m, 4 H), 7.30–7.27 (m, 2 H), 7.23–7.22 (m, 2 H), 6.82–6.80 (m, 1 H), 4.57–4.42 (m, 3 H), 4.00–3.92 (m, 1 H), 3.18 (dd, *J* = 3.5, 9.5 Hz, 1 H), 2.66–2.60 (m, 1 H), 2.24–2.18 (m, 1 H), 2.07–2.00 (m, 1 H), 1.65–1.60 (m, 1 H), 1.51–1.44 (m, 1 H), 1.34–1.28 (m, 1 H), 1.27 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 149.1, 138.2, 134.7, 129.8, 128.5, 128.3, 127.6, 125.2, 62.1, 59.9, 55.9, 38.9, 34.3, 31.3, 29.5, 24.0 (three carbon signals are absent due to incidental equivalence); IR (film) 2962, 1693 cm^{-1}. MS (ESI) 449.2573 (449.2569 calcd for $C_{29}H_{34}N_2O$, M + Na^+).

(2'*S*)-2'-methoxymethyl-5-naphthalen-2-ylmethyl-1,1'-bipyrrolidin-2-one (IV-45). The reaction of 30 mg (0.14 mmol) of **IV-44** with 2-bromonaphthalene (35 mg, 0.17 mmol) was conducted for 16 h at 130 °C according to the general procedure using a catalyst composed of $Pd_2(dba)_3$ (2.6 mg, 0.003 mmol, 2 mol %) and dpp-benzene (2.5 mg, 0.006 mmol, 4 mol %). This procedure afforded 47 mg (98%) of the title compound as an orange oil. The product was observed as a 1:1 mixture of diastereomers. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.87 (m, 6 H), 7.67–7.65 (m, 2 H), 7.49–7.43 (m, 5 H), 7.36–7.33 (m, 2 H), 4.11–4.07 (m, 1 H), 4.00–3.95 (m, 1 H), 3.94–3.88 (m, 1 H), 3.85–3.80 (m, 1 H), 3.72–3.67 (m, 1 H), 3.66–3.64 (m, 1 H), 3.59–3.56 (m, 1 H), 3.44–3.41 (m, 2 H), 3.38 (s, 3 H), 3.36–3.32 (m, 6 H), 3.31–3.24 (m, 2 H), 3.20–3.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.2, 135.7, 135.6, 133.5,

132.2, 128.1, 128.0, 127.6, 127.5, 127.4, 126.1, 125.5, 75.1, 62.6, 60.4, 59.5, 59.4, 59.0, 58.9, 53.0, 50.7, 40.7, 40.4, 29.6, 29.5, 27.1, 27.0, 23.4, 23.0, 22.7, 22.6; IR (film) 2926, 1691 cm^{-1}. MS (ESI) 361.1869 (361.1892 calcd for $C_{21}H_{26}N_2O_2$, M + Na^+).

(±)-1-Benzyl-5-methylpyrrolidin-2-one (IV-27).[15] ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2 H), 7.27–7.26 (m, 1 H), 7.25–7.22 (m, 2 H), 4.97 (d, *J*= 15 Hz, 1 H), 3.99 (d, *J*= 15 Hz, 1 H), 3.56–3.49 (m, 1 H), 2.54–2.47 (m, 1 H), 2.44–2.37 (m, 1 H), 2.19–2.12 (m, 1 H), 1.63–1.56 (m, 1 H), 1.16 (d, *J*= 6.5 Hz, 3 H).

(±)-*N*-benzyl-5-(4-*tert*-butylphenyl)pent-4-enamide (IV-29). ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 3 H), 7.25–7.17 (m, 7 H), 6.39 (d, *J*= 15.5 Hz, 1 H), 6.15–6.11 (m, 1 H), 4.40–4.37 (m, 2 H), 2.56–2.51 (m, 2 H), 2.35–2.32 (m, 2 H), 1.31 (s, 9 H).

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Part Two

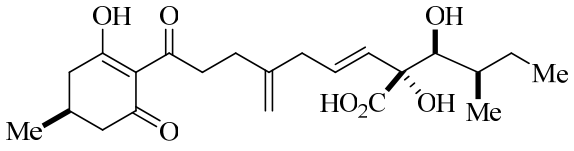
New Methods for Enantioselective Synthesis of Diols and Amino-Alcohols

Chapter V

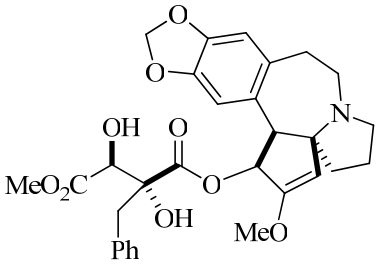
Significance, Utility, and Preparation of α-Alkyl-α,β-Dihydroxy Esters

Substituted α-alkyl-α,β-dihydroxy carboxylic acids and esters are important building blocks for organic synthesis, and are displayed as components of many biologically active molecules. An α-alkyl-α,β-dihydroxy carboxylic acid is a key portion of the antifungal agent alternaric acid **V-1** (Figure V-1).[1,2,3,4] Given its interesting biological properties, this natural product has been the subject of various total synthesis endeavors.[2b,5] The ester-type *Cephalotaxus* alkaloid 3'-*S*-hydroxyneoharringtonine **V-2** is another natural product that contains an α-alkyl-α,β-dihydroxy ester subunit, and has been shown to exhibit antileukemia activity.[6]

Figure V-1. Biologically Active α-Alkyl-α,β-Dihydroxy Acids and Esters

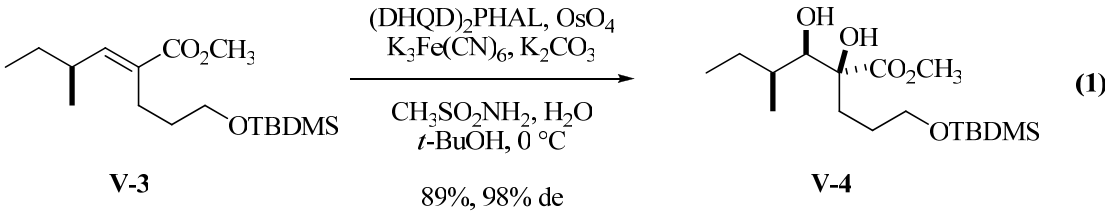


V-1
Alternaric Acid



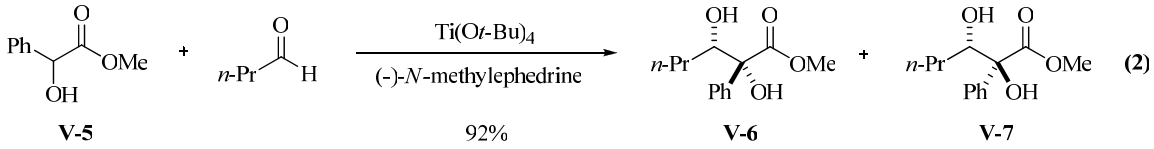
V-2
3'-*S*-Hydroxyneoharringtonine

The enantioselective construction of these types of compounds is often achieved through asymmetric dihydroxylation of α-alkyl-α,β-unsaturated esters,[7] or via asymmetric aldol reactions.[8] Asymmetric dihydroxylation of trisubstituted ester enoate substrates which generate enantioenriched α-alkyl-α,β-dihydroxy esters have also been reported. For example, trisubstituted ester enoate **V-3** was transformed to α-alkyl-α,β-dihydroxy ester **V-4** via osmium-catalyzed Sharpless asymmetric dihydroxylation (eq 1). The ester **V-4** is accessed in excellent yield and selectivity, however use of a this type of method is not without limitations. Preparation of the trisubstituted enoate starting material is often lengthy. Also, the presence of other alkenes appended to the substrate may not be tolerant of the highly electrophilic oxidant.[2b,7,9]



V-3 89%, 98% de **V-4** **(1)**

Only a single study on asymmetric aldol reactions that directly afford α-alkyl-α,β-dihydroxy esters has appeared in the literature.[10] *Syn*-configured aldol products of mandelic acid esters and aldehydes were obtained, although the selectivity for formation of *syn* versus *anti* diols varied widely from substrate to substrate, and *syn*-diol products were obtained with moderate enantioselectivity.[11] For example, aldol reaction of mandelic ester **V-5** with *n*-propyl aldehyde in the presence of titanium(IV) *tert*-butoxide and chinchona alkaloid (-)-*N*-methylephedrine afforded a mixture of esters **V-6** and **V-7** in 92% yield (eq 2).



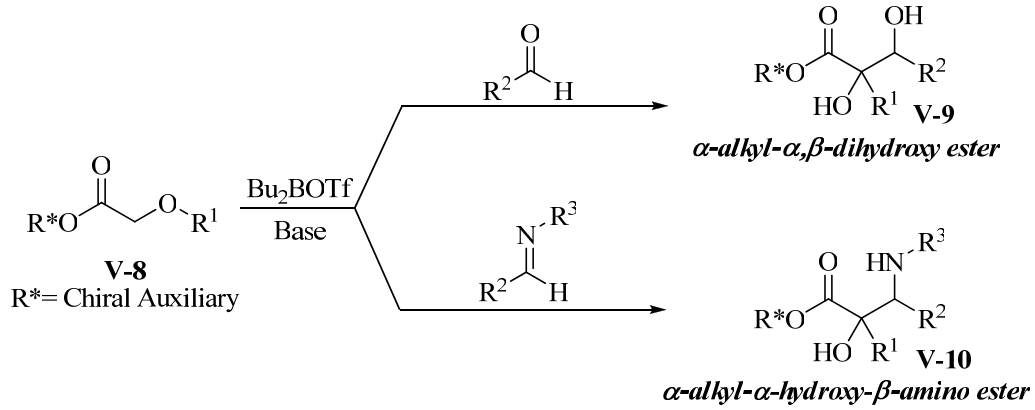
V-5 92% **V-6** **V-7** **(2)**

Ratio **V-6** to **V-7**: 40:60
ee% (*anti*)= 67%

Given the biological and synthetic importance of α-alkyl-α,β-dihydroxy esters, development of methodology towards the asymmetric construction of these compounds is highly desirable. The research presented in Chapters VI-VII will describe development of

a tandem reaction sequence towards a new method for the formation of enantioenriched α-alkyl-α,β-dihydroxy esters **V-9** (Wittig rearrangement/aldol reactions) and α-alkyl-α-hydroxy-β-amino esters **V-10** (Wittig rearrangement/Mannich reactions) involving reaction of chiral glycolate esters **V-8** with various electrophilic coupling partners (Scheme V-1) .

Scheme V-1. Proposed Tandem Wittig/Aldol and Wittig/Mannich Reactions

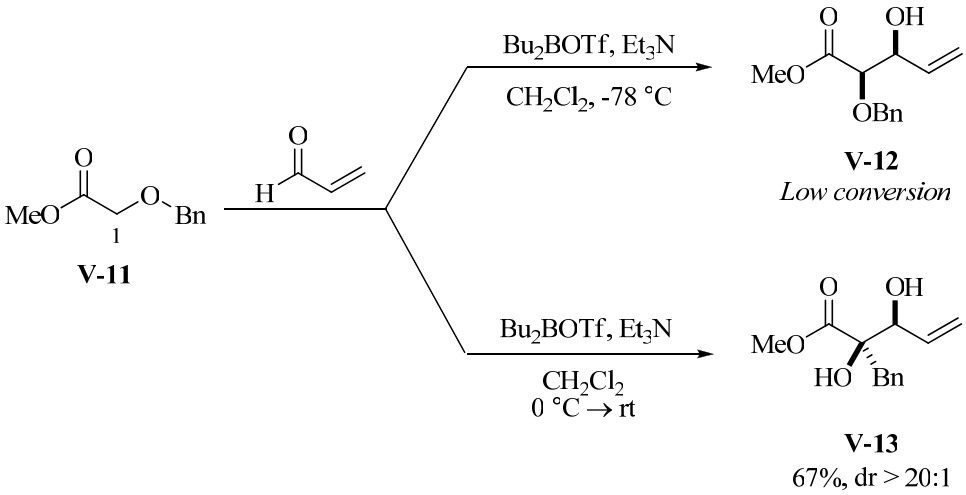


V.1 Discovery and Mechanism of Tandem Wittig/Aldol Reaction

Recently, Bertrand and Wolfe discovered a new route to α-alkyl-α,β-dihydroxy esters which involves tandem Wittig-rearrangement/aldol reactions of simple glycolate esters with aldehydes.[12] The boron-mediated aldol reaction of methyl-*O*-benzyl glycolate **V-11** and acrolein outlined in Scheme V-2 proceeded sluggishly at -78 °C, and minimal conversion to **V-12** was observed.[13] Interestingly, attempting the reaction at 0 °C and

allowing it to warm to room temperature resulted in formation of 1,2-diol **V-13** with >20:1 diastereoselectivity.

Scheme V-2. Discovery of Tandem Wittig/Aldol Reaction

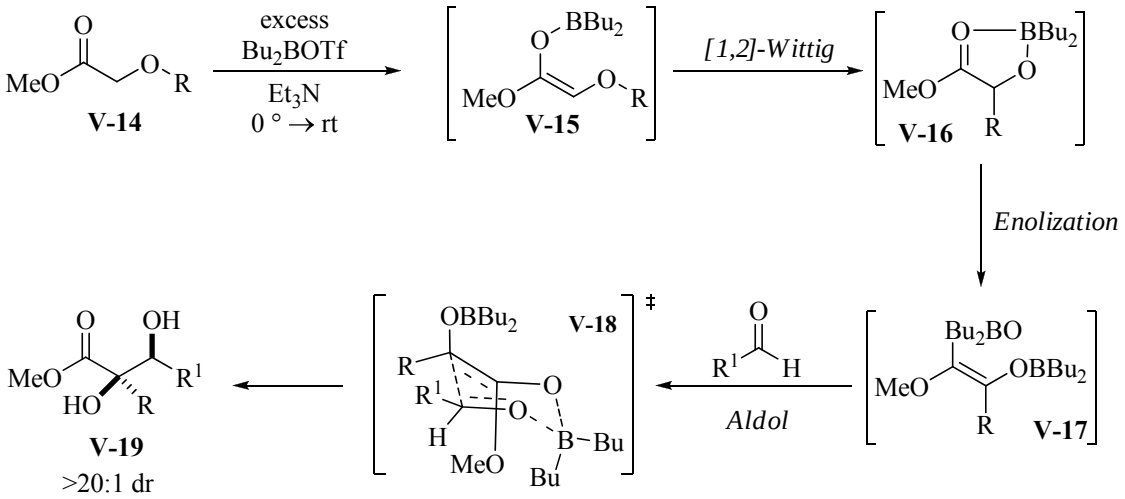


Overall, two C-C bonds and two contiguous stereocenters are generated in a single step from simple starting materials in the transformation. The product **V-13** results from the combination of [1,2]-Wittig rearrangement of the benzyl group from O to C-1, followed by an aldol reaction. This result was quite exciting, as [1,2]-Wittig rearrangements of enolates are rare and previously have only been effected using strongly basic reagents.[14]

The proposed mechanism for the tandem reaction is as outlined in Scheme V-3.[15] In the presence of excess Bu_2BOTf and triethylamine, **V-14** undergoes deprotonation/enolization to intermediate **V-15** followed by [1,2]-Wittig rearrangement and generation of intermediate **V-16**. A second deprotonation/enolization occurs,

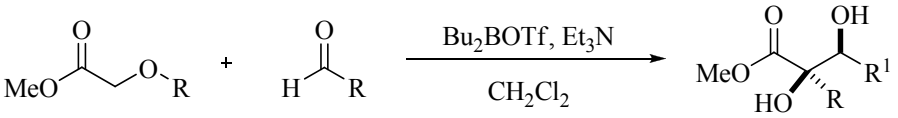
generating intermediate **V-17**, followed by aldol reaction with the aldehyde coupling partner via transition state **V-18** to generate observed α-alkyl-α,β-dihydroxy ester **V-19**.

Scheme V-3. Mechanism of Tandem Wittig/Aldol Reaction



A variety of aldehydes are suitable coupling partners in the reaction, and products with aromatic, aliphatic, and α,β-unsaturated side-chains are formed in good yields and with excellent selectivities (Table V-1). To date, substrates with benzyl **V-11** and allyl **V-20** migrating groups can be utilized successfully in the reaction.

Table V-1. Scope of Tandem Wittig/Aldol Reactions[12]



V-11: R= Bn
V-20: R= Allyl

R	R^1	Yield[b]	dr[c]
Bn	Ph	72%	>20:1
Bn	Cy	75%	>20:1[d]
Bn		67%	>20:1
Allyl	Ph	75%	>20:1
Allyl	 Ph	71%	>20:1
Allyl	 Ph	61%	>20:1[e]

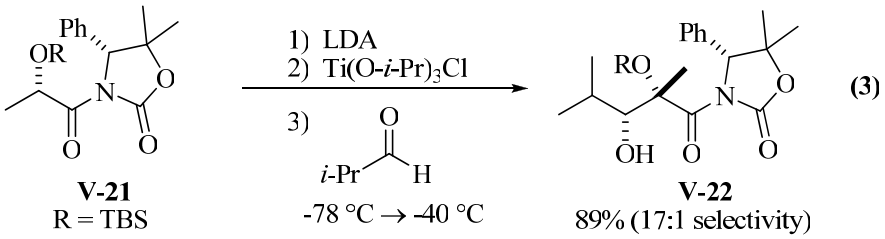
[a] Conditions: 1.0 equiv ester, 3.2 equiv Bu_2BOTf, 4.0 equiv Et_3N, CH_2Cl_2, 0.2 M, rt, 15 min, then add 1.5 equiv aldehyde, 0 °C → rt. [b] Isolated yield (average of two or more experiments). [c] Diastereomeric ratio obtained upon purification. [d] The crude product was obtained in 14:1 dr. [e]The crude product was obtained in 17:1 dr.

While a variety of racemic α-alkyl-α,β-dihydroxy esters have been generated via this method, initial attempts to access enantioenriched products through the use of chiral boron reagents were unsuccessful.[15]

V.2 Chiral Auxiliaries for Asymmetric Aldol Reactions

As mentioned in Section V.1, the use of chiral boron reagents in tandem Wittig/Aldol reactions was unsuccessful. Given these poor results, we felt that use of chiral auxiliaries should be examined. Thus, the remainder of this Chapter will describe common chiral auxiliaries used in asymmetric aldol reactions.

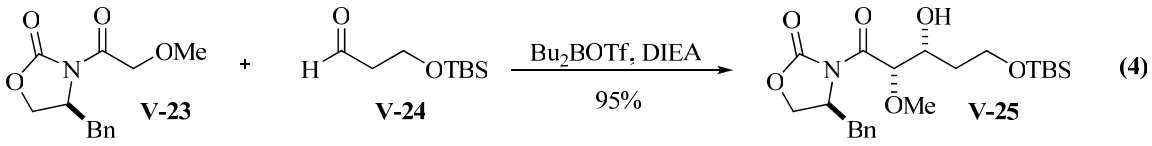
The tandem Wittig/aldol reaction sequence presented in Sections V.1 describes a highly selective and concise method for accessing glycolate aldol products bearing a tertiary stereocenter. To date only a single study on the preparation of enantioenriched α-alkyl-α,β-dihydroxy esters using a chiral auxiliary has been reported. The transformation was accomplished through aldol reactions of *O*-protected glycolate esters **V-21** bearing an oxazolidinone auxiliary (eq 3). Upon treatment of **V-21** with LDA and Ti(O-*i*-Pr)$_3$Cl, **V-22** was obtained in 89% yield and with 17:1 diastereoselectivity.[16,17]



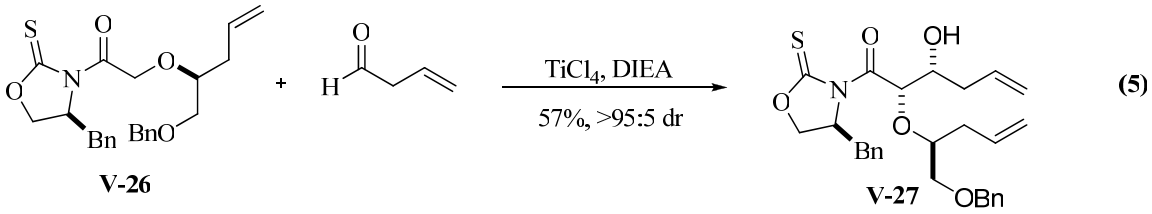
(3)

Much more common are methods to access enantioenriched ester products which lack a tertiary alcohol stereocenter.[18] Asymmetric ester enolate aldol reactions have been reported to access these types of compounds through the use of various chiral auxiliaries.[19] For example, Evans boron enolate aldol additions using *N*-glycolyloxazolidinones **V-23** allow for enantioselective construction of compounds **V-25** with high *syn*-selectivity (eq 4).[20] Treatment of oxazolidinone **V-23** with Bu_2BOTf and diisopropylethyl amine facilitated Evans aldol condensation with TBS-protected aldehyde **V-24**, providing **V-25** in 95% yield as a single diastereomer.[21] Oxazolidinethiones **V-26** have also been used as auxiliaries for transformations of this type. For example, reaction of **V-26** with 3-butenal in the presence of $TiCl_4$ and diisopropylethyl amine afforded **V-27** in 57% yield and >95:5 selectivity (eq 5).[22,23] Methodology for asymmetric

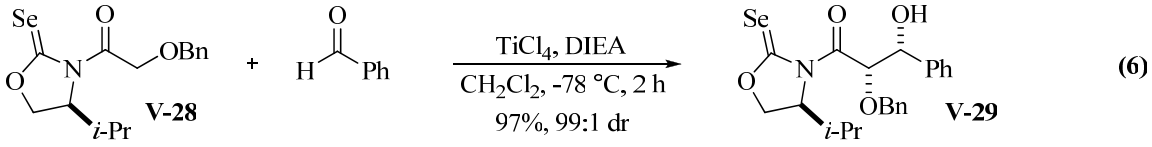
transformations involving chiral *N*-acyl selones **V-28** has also been described (eq 6).[24] High *syn*-aldol selectivity in generation of products **V-29** is also typical in these reactions.



(4)

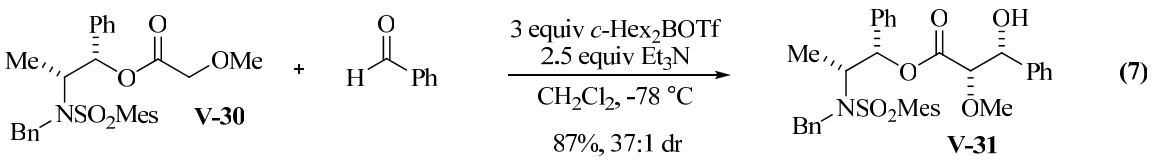


(5)



(6)

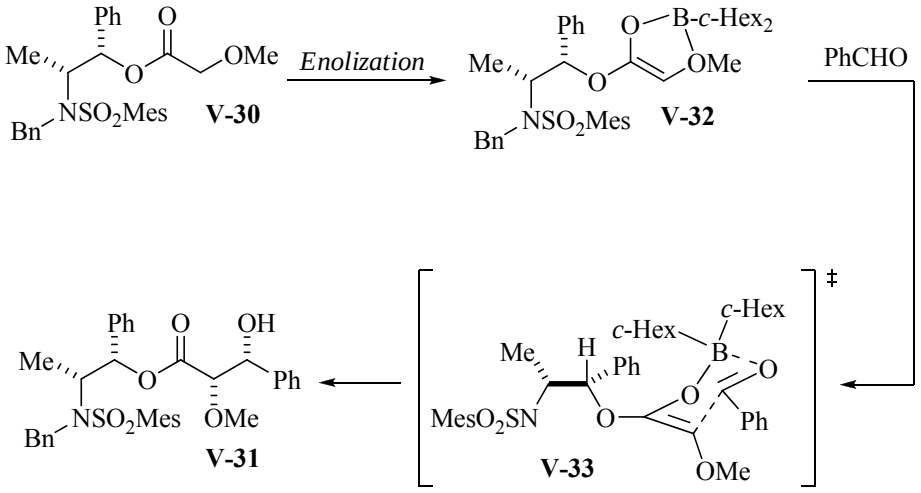
Highly selective *syn*-glycolate aldol reactions using Masamune norephedrine esters **V-30** have been reported.[25] The best yields and selectivities for products such as **V-31** are observed through the use of excess *c*-Hex$_2$BOTf and triethylamine in these reactions (eq 7).



(7)

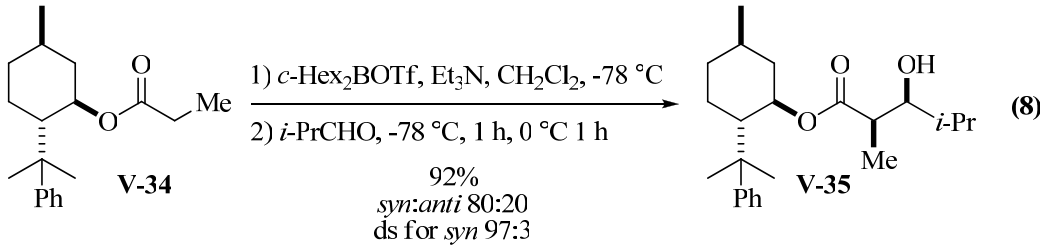
The reaction pathway for the transformation outlined in Equation 7 is similar to that described for the reactions described in Equations 4-6. Initial *Z*-enolate formation resulting in 5-membered boron chelate **V-32** is proposed (Figure V-2). A closed, Zimmerman-Traxler transition state **V-33** is consistent with the high *syn*-aldol selectivity observed in the reaction.

Figure V-2. Proposed Transition State



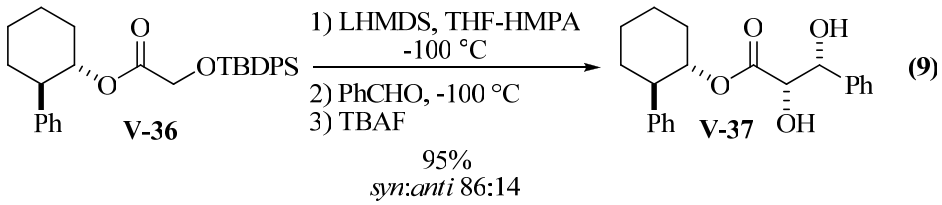
Cyclohexyl-based chiral auxiliaries have also been used to achieve asymmetric induction in aldol reactions. One of the first examples of an asymmetric boron-mediated aldol reaction of a chiral carboxylic ester was reported by Abiko.[26] For example, treatment of 8-phenylmenthyl carboxylic ester **V-34** with *c*-Hex$_2$BOTf and triethylamine

at -78 °C results in formation of an enolate which undergoes subsequent aldol reaction with isobutyraldehyde affording **V-35** in 92% yield and 80:20 *syn*:*anti* ratio (eq 8). Aldol reactions of glycolate ester substrates using this auxiliary have not been reported.



(8)

A single example of an asymmetric glycolate aldol reaction of a 2-phenylcycloexyl ester enolate has been described in the literature.[27] The (–)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl ester **V-36** was treated with LHMDS and reacted with benzaldehyde to afford an aldol addition product which was subsequently deprotected resulting in 95% yield of **V-37** (eq 9). However, the asymmetric induction observed in this process was moderate as **V-37** was isolated as a 86:14 mixture of *syn*:*anti* diastereomers.

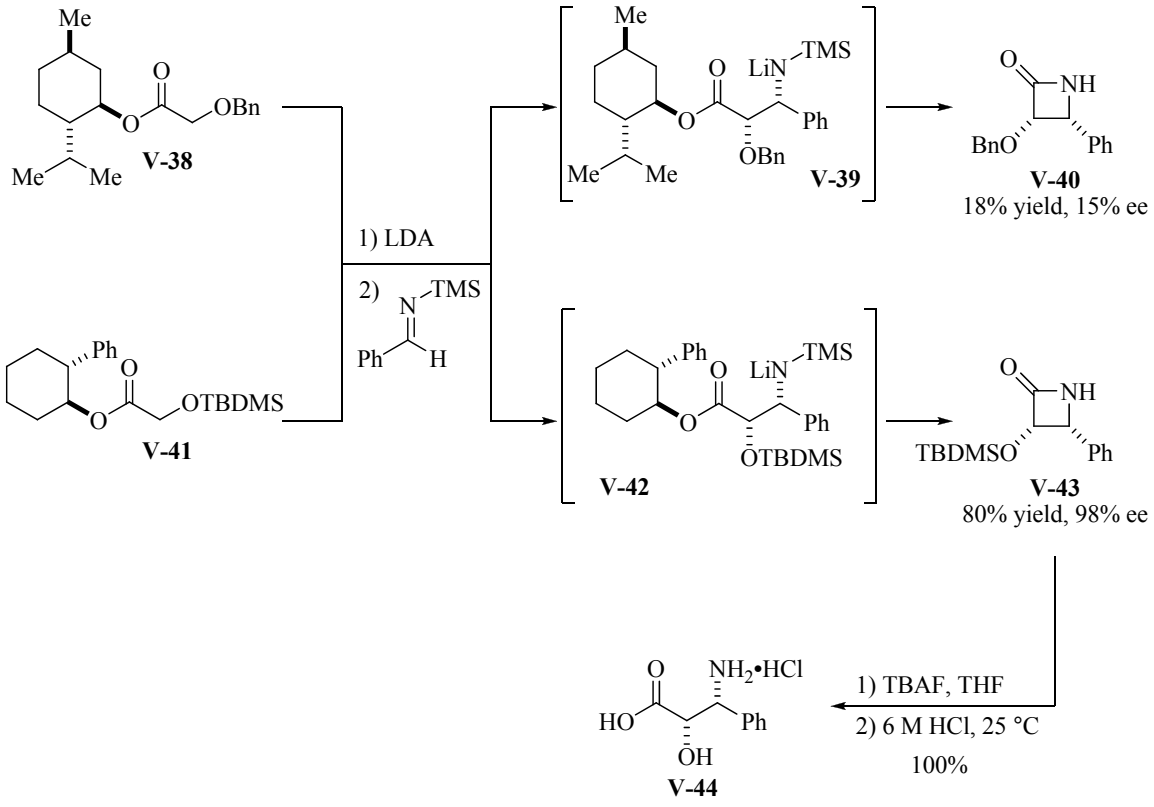


(9)

Asymmetric Mannich reactions of chiral carboxylic esters derived from (-)-menthol **V-38** and (+)-2-phenylcyclohexanol **V-41** have also been described.[28] Generation of chiral lithium ester enolates from benzyloxy- or silyloxyacetates and

subsequent reaction with *N*-trimethylsilylimines gave the corresponding β-lactams **V-40** and **V-43** presumably through intermediates **V-39** and **V-42** respectively (Scheme V-4). Use of substrate **V-41** bearing the (+)-(1*S*,2*R*)-2-phenylcyclohexanol auxiliary provided superior results, generating **V-43** in 80% yield and 98% ee. Deprotection and ring-opening of lactam product **V-43** was accomplished in two steps, quantitatively generating amino-alcohol **V-44**.

Scheme V-4. Use of (-)-Menthol and (+)-*trans*-2-Phenylcyclohexanol as Chiral Auxiliaries



As described, chiral auxiliaries have been relied on extensively for the generation of enantioenriched α-alkyl-α,β-dihydroxy esters and related compounds through aldol and Mannich reactions. The development of asymmetric tandem reaction sequences through the examination of chiral auxiliaries such as those mentioned in this Chapter will be the focus of Chapters VI-VII.

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Chapter VI

Asymmetric, Tandem Wittig Rearrangement/Aldol Reactions

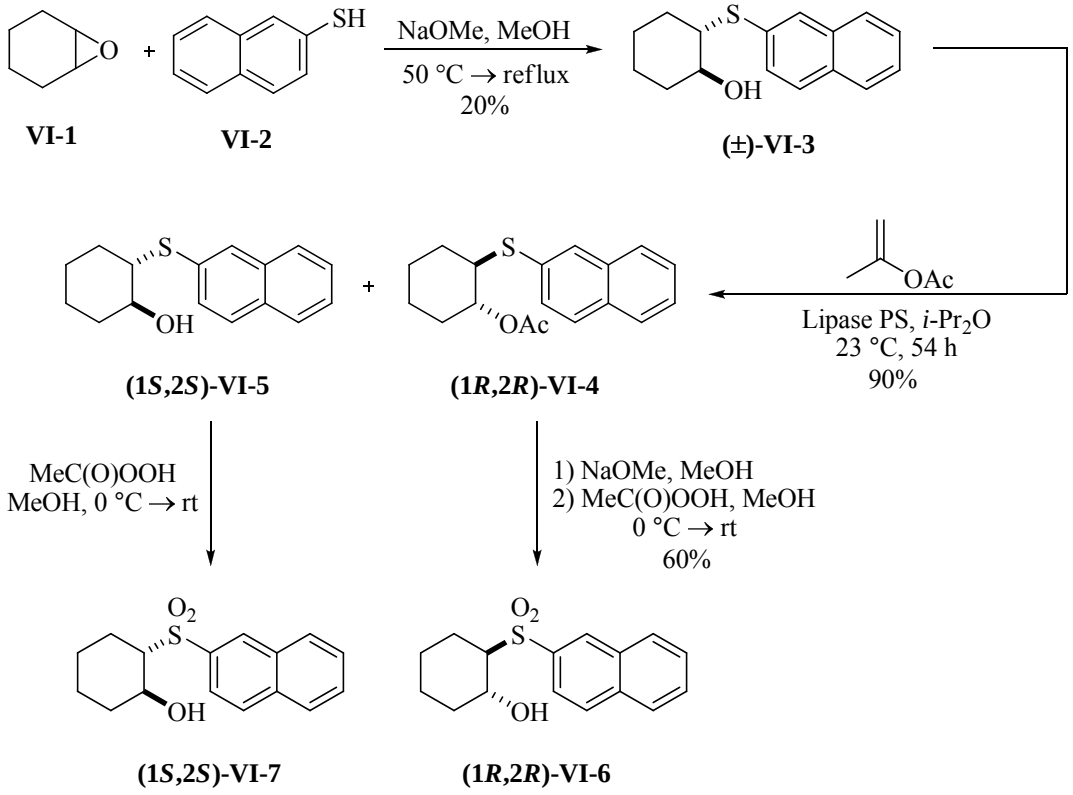
In this Chapter, the development of asymmetric, tandem Wittig/Aldol reactions that provide enantiomerically enriched α-alkyl-α,β-dihydroxy esters will be described.[1] These are the first examples of tandem reactions involving enolate [1,2]-Wittig rearrangements that afford nonracemic products, and are also the first asymmetric aldol reactions of α-alkyl-α-hydroxy ester enolates that generate unprotected diol products with both high *syn*:*anti* selectivity and high ee. In addition, this new method provides a significantly improved route to a key intermediate in the synthesis of alternaric acid.[2]

VI.1 Chiral Auxiliary Screening

In our preliminary studies we sought to achieve asymmetric induction through use of esters derived from chiral alcohols. Therefore, a series of substrates containing chiral auxiliaries were synthesized (Table VI-1). The Masamune auxiliary, (–)-Borneol, and (–)-Menthol were commercially available and used as obtained. The Corey sulfonyl auxiliaries[3] **VI-6** and **VI-7** were synthesized from cyclohexene oxide **VI-1** and 2-naphthalenethiol **VI-2** as outlined in Scheme VI-1. Reaction of **VI-2** with **VI-1** in the presence of sodium methoxide in methanol yielded **VI-3**. Kinetic resolution of **VI-3**

was accomplished using Lipase PS, giving a separable mixture of **VI-5** and **VI-6**. Each of these compounds could be carried on to enantiomerically pure alcohols via deprotection/oxidation of **VI-4** or oxidation of **VI-5** to afford **VI-6** and **VI-7** respectively. For experiments in this Chapter, **VI-4** was treated with sodium methoxide in methanol followed by oxidation to afford **VI-6** in 60% yield.

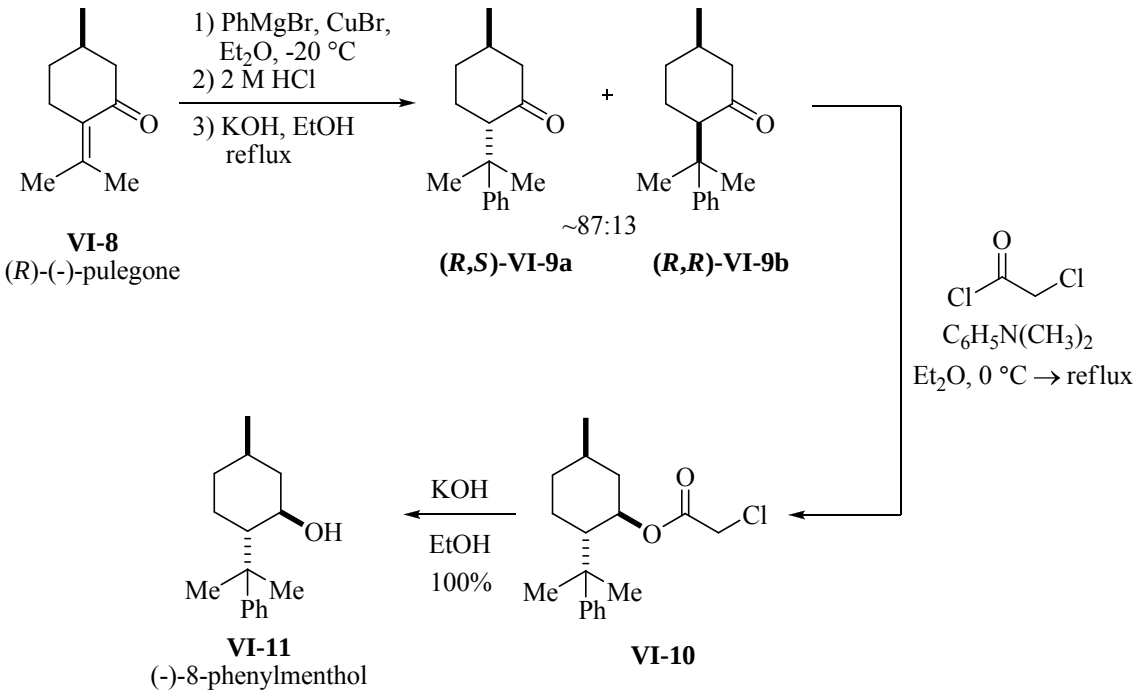
Scheme VI-1. Synthesis of Corey Sulfonyl Cyclohexyl Auxiliaries



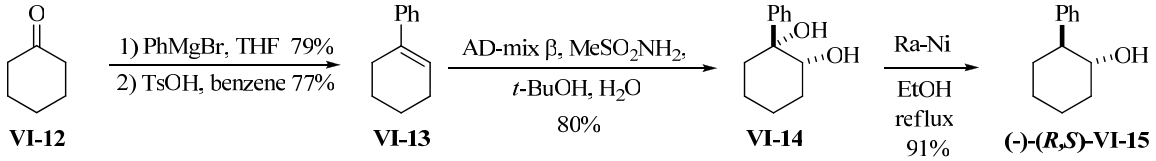
Although (–)-8-phenylmenthol **VI-11** is commercially available, it was synthesized from (*R*)-(+)-pulegone **VI-8** via the procedure outlined in Figure VI-2.[4,5] Intermediate **VI-9** is formed as a mixture of diastereomers that are separable via column chromatography. Therefore, the major diastereomer **VI-9a** is carried through the

sequence to provide (–)-8-phenylmenthol **VI-11**. It should also be noted that as an alternative to purchasing the commercially available chiral auxiliary (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol **VI-15**, it may be prepared in multi-gram quantities simply from cyclohexanone **VI-12** in four steps (Scheme VI-2).[6] Addition of phenylmagnesium bromide to **VI-12** followed by dehydration with TsOH affords **VI-13**. Sharpless dihydroxylation of **VI-13** results in formation of diol **VI-14** which is reduced to yield (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol **VI-15**.

Scheme VI-2. Synthesis of (–)-8-Phenylmenthol Auxiliary



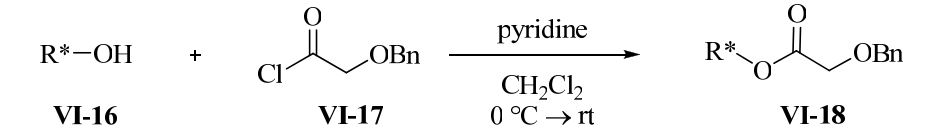
Scheme VI-3. Synthesis of (–)-(1*R*,2*S*)-*trans*-2-Phenylcyclohexanol Auxiliary



VI-12 **VI-13** **VI-14** **(-)-(*R*,*S*)-VI-15**

The chiral substrates initially screened were synthesized via reaction of the mentioned chiral alcohols with benzyloxyacetyl chloride **VI-17** (Scheme VI-4). In this way, a series of *O*-benzyl glycolate ester substrates **VI-19–VI-24** were synthesized as outlined in Scheme VI-4.

Scheme VI-4. Synthesis of Chiral *O*-Benzyl Glycolate Ester Substrates

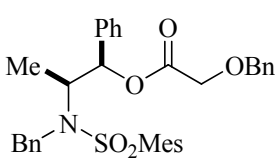


VI-16
Chiral Alcohol

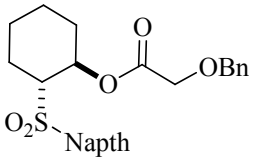
VI-17

VI-18
R* = Chiral Auxiliary

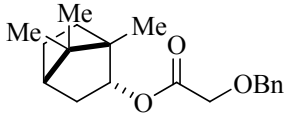
Figure VI-1. Enantiopure *O*-Benzyl Glycolate Ester Substrates



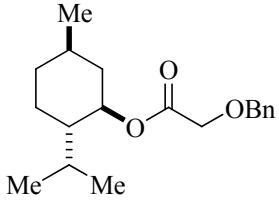
VI-19[a]
Masamune Auxiliary



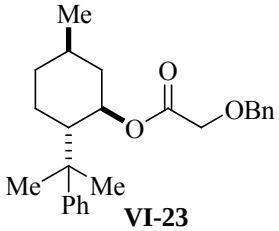
VI-20
Sulfonyl Auxiliary



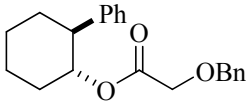
VI-21
(-)-Borneol
83%



VI-22[b]
(-)-Menthol



VI-23
(-)-*8-Phenylmenthol*
99%

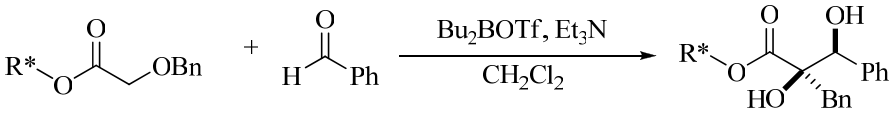


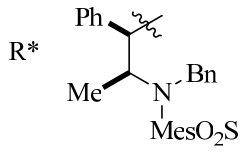
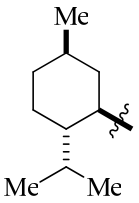
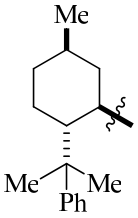
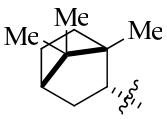
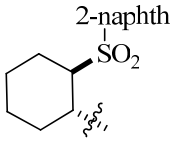
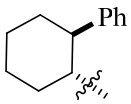
VI-24
(-)-(1*R*,2*S*)-*2-Phenylcyclohexanol*
67%

[a]This compound prepared by Myra Bertrand. [b]This compound prepared by Nikki Guthrie.

With our desired substrates in hand, compounds **VI-19–VI-24** were screened under our previously developed reaction conditions. Although the Masamune auxiliary has been shown to provide excellent results in aldol reactions of trisubstituted ester enolates,[7] an *O*-benzyl glycolate ester bearing this group (**VI-19**) failed to undergo [1,2]-Wittig rearrangement.[8] In contrast, promising results were obtained with menthyl ester **VI-22**, as product **VI-25** was observed and isolated in 62% yield. Similarly low diastereoselectivity was observed in reactions of **VI-23** and **VI-21** yielding tandem products **VI-26** and **VI-27** in 27% and 82% yield respectively. Further experiments indicated the *O*-benzyl glycolate ester **VI-24** prepared from commercially available (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol[6,9] was transformed to **VI-28** with excellent stereoselectivity (20:1).

Table VI-1. Examination of Chiral Auxiliaries in Tandem Wittig/Aldol Reaction[a]

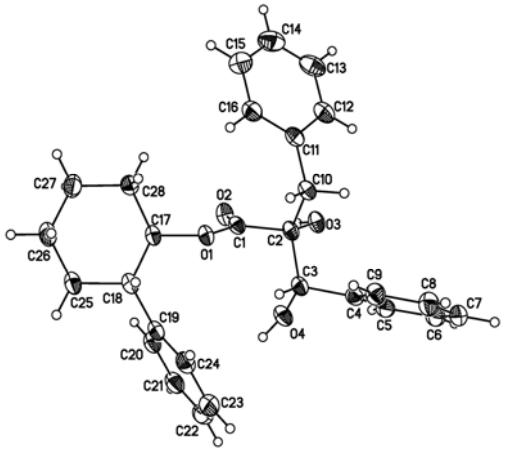


R*	 **VI-19**	 **VI-22**	 **VI-23**	 **VI-21**	 **VI-20**	 **VI-24**
	a	**b**	**c**	**d**	**e**	**f**
Yield 9[b]	0%[d]	62%	27%	82%	0%	83%
dr[c]	–	5:1	3:1	3:1	–	20:1
Product	–	**VI-25**	**VI-26**	**VI-27**	–	**VI-28**

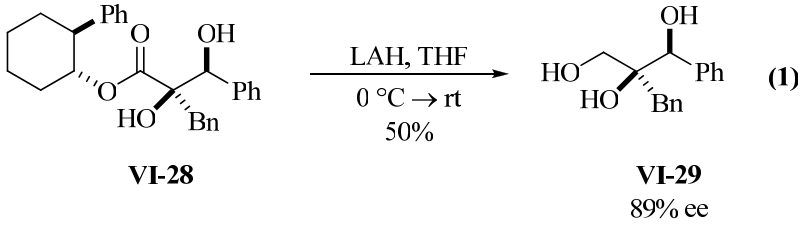
[a]Conditions: 1.0 equiv ester, 1.5 equiv PhCHO, 3.2 equiv Bu_2BOTf, 4 equiv Et_3N, CH_2Cl_2, 0°C → rt → 0°C. [b] Isolated yield (average of two or more experiments). [c] Diastereomeric ratios were determined by ^1H NMR analysis. [d]This experiment conducted by Myra Bertrand. See Ref. 8.

In order to determine the absolute stereochemistry of **VI-28**, an x-ray crystal structure was obtained (Figure VI-2).[10] This indicated that the product **VI-28** had the illustrated (2'*R*,3'*S*) stereochemistry.

Figure VI-2. X-ray Crystal Structure of **VI-28**



In order to determine the enantiopurity of **VI-28**, the 2-phenylcyclohexanol auxiliary was cleaved via reduction of **VI-28** to triol **VI-29** (eq 1). High performance liquid chromatography (HPLC) analysis of **VI-29** indicated that the product was formed in 89% ee.

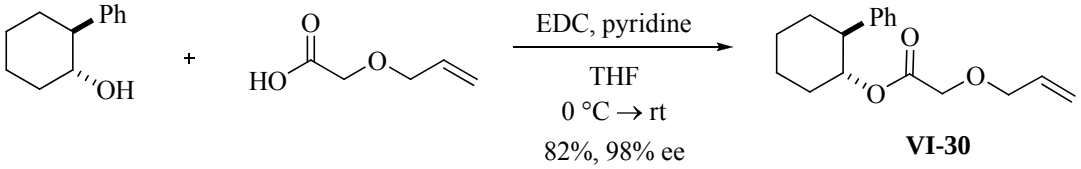


VI-28 **VI-29**
89% ee

(1)

With these results, it was determined that (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol would be used as the optimal auxiliary for our tandem transformation. Another substrate for examination in the tandem reaction was synthesized bearing the (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol auxiliary (Scheme VI-5). This *O*-allyl glycolate ester **VI-30** was synthesized in excellent yield and enantiopurity using the coupling reagent EDC.

Scheme VI-5. Synthesis of Chiral *O*-Allyl Glycolate Ester Substrate **VI-30**

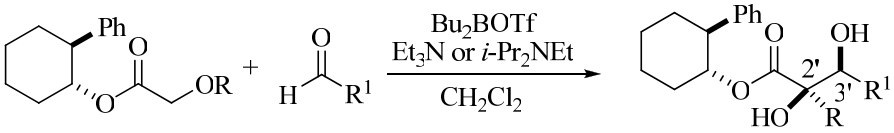


VI-30

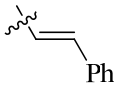
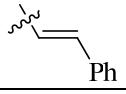
VI.2 Asymmetric Wittig/Aldol Reaction Scope

As shown below in Table VI-2, the asymmetric Wittig rearrangement/aldol reactions are effective for the conversion of *O*-benzyl or *O*-allyl glycolate esters **VI-24** and **VI-30** to a number of different diol products. A wide range of aldehydes, including aromatic, aliphatic, and α,β-unsaturated, are transformed in good yield, and all reactions proceeded with at least 20:1 *syn:anti*-diol selectivity. In seven of eight cases examined the ratio of (2'*R*,3'*S*):(2'*S*,3'*R*) diol stereoisomers was ≥ 20:1, and cleavage of the auxiliary from these seven products with $LiAlH_4$ afforded enantiomerically enriched triols with 89–95% ee.

Table VI-2. Asymmetric, Tandem Wittig/Aldol Reactions

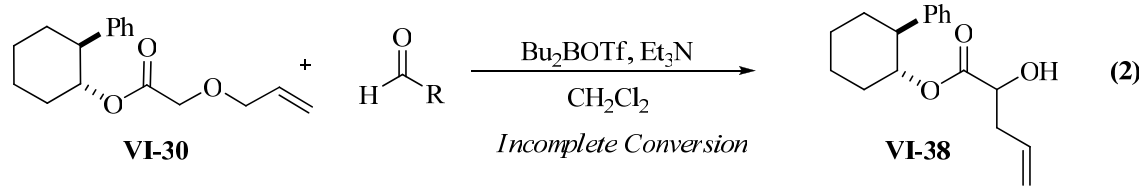


VI-24: R = Bn
VI-30: R = allyl

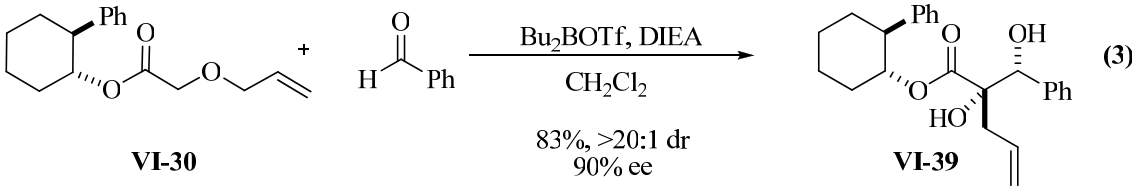
Entry	R	R^1	Product	Yield[b]	(2'*R*,3'*S*):[c] (2'*S*,3'*R*)	ee after $LiAlH_4$ reduction[d]
1	Bn	Ph	**VI-28**	83%	20:1	89%
2	Bn	C_9H_{19}	**VI-31**	88%	20:1	95%
3	Bn	Cy	**VI-32**	71%	20:1	91%
4	Bn		**VI-33**	81%	>20:1	93%
5	Allyl	Ph	**VI-34**	83%	20:1	90%
6	Allyl	C_9H_{19}	**VI-35**	79%	8:1	75%
7	Allyl	*i*-Pr	**VI-36**	68%	20:1	89%
8	Allyl		**VI-37**	59%	>20:1	95%

[a] Conditions: 1.0 equiv **VI-24** or **VI-30**, 1.5–2 equiv R^1CHO, 3.2 equiv Bu_2BOTf, 4 equiv Et_3N (R = Bn) or *i*-$PrNEt_2$ (R = allyl), CH_2Cl_2, 0°C → rt → 0°C. [b] Isolated yield (average of two or more experiments). [c] Ratios were determined by ^1H NMR analysis. All products were obtained with >20:1 *syn*:*anti* selectivity. [d] Enantiomeric excess was determined by chiral HPLC or Mosher ester analysis after reduction to the corresponding triol with $LiAlH_4$.

The reaction conditions for tandem product formation from *O*-benzyl glycolate ester **VI-23** were not optimal for tandem product formation from *O*-allyl glycolate ester substrate **VI-30**. Use of triethylamine as a base in reactions with *O*-allyl glycolate ester **VI-30** resulted in incomplete conversion to rearranged intermediate **VI-33** (eq 2). However, use of diisopropylethylamine resulted in complete rearrangement of **VI-30**, and formation of tandem product **VI-39** in good yield and enantiopurity (eq 3).

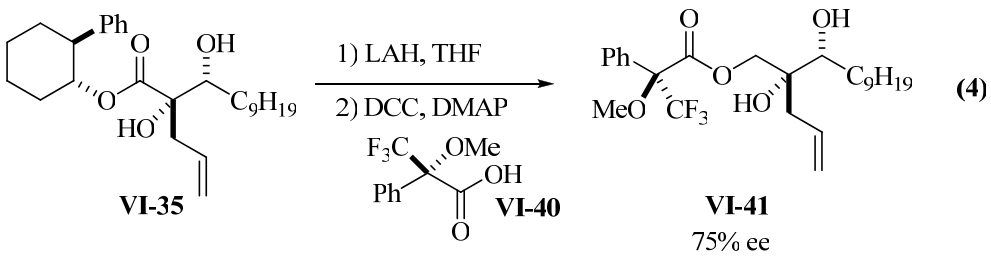


VI-30 **VI-38** **(2)**



VI-30 **VI-39** **(3)**

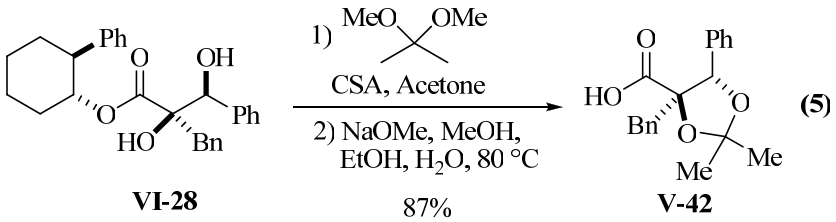
As an alternative method to access enantiopurity of the tandem Wittig/Aldol products, Mosher ester analysis was utilized. For example, reduction of **VI-35** to the triol followed by coupling Mosher acid **VI-40** afforded **VI-41** (eq 4). Analysis via ^{19}F NMR spectroscopy confirmed the product **VI-41** was formed in 75% enantiopurity.



(4)

VI.3 *trans*-2-Phenylcyclohexanol: Auxiliary Cleavage

Removal of the chiral auxiliary from **VI-28** was accomplished using one of two methods. As previously mentioned, treatment of **VI-28** with $LiAlH_4$ afforded enantiomerically enriched triol **VI-29** (eq 1). Alternatively, a two-step sequence involving conversion of **VI-28** to an acetonide followed by hydrolysis of the ester afforded carboxylic acid **VI-42** in good yield (eq 5).

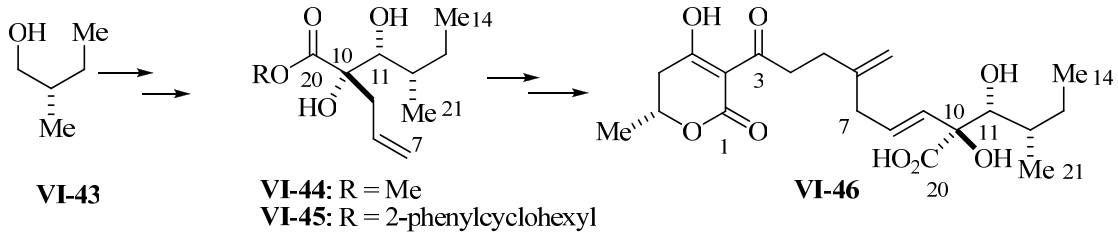


(5)

VI.4 Accessing an Advanced Alternaric Acid Intermediate

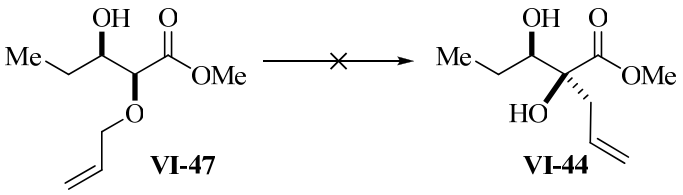
In order to illustrate the synthetic utility of this transformation we sought to prepare **VI-45**, which is closely related to a key intermediate (**VI-244**) in Trost's synthesis of alternaric acid (Scheme VI-6).[2] Ester **VI-44** was previously generated from commercially available (*S*)-2-methyl-1-butanol (**VI-43**) in seven steps (longest linear sequence).[2] The C10–11 diol functionality of **VI-46** was introduced via Sharpless asymmetric dihydroxylation of a trisubstituted enoate (Chapter V, Equation 1), and the pendant terminal alkene was installed in subsequent steps.

Scheme VI-6. Key Intermediate in Alternaric Acid Synthesis[2]

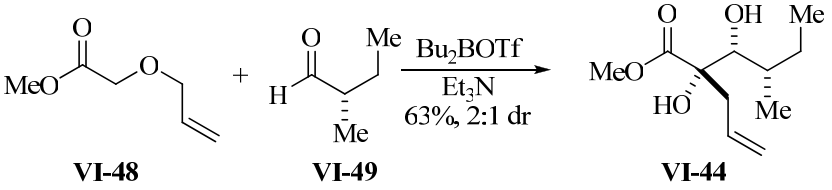


Interestingly, Trost reported an attempted Wittig rearrangement of **VI-47** as a means of more directly accessing **VI-44** (Figure VI-3). However, this attempt was unsuccessful, presumably due to the propensity of these types of molecules to undergo β–elimination.

Figure VI-3. Attempted Wittig Rearrangement Towards Alternaric Acid Synthesis

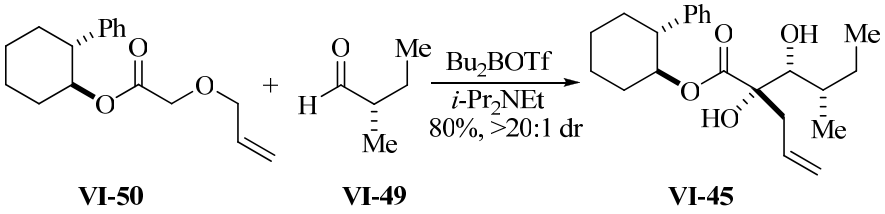


We realized that in principle **VI-45** could be generated through a Wittig rearrangement/aldol reaction sequence between methyl ester **VI-48** and enantiopure aldehyde **VI-49** (prepared in one step from **VI-43**).[11] However, addition reactions of nucleophiles to **VI-43** are known to occur with poor diastereoselectivity due to the similar steric properties of the aldehyde C2-substituents (Me vs. Et). As anticipated, the coupling of **VI-48** with **VI-49** proceeded with modest Felkin selectivity to afford **VI-44** with only 2:1 dr (eq 6).

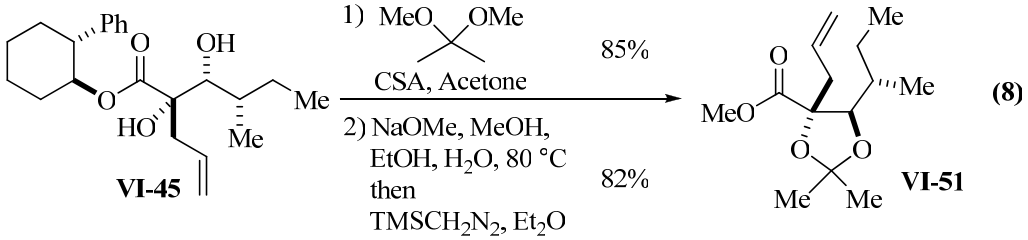


(6)

In contrast, the (–)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl ester **VI-50** was transformed to **VI-45** in 80% yield as a single stereoisomer (eq 7). In order to confirm the stereochemistry of **VI-45**, conversion to another intermediate **VI-51** in Trost's synthesis was completed (Figure VI-4). Protection of **VI-45** as an acetonide, followed by cleavage of the auxiliary to the carboxylic acid, and treatment with trimethylsilyl diazomethane afforded **VI-51** (eq 8).



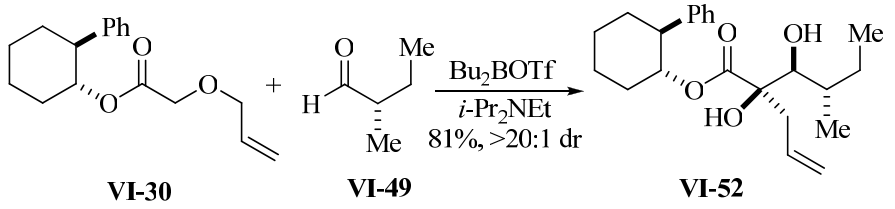
VI-50 **VI-49** **VI-45** **(7)**



VI-45 **VI-51** **(8)**

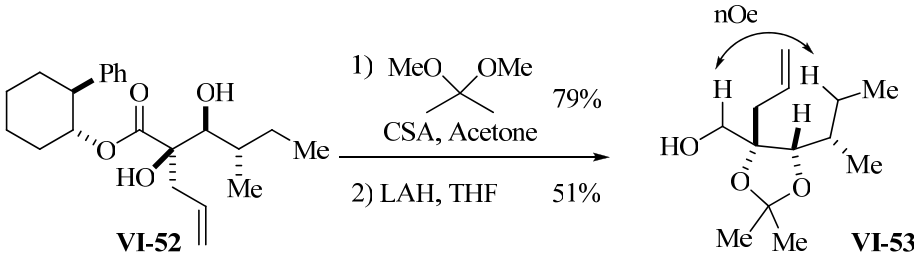
Overall our synthesis of **VI-45** requires only three steps in the longest linear sequence, as ester **VI-50** was prepared in two steps from commercially available materials. Importantly, our strategy complements Sharpless AD chemistry, as the Wittig rearrangement/aldol reaction allows for preparation of α,β-dihydroxy esters bearing relatively nucleophilic alkenes that would not tolerate typical dihydroxylation conditions.[2]

Given the high selectivity observed in reactions of achiral aldehydes with glycolate esters derived from 2-phenylcyclohexanol, it seemed likely the chiral auxiliary could override the slight preference for Felkin selectivity typically observed with chiral aldehyde **VI-49**. This hypothesis proved to be correct, as the tandem Wittig rearrangement/aldol reaction of (+)-(1*R*,2*S*)-*trans*-enantiomer **VI-30** with **VI-49** provided **VI-52** in 81% yield with >20:1 dr (eq 9).



The stereochemistry of **VI-52** was determined via nOe analysis upon protection of the diol as an acetonide, followed by cleavage of the auxiliary with lithium aluminum hydride yielding **VI-53** (Figure VI-4).

Figure VI-4. Determination of Stereochemistry of **VI-53**

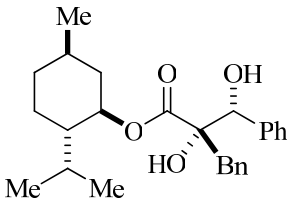


VI.5 Improving Enantioselectivity: Ligand Design

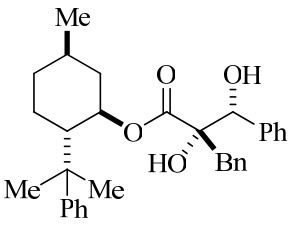
While 2-phenylcyclohexanol provides good yields and levels of asymmetric induction in tandem Wittig/Aldol reactions, we hope to further improve levels of enantioselectivity observed in these reactions through chiral ligand design. From our initial chiral auxiliary screen, cyclohexyl-based chiral auxiliaries appended to substrates were suitable for inducing enantioselectivity in the formation of 1,2-diol products (Table VI-1). However, it appeared as though the placement of the aryl substituent at the carbon

α- to the oxygen on the cyclohexane ring was key to achieving high levels of asymmetric induction (Figure VI-5).

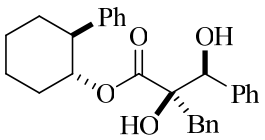
Figure VI-5. Cyclohexyl-Based Auxiliaries and Asymmetric Induction



(-)-Menthol
VI-25
62%, 5:1 dr



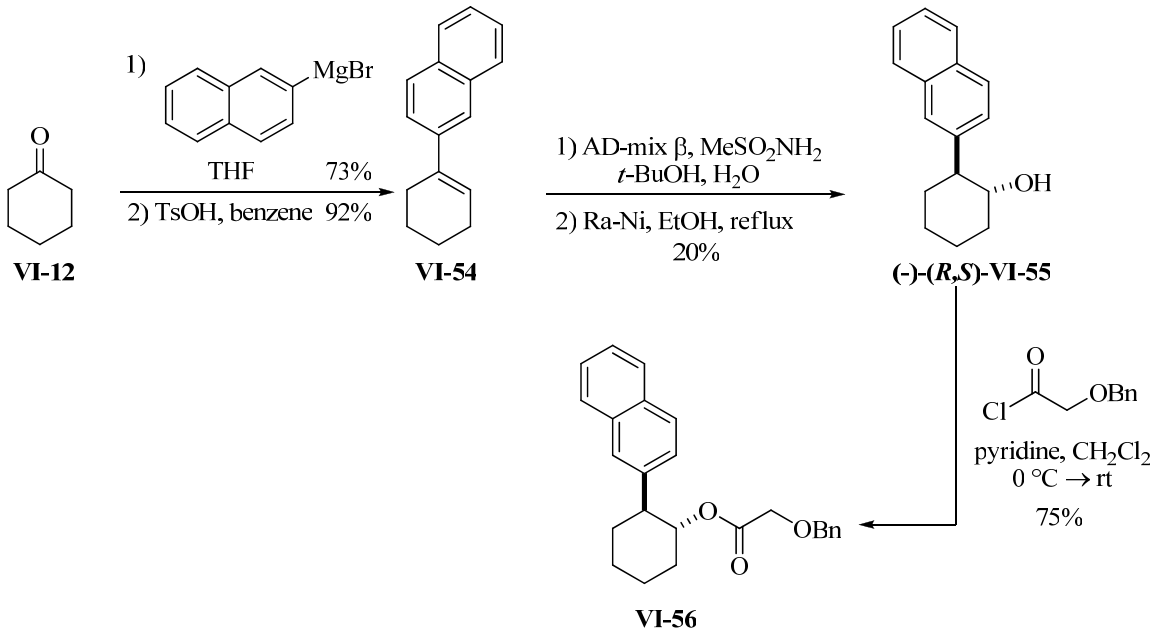
8-Phenylmenthol
VI-26
27%, 3:1 dr



2-Phenylcyclohexanol
VI-28
83%, 20:1

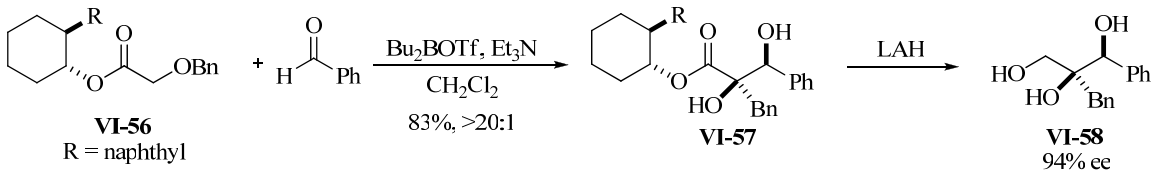
The phenyl substituent may serve to block one face of the enolate in the aldol reaction. Therefore, we hypothesized that an increase in the size of the aryl group may increase enantioselectivity. To this end, 2-naphthylcyclohexanol was synthesized, and substrate **VI-56** was obtained via the same method used to prepare **VI-30** (Scheme VI-7).

Scheme VI-7. Synthesis of Substrate Bearing 2-NaphthylCyclohexyl Auxiliary



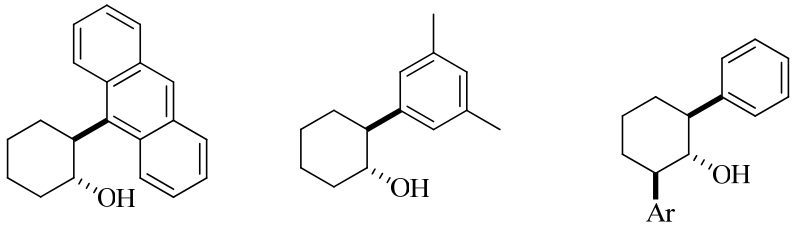
Tandem Wittig/Aldol reaction of **VI-56** provided **VI-57** in 83% yield and with >20:1 diastereoselectivity (Scheme VI-8). Cleavage of the chiral auxiliary via reduction of **VI-57** to the triol **VI-58** revealed the product was formed in 94% enantiopurity. Overall, a 5% increase in enantiopurity was observed in using the substrate **VI-56** derived from 2-naphthylcyclohexanol (94% ee) versus 2-phenylcyclohexanol (89% ee).

Scheme VI-8. Examination of 2-NaphthylCyclohexyl-Derived Substrate in Tandem Wittig/Aldol Reaction



These initial results are promising, however the synthesis of auxiliaries with other aryl groups in place of phenyl is merited (Figure VI-6). Installation of an anthracene **VI-59** or 3,5-dimethylphenyl **VI-60** moiety should be feasible via the previously described route. Another interesting extension may involve examination of a substrate **VI-61** bearing aryl substituents at both carbon atoms α to the oxygen substituent of the cyclohexyl ring.

Figure VI-6. Future Directions: Chiral Auxiliary Design

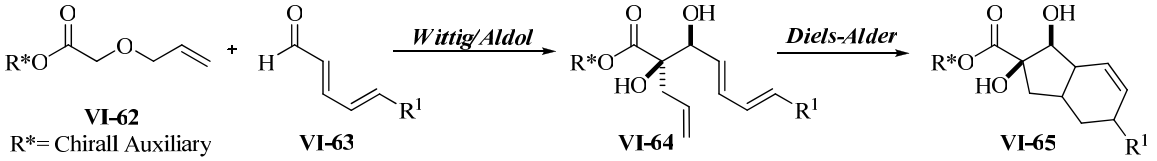


VI-59 **VI-60** **VI-61**

VI.6 Tandem Wittig/Aldol/Diels-Alder Reactions

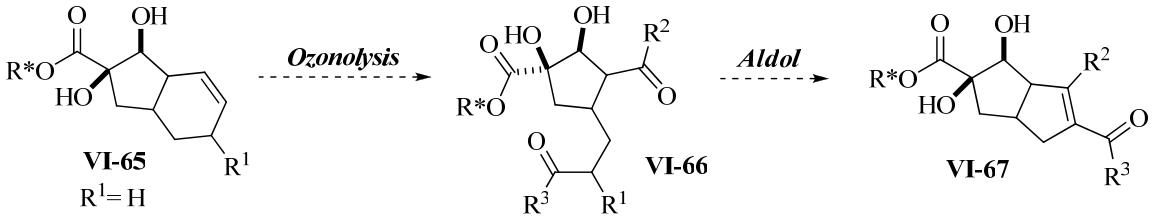
With the successful development of asymmetric, tandem Wittig/Aldol reactions, we realized that the products of these reactions could be useful precursors to other complex molecules. For example, if the electrophilic coupling partner used in the reaction were a dienal such as **VI-63**, the product of the tandem Wittig/Aldol reaction with *O*-allyl glycolate ester **VI-62** would be an interesting Diels-Alder substrate **VI-64** for complex carbocycle **VI-65** synthesis (Scheme VI-9).

Scheme VI-9. Complex Carbocycle Synthesis



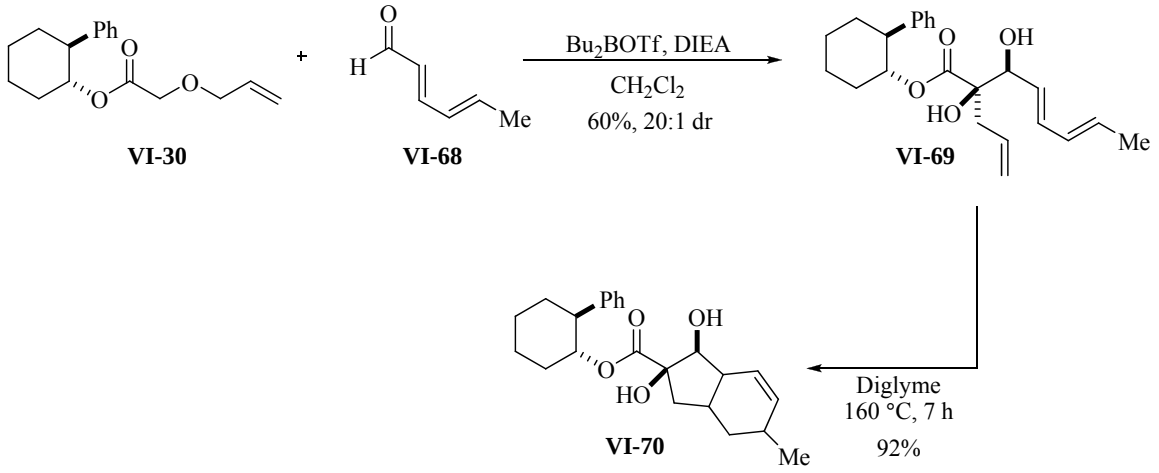
This reaction sequence has the potential to generate enantioenriched products with up to five stereocenters in a concise sequence. The carbocyclic products of this reaction sequence can be further transformed into other useful scaffolds. For example, oxidative cleavage of the double bond of **VI-65** would give rise to cyclopentane **VI-66** (Scheme VI-10). Treatment of **VI-66** with base in order to induce an intramolecular aldol reaction would generate **VI-67**, which is a complex scaffold displayed in various natural products.[1213]

Scheme VI-10. Potential Carbocycle Transformation



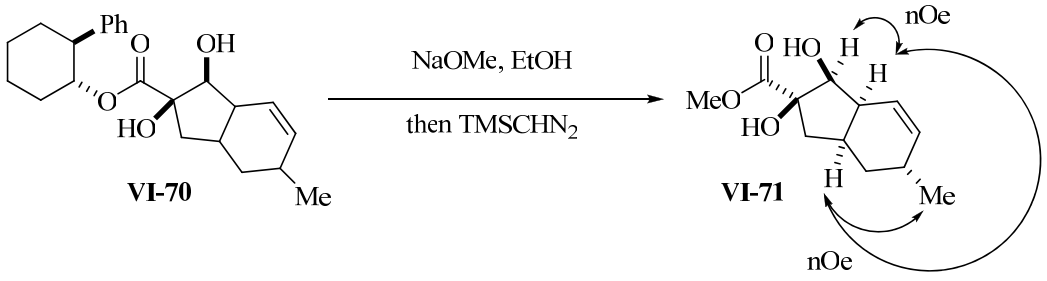
Initial studies in this area have been undertaken. Reaction of *O*-allyl glycolate ester **VI-30** in the presence of Bu_2BOTf and diisopropyl ethyl amine using dienal **VI-68** as a coupling partner afforded **VI-69** in 60% yield and 20:1 dr (Scheme VI-11). Intramolecular Diels-Alder cycloaddition was accomplished via heating **VI-69** in diglyme at 160 °C for 7 hours, providing 92% yield of carbocycle **VI-70**.

Scheme VI-11. Tandem Wittig/Aldol/Diels-Alder Reaction Sequence



For ease of stereochemical analysis, **VI-70** was treated with sodium methoxide in ethanol, followed by $TMSCHN_2$ afforded methyl ester **VI-71** (Figure VI-7). The stereochemistry of **VI-71** was determined by nOe analysis. Although a mixture of stereoisomers of **VI-71** was obtained, the isomer **VI-71** shown represented ca. 65% of this mixture. The stereochemistry of **VI-71** was assigned based on the nOe signals depicted.

Figure VI-7. Assignment of Wittig/Diels-Alder Product Stereochemistry

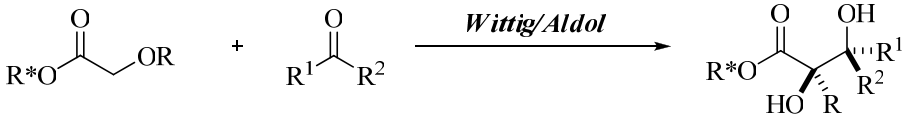


A range of substituted dienals could be examined in the tandem reaction, as stereocontrol in the Diels-Alder reaction will likely be substrate dependant. It should be noted that synthetically useful selectivities have been obtained in related systems.[14] For this reason, future investigations in this area are merited.

VI.7 Generation of Vicinal Quaternary Stereocenters via Tandem Wittig/Aldol Reactions

The successful development of asymmetric, tandem Wittig/aldol reactions sparked our interest in examining the use of other electrophilic coupling partners in the reaction sequence. Since the asymmetric construction of vicinal quaternary stereocenters remains a significant challenge in organic synthesis, we hoped to extend the developed methodology towards using ketones as electrophiles in the tandem reaction (Figure VI-8). For example, reaction of **VI-72** with a ketone **VI-73** would generate tandem Wittig/aldol product **VI-74** which contains vicinal quaternary stereocenters.

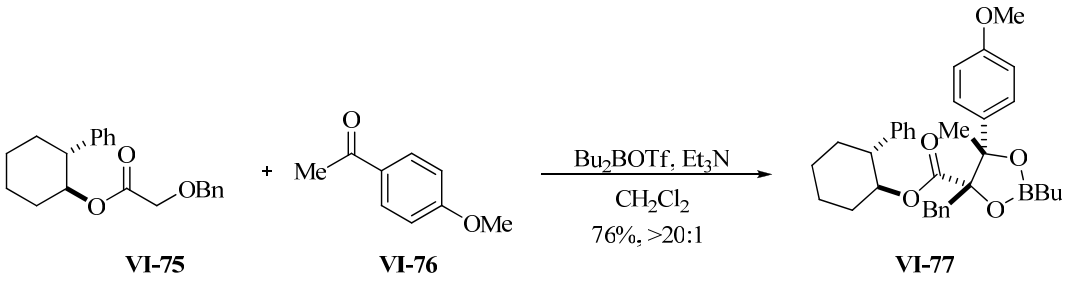
Figure VI-8. Generation of Vicinal Quaternary Stereocenters via Tandem Wittig/Aldol Reaction



VI-72 **VI-73** **VI-74**

R*= Chiral Auxiliary
R= Bn or Allyl

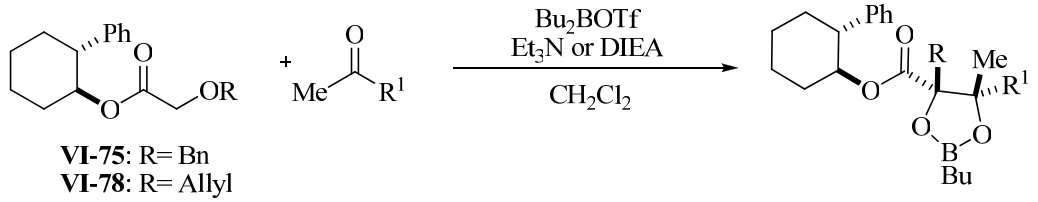
In an initial experiment, treatment of *O*-benzyl glycolate ester **VI-75** with Bu_2BOTf and triethylamine in the presence of *p*-methoxyacetophenone **VI-76** results in formation of boronate ester **VI-77** in 72% and with >20:1 *syn*:*anti* selectivity (eq 8).



VI-75 **VI-76** **VI-77** **(8)**

Several other ketones have been examined in the tandem process (Table VI-2). As shown in Table VI-2, reactions generally proceed in good yield and with good selectivity. Di-aliphatic ketones are suitable coupling partners in the reaction, yielding products such as **VI-79** and **VI-80** in 74% and 67% yields respectively. However, mixtures of *syn*:*anti* diastereomers are formed in the reaction due to the similar steric size of the ketone aliphatic substituents (Figure VI-9).

Table VI-2. Tandem Wittig/Aldol Reaction with Ketones[a]



VI-75: R= Bn
VI-78: R= Allyl

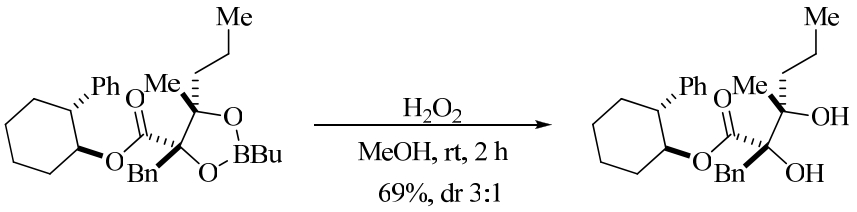
Entry	R	R^1	Product	Yield[b]	(2'*S*,3'*S*):[c] (2'*S*,3'*R*)	ee (2'*S*,3'*S*) after $LiAlH_4$ reduction[d]
1	Bn	$(CH_2)_2Ph$	**VI-79**	74%	4:1	96%
2	Bn	C_3H_7	**VI-80**	67%	3:1	93%
3	Bn	*p*-F-Ph	**VI-81**	56%	20:1	91%
4	Allyl		**VI-82**	55%	7:1	79%

[a] Conditions: 1.0 equiv ester, 1.5 equiv ketone, 3.2 equiv Bu_2BOTf, 4.0 equiv base, CH_2Cl_2, 0 °C → rt → 0 °C → rt. [b] Isolated yield (average of two or more experiments). [c] Diastereomeric ratio of isolated material (determined by ^1H NMR analysis). The dr value of the crude product could not be determined due to signal overlap with boron-containing by-products. [d] The enantiomeric excess was determined by Mosher ester analysis after reduction to the diol.

Cleavage of the boronate ester can be accomplished via treatment of **VI-80** with H_2O_2 in methanol to give **VI-83** in 69% yield (Scheme VI-12). The diastereoselectivity of the boronate ester products from the tandem reactions is difficult to assess. However, upon cleavage of the boronate ester **VI-83** was isolated with 3:1 dr. In order to determine the enantiopurity of all products in Table VI-2, a three-step sequence involving cleavage of the boronate ester, reduction to the triol, and conversion to Mosher esters (Figure VI-9). For example, **VI-79** was treated with H_2O_2 in methanol to give **VI-84** in 58% yield and with 3:1 dr (Figure VI-9). Reduction of **VI-84** followed by peptide coupling of the resulting triols with Mosher ester **VI-85** results in formation of **VI-86**. ^{19}F NMR analysis of the Mosher esters **VI-86** revealed the enantiopurity of the major (3'*S*,4'*S*) diastereomer

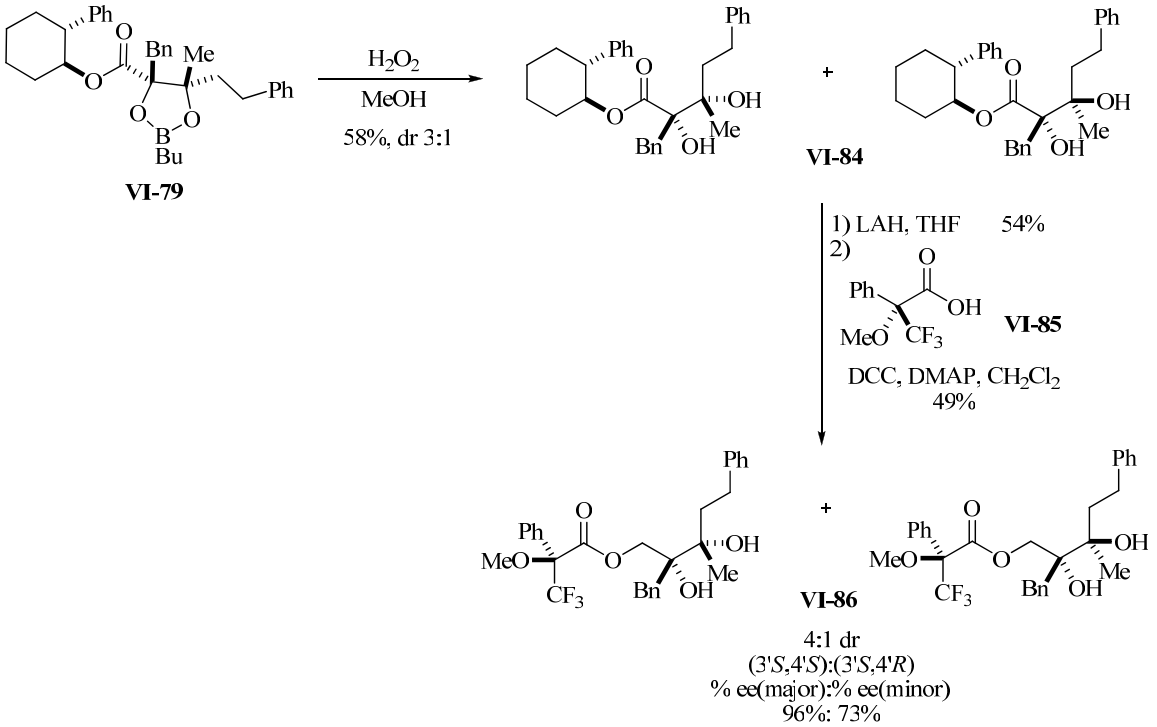
was 96% ee while the minor (3'*S*,4'*R*) isomer was formed in 73% ee. Overall, enantioenriched triols obtained via this method are obtained in 79-96% ee.

Scheme VI-12. Cleavage of Boronate Ester from **VI-80**



VI-80 **VI-83**

Figure VI-9. Enantiopurity Determination of Tandem Wittig/Aldol Products



VI-79 **VI-84** **VI-85** **VI-86**

4:1 dr
(3'*S*,4'*S*):(3'*S*,4'*R*)
% ee(major):% ee(minor)
96%: 73%

VI.8 Summary and Conclusions

In conclusion, we have developed an asymmetric tandem Wittig rearrangement/aldol reaction sequence that affords enantiomerically enriched α-alkyl-α,β-dihydroxy esters in good yield with excellent stereoselectivity. These transformations provide a new means for the enantioselective construction of quaternary carbon stereocenters, and allow for straightforward preparation of compounds that are cumbersome to access with existing methods. Further studies on extensions and applications of this chemistry are currently underway.

VI.9 Experimental

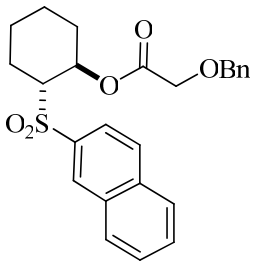
General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. Dibutylboron triflate (1.0 M solution in dichloromethane) was purchased from Aldrich Chemical Co. and was used as obtained. All aldehydes were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were purified by distillation from crushed anhydrous Ca_2SO_4. Triethylamine and diisopropylethylamine were obtained from Aldrich Chemical Co. and were purified by distillation from CaH_2. Phosphate buffer solution (pH 7), 2-(benzyloxy)acetyl chloride, and (–)-borneol were obtained from commercial sources and were used as obtained. (–)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-2-(benzyloxy)acetate was prepared according to published procedures.[15] Methylene chloride, tetrahydrofuran, and ether were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis. The yields reported in the supporting information describe the result of a single experiment. Thus, the yields reported in the supporting information may differ from those shown in this Chapter.

Preparation of Substrates

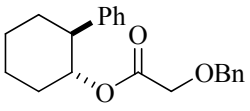
General Procedure A: Synthesis of *O*-Benzyl Esters. A flame-dried flask was cooled under a stream of nitrogen and charged with the appropriate alcohol (2 equiv) and a solution of 2-(benzyloxy)acetyl chloride (1 equiv) in CH_2Cl_2 (0.3 M). The resulting mixture was cooled to 0 °C, pyridine (2.1 equiv) was added dropwise, and the reaction

mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (5–12 h). The mixture was then concentrated *in vacuo*, the crude residue was diluted with water (1 mL/mmol substrate), and the resulting mixture was extracted with Et_2O (3 x 10 mL/mmol substrate). 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 B: Synthesis of *O*-Allyl Esters. A flame-dried flask was cooled under a stream of nitrogen and charged with the appropriate alcohol (1 equiv), EDC (1 equiv) and DMAP (1 equiv). THF was added to provide a 0.2 M solution, which was cooled to 0 °C and stirred. Neat 2-(allyloxy)acetic acid[16] (1 equiv) in THF (1 M) was added dropwise, and the reaction mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca 5–12 h). The mixture was then cooled to 0 °C, and quenched with H_2O (1 mL/mmol substrate). The resulting mixture was transferred to a separatory funnel and extracted with Et_2O (10 mL/mmol substrate). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

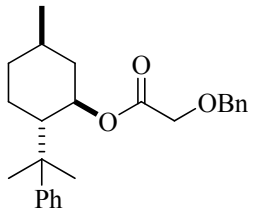


(1*R*,2*R*)-2-(Naphthalen-2-ylsulfonyl)cyclohexyl-2-benzyloxyacetate (VI-20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 7.98–7.95 (m, 2 H), 7.94–7.90 (m, 1 H), 7.84–7.82 (m, 1 H), 7.68–7.65 (m, 1 H), 7.62–7.59 (m, 1 H), 7.36–7.26 (m, 5 H), 5.27–5.22 (m, 1 H), 4.45 (d, *J*= 11.5 Hz, 1 H), 4.31 (d, *J*= 12 Hz, 1 H), 3.70 (d, *J*= 16.5 Hz, 1 H), 3.46 (d, *J*= 16.5 Hz, 1 H), 3.40–3.45 (m, 1 H), 2.32–2.29 (m, 1 H), 2.15–2.12 (m, 1 H), 1.85–1.82 (m, 1 H), 1.73–1.71 (m, 1 H), 1.62–1.54 (m, 1 H), 1.35–1.24 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 137.0, 136.0, 135.1, 132.0, 130.2, 129.4, 129.2, 128.3, 127.9, 127.8, 127.7, 123.2, 73.0, 70.7, 66.8, 65.5, 31.5, 24.9, 24.0, 23.2 (two carbon signals are absent due to incidental equivalence); IR (film) IR (film) IR (film) 2942, 1754 cm^{-1}.

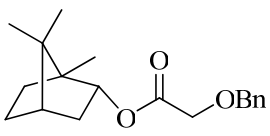


(–)-(1*R*,2*S*)-2-Phenylcyclohexyl-2'-(benzyloxy)acetate (VI-24). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexanol[6] (180 mg, 1.0 mmol) with 2-(benzyloxy)acetyl chloride (78 μL, 0.5 mmol) was conducted for 15 h according to General Procedure A. The crude product was purified by flash chromatography on silica gel to afford 110 mg (67%) of the title compound as a pale yellow oil. $[\alpha]^{23}_{D}$ –13.9 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.24 (m, 5 H), 7.20–7.17 (m, 5 H), 5.16–5.10 (m, 1 H), 4.26 (s, 2 H), 3.84 (d, *J* = 16.5 Hz, 1 H), 3.73 (d, *J* = 16.5 Hz, 1 H), 2.72–2.66 (m, 1 H), 2.16–2.13 (m, 1 H), 1.97–1.92 (m, 1 H), 1.89–1.86 (m, 1 H), 1.81–1.78 (m, 1 H), 1.62–1.52 (m, 2 H), 1.50–1.43 (m, 1 H), 1.40–1.31 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 142.8, 137.1, 128.3, 128.2, 127.9, 127.7, 127.4, 126.5, 76.4, 72.7, 66.8, 49.8, 33.9, 32.2, 25.7, 24.7; IR (film) 2937, 1742 cm^{-1}. MS (ESI) 347.1615 (387.1623 calcd for $C_{21}H_{24}O_3$, M + Na^+).

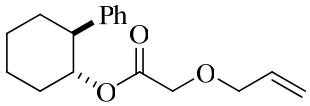
The enantiopurity of the title compound was determined to be 99% ee by chiral HPLC analysis (*R*,*R*-Welk-O 0.46 cm x 25 cm, 2% isopropanol/hexanes, 0.5 mL/min, RT = 20.1 and 24.4 min).



(+)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl-2'-(benzyloxy)acetate (VI-23). The reaction of (+)-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexanol[4] (420 mg, 1.92 mmol) with 2-(benzyloxy)acetyl chloride (0.27 mL, 1.75 mmol) was conducted for 24 h according to General Procedure A. The crude product was purified by flash chromatography on silica gel to afford 570 mg (99%) of the title compound as a colorless oil. $[\alpha]^{23}_{D}$ +8.8 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 4 H), 7.28–7.19 (m, 5 H), 7.07–7.03 (m, 1 H), 4.95–4.88 (m, 1 H), 4.49 (s, 2 H), 3.53 (d, *J* = 16.4 Hz, 1 H), 3.15 (d, *J* = 16.4 Hz, 1 H), 2.06–2.00 (m, 1 H), 1.89–1.83 (m, 1 H), 1.82–1.76 (m, 1 H), 1.69–1.65 (m, 1 H), 1.50–1.44 (m, 1 H), 1.30 (s, 3 H), 1.89 (s, 3 H), 1.18–1.09 (m, 1 H), 0.99–0.91 (m, 2 H), 0.89–0.86 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 151.6, 137.2, 128.3, 128.0, 127.8, 125.2, 124.9, 74.4, 73.0, 66.7, 50.1, 41.7, 39.4, 34.4, 31.2, 28.9, 26.3, 23.6, 21.7; IR (film) 2954, 1744 cm^{-1}. MS (ESI) 403.2247 (403.2249 calcd for $C_2H_{32}O_3$, M + Na^+).



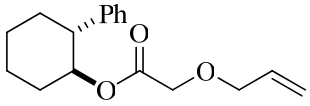
(–)-(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl-2-(benzyloxy)acetate (VI-21). The reaction of (–)-borneol (6.94 g, 45 mmol) with 2-(benzyloxy)acetyl chloride (4.66 mL, 30 mmol) was conducted for 15 h according to General Procedure A. The crude product was purified by flash chromatography on silica gel to afford 7.55 g (83%) of the title compound as a colorless oil. $[\alpha]^{23}_{D}$ –27.2 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5 H), 5.03–4.99 (m, 1 H), 4.64 (s, 2 H), 4.11 (s, 2 H), 2.45–2.35 (m, 1 H), 1.94–1.88 (m, 1 H), 1.79–1.67 (m, 2 H), 1.34–1.19 (m, 2 H), 1.07–0.96 (m, 1 H), 0.91 (s, 3 H), 0.87 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 137.2, 128.4, 127.9, 127.8, 80.4, 73.2, 67.3, 48.8, 47.8, 44.8, 36.6, 27.9, 27.0, 19.6, 18.7, 13.4; IR (film) 2954, 1754 cm^{-1}. MS (ESI) 325.1768 (325.1780 calcd for $C_{19}H_{26}O_3$, M + Na^+).



(–)-(1*R*,2*S*)-2-Phenylcyclohexyl-2'-(allyloxy)acetate (VI-30). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexanol (250 mg, 1.42 mmol) with 2-(allyloxy)acetic acid (165 mg, 1.42 mmol) was conducted for 5 h according to General Procedure B. The crude product was purified by flash chromatography on silica gel to afford 320 mg (82%) of the title compound as a colorless oil. $[\alpha]^{23}_{D}$ –12.2 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2 H), 7.19–7.15 (m, 3 H), 5.80–5.70 (m, 1 H), 5.13–5.06 (m, 3 H), 3.85–3.80 (d, *J* = 16.8 Hz, 1 H), 3.74–3.69 (m, 3 H), 2.72–2.65 (m, 1 H), 2.16–2.12 (m, 1 H), 1.97–1.85 (m, 2 H), 1.81–1.77 (m, 1 H), 1.62–1.47 (m, 3 H), 1.45–1.33 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 142.9, 133.7, 128.3, 127.5, 126.5, 117.9, 76.5,

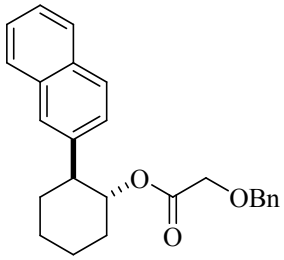
71.9, 66.9, 49.8, 33.9, 32.3, 25.7, 24.7; IR (film) 2932, 1749 cm^{-1}. MS (ESI) 297.1472 (297.1467 calcd for $C_{17}H_{22}O_3$, M + Na^+).

The enantiopurity of the title compound was determined to be 98% ee by chiral HPLC analysis (*R,R*-Welk-O 0.46 cm x 25 cm, 5% isopropanol/hexanes, 0.2 mL/min, RT = 15.1 and 16.9 min).



(+)-(1*S*,2*R*)-2-phenylcyclohexyl-2-(allyloxy)acetate (VI-50). The reaction of (+)-(1*S*,2*R*)-2-phenylcyclohexanol (610 mg, 3.48 mmol) with 2-(allyloxy)acetic acid (400 mg, 3.48 mmol) was conducted for 15 h according to General Procedure B. The crude product was purified by flash chromatography on silica gel to afford 750 mg (79%) of the title compound as a colorless oil. $[\alpha]^{23}_D$ +14.1 (*c* 0.10, CH_2Cl_2). NMR spectra were identical to those reported above for (–)-(**8**).

The enantiopurity of the title compound was determined to be 96% ee by chiral HPLC analysis (chiracel *R,R*-Welk-O 0.46 cm x 25 cm, 2% isopropanol/ hexanes, 0.5 mL/min, RT= 15.2 and 19.7 min).



(1*R*,2*S*)-2-(Naphthalen-2-yl)cyclohexyl-2-benzyloxyacetate (VI-56). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.74 (m, 3 H), 7.62 (s, br, 1 H), 7.45–7.40 (m, 2 H), 7.37–7.35 (m,

1 H), 7.19–7.14 (m, 3 H), 6.96–6.94 (m, 2 H), 5.28–5.23 (m, 1 H), 4.13 (d, *J*= 12.5 Hz, 1 H), 4.08 (d, *J*= 12 Hz, 1 H), 3.79 (d, *J*= 17 Hz, 1 H), 3.65 (d, *J*= 16.5 Hz, 1 H), 2.89–2.84 (m, 1 H), 2.21–2.17 (m, 1 H), 2.02–1.98 (m, 1 H), 1.92–1.89 (m, 1 H), 1.84–1.81 (m, 1 H), 1.70–1.63 (m, 1 H), 1.54–1.48 (m, 2 H), 1.44–1.39 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 140.4, 133.5, 132.4, 128.2, 128.0, 127.7, 127.6, 127.5, 126.1, 125.9, 125.8, 125.4, 72.6, 66.8, 50.0, 34.0, 32.3, 25.6, 24.7 (three carbon signals are absent due to incidental equivalence); IR (film) IR (film) IR (film) 2936, 1745 cm^{-1}. MS (ESI) 397.1778 (397.1780 calcd for $C_{25}H_{26}O_3$, M + Na^+).

Preparation of Products

General Procedure A: Tandem Wittig rearrangement/Aldol reactions. A flame-dried flask was cooled under a stream of nitrogen and charged with a 1 M solution of dibutylboron triflate in dichloromethane (3.2 equiv). The pale yellow solution was cooled to 0 °C, and triethylamine or diisopropyl ethylamine (4.0 equiv) was added dropwise to afford a colorless solution. The ester substrate (1 equiv) was then added dropwise, and the reaction mixture was warmed rt, stirred for 0.5–1.5 h, and then cooled to 0 °C. The aldehyde (1.5 or 2 equiv) was then added dropwise, and the reaction mixture was warmed to rt and stirred for 3–12 h. The reaction vessel was then opened to air, and pH 7 buffer (1 mL/mmol substrate), and methanol (2 mL/mmol substrate) were added. The resulting mixture was cooled to 0 °C, 30% aqueous H_2O_2 (2 mL/mmol substrate) was added slowly, and the reaction mixture was warmed to rt and stirred for 1 h. The mixture was

diluted with ether (10 mL/mmol substrate) and water (5 mL/mmol substrate), then was transferred to a separatory funnel. The layers were separated, and the organic layer was washed with a saturated aqueous solution of $FeSO_4$ (4 x 5 mL/mmol substrate) until a red-orange aqueous phase no longer persisted in order to quench any remaining peroxide. *Caution! This procedure is exothermic. The $FeSO_4$ solution should be added via glass pipette SLOWLY DROPWISE.* The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

General Procedure B: Method to Assess Enantiopurity of Products Derived from *O*-benzyl Glycolate Esters. In order to assess the enantiomeric purity of the products formed in the tandem Wittig-rearrangement aldol reactions of *O*-benzyl glycolate esters, the products were reduced to the corresponding triols with $LiAlH_4$ according to the following procedure. The diol (1.0 equiv) was dissolved in THF (0.1 M) and cooled to 0 °C. A solution of $LiAlH_4$ (2 equiv/mmol substrate, 1 M in THF) was added dropwise, and the reaction mixture was warmed to rt and stirred until the starting material had been completely consumed as judged by TLC analysis. The reaction mixture was cooled to 0 °C and quenched with H_2O (1 mL/mmol substrate). The crude residue was diluted with Et_2O (2 mL/mmol substrate), 10 M NaOH was added (1 mL/mmol substrate), then H_2O (0.5 mL/mmol substrate) was added. The phases were separated, the inorganic precipitate was washed with ether (3 x 2 mL), and the combined organic solutions were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was

purified by flash chromatography on silica gel. The enantiopurity was subsequently determined by chiral HPLC analysis.

For purposes of comparison, racemic triols were prepared from the corresponding *O*-benzyl methyl esters,[17] using a procedure identical to that described above.

General Procedure C: Method to Assess Enantiopurity of Products Derived from *O*-allyl Glycolate Esters via Reduction to Triol and Benzoyl Protection. In order to assess the enantiomeric purity of products formed in the tandem Wittig-rearrangement aldol reaction of *O*-allyl glycolate esters, the product was converted to the corresponding benzoyl ester using the following procedure. The diol (1.0 equiv) was dissolved in THF (0.1 M) and cooled to 0 °C. A solution of $LiAlH_4$ (2 equiv/mmol substrate, 1.0 M in THF) was added, and the reaction was warmed to rt and stirred until the starting material had been completely consumed as judged by TLC analysis. The reaction mixture was cooled to 0 °C and quenched with H_2O (1 mL/mmol substrate). The crude residue was diluted with Et_2O (2 mL/mmol substrate), 10 M NaOH was added (1 mL/mmol substrate), then H_2O (0.5 mL/mmol substrate) was added. The phases were separated, the inorganic precipitate was washed with ether (3 x 2 mL), and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a triol product that was used without further purification.

The resulting crude triol was dissolved in THF (0.1 M) and benzoyl chloride (1 equiv) and pyridine (1.1 equiv) were added. The resulting solution was stirred at room

temperature until the starting material had been completely consumed as judged by TLC analysis. The reaction mixture was quenched with H_2O (1 mL/mmol substrate) and extracted with CH_2Cl_2. The organic layer was washed with saturated KH_2PO_4 (1 mL/mmol substrate), $NaHCO_3$ (1 mL/mmol substrate), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel. The enantiopurity was subsequently determined by chiral HPLC analysis.

For purposes of comparison, racemic dihydroxybenzoates were prepared from the corresponding *O*-allyl methyl esters,[5] using a procedure identical to that described above.

General Procedure D: Method to Assess Enantiopurity of Products Derived from *O*-allyl Glycolate Ester via Reduction to Triol and Conversion to Mosher Ester. In order to assess the enantiomeric purity of the products formed in the tandem Wittig-rearrangement aldol reactions, the esters were converted to the corresponding Mosher esters using the following procedure. The glycolate ester (1.0 equiv) was dissolved in THF (0.1 M) and cooled to 0 °C. A solution of $LiAlH_4$ (2 equiv/mmol substrate, 1.0 M in THF) was added, and the reaction was allowed to warm to rt and stirred until completion. The reaction mixture was cooled to 0 °C and quenched with H_2O (1 mL/mmol substrate). The crude residue was diluted with Et_2O (2 mL/mmol substrate), 10 M NaOH was added (1 mL/mmol substrate), then H_2O (0.5 mL/mmol substrate) was added. The phases were separated, the inorganic precipitate was washed with ether (3 x 2 mL), and the combined

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

A solution of the triol in CH_2Cl_2 (0.2 M), DCC (1.1 equiv), DMAP (0.2 equiv) and (–)-(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (1.1 equiv) were combined and stirred at room temperature until the triol had been completely consumed as judged by TLC analysis. The reaction mixture was diluted with CH_2Cl_2, filtered through a cotton plug, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel. The enantiopurity was subsequently determined by ^{19}F NMR analysis.

For purposes of comparison, racemic dihydroxy Mosher esters were prepared from the corresponding *O*-allyl methyl esters,[5] using a procedure identical to that described above.

(–)-(1*R*,2*S*,5*R*,2'*R*,3'*S*)-2-Isopropyl-5-methylcyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-phenylpropanoate (VI-25). The reaction of (–)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-2'-(benzyloxy)acetate[3] (**VI-22**) (74 mg, 0.24 mmol) with benzaldehyde (37 μL, 0.37 mmol) was conducted according to General Procedure A using triethylamine as base to afford 62 mg (62%) of the title compound as a colorless oil. ^1H NMR analysis of the crude reaction mixture indicated that the product was formed as a 5:1 mixture of diastereomers; the isolated product was obtained with 9:1 dr following purification. $[\alpha]^{23}_D$ –31.2 (*c* 0.10, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2 H), 7.40–7.32 (m, 3 H), 7.21–7.15 (m, 5 H), 4.93–4.91 (m, 1 H), 4.70–4.64 (m, 1 H), 3.47 (s, 1 H), 3.26 (s, 1 H), 2.99–2.96 (m, 1 H), 2.82 (d, *J* = 8.5 Hz, 1 H), 2.52 (d, *J* =

13.5 Hz, 1 H), 1.76–1.73 (m, 1 H), 1.68–1.65 (m, 4 H), 1.43–1.38 (m, 2 H), 1.02–0.97 (m, 1 H), 0.90–0.81 (m, 8 H), 0.64 (d, J = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 139.2, 135.3, 130.3, 128.3, 128.2, 128.1, 128.0, 126.8, 80.9, 78.2, 46.9, 41.8, 40.8, 34.1, 31.4, 25.5, 22.9, 21.9, 20.9, 15.8; IR (film) 3498, 2956, 1725 cm^{-1}. MS (ESI) 433.2358 (433.2355 calcd for $C_{26}H_{34}O_4$, M + Na^+).

(–)-(1*R*,2*S*,5*R*,2'*R*,3'*S*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-phenylpropanoate (VI-26). The reaction of (+)-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-2'-(benzyloxy)acetate (**VI-23**) (90 mg, 0.24 mmol) with benzaldehyde (36 μL, 0.35 mmol) was conducted according to General Procedure A using triethylamine as base to afford 31 mg (27%) of the title compound as a colorless oil. ^{1}H NMR analysis of the crude reaction mixture indicated that the product was formed as a 3:1 mixture of diastereomers; the isolated product was obtained with 11:1 dr following purification. $[\alpha]^{23}_D$ –21.4 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 7 H), 7.20–7.16 (m, 8 H), 4.72–4.67 (m, 1 H), 4.40 (d, J = 8.0 Hz, 1 H), 2.94 (s, 1 H), 2.82 (d, J = 13.5 Hz, 1 H), 2.69 (d, J = 7.5 Hz, 1 H), 2.46 (d, J = 13.5 Hz, 1 H), 2.10–2.04 (m, 1 H), 1.65–1.61 (m, 1 H), 1.51–1.47 (m, 2 H), 1.41–1.33 (m, 2 H), 1.30–1.15 (m, 4 H), 1.07 (s, 3 H), 1.03 (s, 3 H), 0.89–0.88 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.5, 139.9, 135.4, 130.7, 128.1, 128.0, 127.9, 127.8, 126.8, 125.4, 125.3, 125.2, 80.8, 78.6, 49.3, 41.5, 39.6, 34.5, 31.3, 27.0, 26.9, 26.2, 21.6 (one carbon signal is absent due to incidental equivalence); IR (film) 3501, 2957, 1723 cm^{-1}. MS (ESI) 509.2670 (509.2668 calcd for $C_{32}H_{38}O_4$, M + Na^+).

(–)-(1*S*,2*R*,4*S*,2'*R*,3'*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl-2'-benzyl-2',3'-dihydroxy-3-phenylpropanoate (VI-27). The reaction of (–)-(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-2'-(benzyloxy)acetate (**VI-21**) (78 mg, 0.26 mmol) with benzaldehyde (39 μL, 0.39 mmol) was conducted according to General Procedure A using triethylamine as base to afford 87 mg (82%) of the title compound as a colorless oil. ^{1}H NMR analysis of the crude reaction mixture indicated that the product was formed as a 3:1 mixture of diastereomers; the isolated product was obtained with 4:1 dr following purification. $[\alpha]^{23}_D$ –21.4 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.48 (m, 2 H), 7.41–7.34 (m, 4 H), 7.21–7.15 (m, 4 H), 4.92–4.90 (m, 1 H), 4.86–4.82 (m, 1 H), 3.50 (s, 1 H), 3.01–2.98 (m, 1 H), 2.84–2.82 (m, 1 H), 2.27–2.19 (m, 1 H), 1.95–1.88 (m, 1 H), 1.82–1.74 (m, 1 H), 1.68–1.63 (m, 1 H), 1.41–1.33 (m, 1 H), 1.30–1.23 (m, 1 H), 0.87–0.85 (m, 7 H), 0.84–0.82 (m, 1 H), 0.79 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 139.1, 135.4, 130.1, 128.4, 128.2, 128.0, 126.9, 82.3, 80.8, 78.4, 49.0, 47.8, 44.8, 41.8, 35.8, 27.9, 27.3, 19.6, 18.8, 13.3; IR (film) 3381, 2954, 1724 cm^{-1}. MS (ESI) 431.2190 (431.2198 calcd for $C_{26}H_{32}O_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-phenylpropanoate (VI-28). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VI-24**) (50 mg, 0.16 mmol) with benzaldehyde (23 μL, 0.23 mmol) was conducted according to General Procedure A using triethylamine as base to afford 59

mg (88%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –25.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 7 H), 7.23–7.18 (m, 3 H), 7.16–7.13 (m, 5 H), 5.00–4.95 (m, 1 H), 4.15 (d, *J* = 7.0 Hz, 1 H), 3.26 (s, 1 H), 2.86–2.81 (m, 1 H), 2.77 (d, *J* = 13.5 Hz, 1 H), 2.38 (d, *J* = 13.5 Hz, 1 H), 2.01–1.94 (m, 2 H), 1.87–1.81 (m, 2 H), 1.65–1.56 (m, 1 H), 1.48–1.36 (m, 3 H), 1.09 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 143.4, 138.8, 135.4, 130.2, 128.7, 128.1, 128.0, 127.9, 127.8, 127.7, 127.1, 126.7, 80.6, 79.2, 77.7, 50.2, 41.1, 33.8, 32.2, 26.7, 24.7; IR (film) 3499, 2934, 1731 cm^{-1}. MS (ESI) 453.2050 (453.2042 calcd for $C_{28}H_{30}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding triol (**VI-29**) through reduction with $LiAlH_4$ using General Procedure B. This procedure afforded 19 mg (59%) of **VI-29**. The enantiopurity of the triol was determined to be 89% ee by chiral HPLC analysis (chiracel OD-H 0.46 cm x 15 cm, 10% isopropanol/ hexanes, 0.2 mL/min, RT= 33.1 and 41.3 min).

(+)-(1*S*,2*S*)-2-Benzyl-1-phenylpropane-1,2,3-triol (VI-29). $[\alpha]^{23}_D$ +8.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2 H), 7.41–7.38 (m, 2 H), 7.36–7.32 (m, 1 H), 7.29–7.21 (m, 3 H), 7.19–7.17 (m, 2 H), 4.91 (d, *J* = 3.5 Hz, 1 H), 3.57–3.49 (m, 2 H), 2.91 (d, *J* = 14.0 Hz, 1 H), 2.80 (d, *J* = 3.5 Hz, 1 H), 2.56–2.52 (m, 2 H), 1.99–1.96 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 136.3, 130.6, 128.3, 128.1,

127.6, 126.6, 77.4, 75.6, 65.4, 38.8 (one carbon signal is absent due to incidental equivalence); IR (film) 3413, 2930 cm^{-1}. MS (ESI) 281.1148 (281.1154 calcd for $C_{16}H_{18}O_3$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-dodecanoate (VI-31). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VI-24**) (68 mg, 0.21 mmol) with decanal (59 μL, 0.31 mmol) was conducted according to General Procedure A using triethylamine as base to afford 92 mg (91%) of the title compound as a white solid, m.p. 103–105 °C. The diastereoselectivity of the transformation could not be determined prior to purification through ^1H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –18.0 (*c* 0.10, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 2 H), 7.28–7.17 (m, 8 H), 4.94–4.89 (m, 1 H), 3.12 (s, 1 H), 3.10–3.06 (m, 1 H), 2.94 (d, *J* = 14.0 Hz, 1 H), 2.87 (d, *J* = 13.5 Hz, 1 H), 2.80–2.74 (m, 1 H), 1.99–1.95 (m, 2 H), 1.86–1.78 (m, 2 H), 1.57–1.52 (m, 2 H), 1.47–1.32 (m, 4 H), 1.31–1.21 (m, 8 H), 1.20–1.10 (m, 3 H), 1.00–0.96 (m, 1 H), 0.91–0.88 (m, 4 H), 0.55–0.51 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 143.2, 135.8, 130.4, 129.0, 127.9, 127.4, 127.2, 126.7, 80.2, 79.3, 75.5, 50.0, 40.7, 34.1, 32.2, 31.9, 30.4, 29.6, 29.5, 29.3, 26.2, 25.6, 24.6, 22.7, 14.1; IR (film) 3378, 2921, 1726 cm^{-1}. MS (ESI) 503.3130 (503.3137 calcd for $C_{31}H_{44}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding triol (**VI-S1**) through reduction with $LiAlH_4$ using General Procedure B. This procedure afforded 23 mg (47%) of **VI-S1**. The enantiopurity of the triol was

determined to be 95% ee by chiral HPLC analysis (chiracel AD 0.46 cm x 25 cm, 5% isopropanol/ hexanes, 0.2 mL/min, RT= 58.6 and 80.7 min).

(–)-(2*S*,3*S*)-2-Benzyldodecane-1,2,3-triol (VI-S1). $[\alpha]^{23}_{D}$ –1.7 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2 H), 7.27–7.24 (m, 3 H), 3.71–3.69 (m, 1 H), 3.57–3.56 (m, 2 H), 2.99 (d, *J* = 14.0 Hz, 1 H), 2.69 (d, *J* = 14.0 Hz, 1 H), 2.46 (s, 1 H), 2.18–2.17 (m, 1 H), 2.01–1.99 (m, 1 H), 1.70–1.52 (m, 4 H), 1.38–1.25 (m, 12 H), 0.89 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 130.5, 128.5, 126.8, 75.8, 75.2, 66.2, 39.2, 31.9, 31.0, 29.7, 29.6, 29.5, 29.3, 26.5, 22.7, 14.1; IR (film) 3400, 2923 cm^{-1}. MS (ESI) 331.2246 (331.2249 calcd for $C_{19}H_{32}O_3$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'S)-2-Phenylcyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-cyclohexylpropanoate (VI-32). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VI-24**) (65 mg, 0.20 mmol) with cyclohexanecarboxaldehyde (36 μL, 0.30 mmol) was conducted according to General Procedure A using triethylamine as base to afford 69 mg (79%) of the title compound as a white solid, m.p. 140–142 °C. The diastereoselectivity of the transformation could not be determined prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_{D}$ –25.7 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 2 H), 7.25–7.17 (m, 8 H), 4.88–4.81 (m, 1 H), 3.15 (s, 1 H), 2.98–2.97 (m, 1 H), 2.94 (d, *J* = 13.0 Hz, 1 H), 2.82 (d, *J* = 13.5 Hz, 1 H), 2.77–2.72 (m, 1 H), 1.96–1.94 (m, 2 H),

1.84–1.78 (m, 1 H), 1.70–1.67 (m, 1 H), 1.60–1.47 (m, 4 H), 1.45–1.32 (m, 5 H), 1.26–1.00 (m, 5 H), 0.72 (d, J = 9.5 Hz, 1 H), 0.68–0.63 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 143.3, 135.7, 130.4, 128.8, 127.9, 127.5, 127.0, 126.7, 80.6, 79.4, 78.6, 50.1, 41.4, 38.7, 33.8, 32.1, 31.4, 26.6, 26.1, 26.0, 25.8, 25.7, 24.6; IR (film) 3504, 2929, 1728 cm^{-1}. MS (ESI) 459.2517 (459.2511 calcd for $C_{28}H_{36}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding triol (**VI-S2**) through reduction with $LiAlH_4$ using General Procedure B. This procedure afforded 13 mg (53%) of **VI-S2**. The enantiopurity of the triol was determined to be 91% ee by chiral HPLC analysis (chiracel OD-H 0.46 cm x 15 cm, 5% isopropanol/ hexanes, 0.2 mL/min, RT= 29.2 and 33.8 min).

(+)-(1*S*,2*S*)-2-Benzyl-1-cyclohexylpropane-1,2,3-triol (VI-S2). $[\alpha]^{23}_D$ +4.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2 H), 7.28–7.24 (m, 3 H), 3.52–3.50 (m, 2 H), 3.48–3.46 (m, 1 H), 3.00 (d, J = 9.0 Hz, 1 H), 2.70–2.67 (m, 2 H), 2.51–2.49 (m, 1 H), 2.08–2.06 (m, 1 H), 1.98–1.97 (m, 1 H), 1.81–1.73 (m, 2 H), 1.67–1.62 (m, 1 H), 1.61–1.59 (m, 1 H), 1.47–1.36 (m, 1 H), 1.34–1.15 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 130.3, 128.5, 126.7, 78.8, 75.6, 67.4, 40.3, 39.2, 31.7, 26.8, 26.7, 26.3, 26.2; IR (film) 3436, 2924 cm^{-1}. MS (ESI) 287.1623 (287.1623 calcd for $C_{16}H_{24}O_3$, M + Na^+).

(–)-(*E*)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-2',3'-dihydroxy-5'-phenylpent-4'-enoate (VI-33). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-

(benzyloxy)acetate (**VI-24**) (51 mg, 0.16 mmol) with *trans*-cinnamaldehyde (30 μL, 0.24 mmol) was conducted according to General Procedure A using triethylamine as base to afford 59 mg (81%) of the title compound as a white solid, m.p. 129–131 °C. The diastereoselectivity of the transformation could not be determined prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_D$ –31.7 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 4 H), 7.31–7.29 (m, 4 H), 7.28–7.17 (m, 7 H), 6.37 (d, *J* = 15.5 Hz, 1 H), 6.00–5.95 (m, 1 H), 4.97–4.88 (m, 1 H), 3.77–3.73 (m, 1 H), 3.21 (s, 1 H), 2.88–2.77 (m, 3 H), 2.01–1.94 (m, 2 H), 1.87–1.79 (m, 2 H), 1.61–1.53 (m, 1 H), 1.48–1.35 (m, 3 H), 0.94 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 143.3, 136.4, 135.5, 133.6, 130.3, 128.9, 128.5, 128.3, 127.9, 127.8, 127.6, 127.2, 126.8, 126.7, 126.1, 80.3, 79.3, 50.2, 40.8, 34.0, 32.2, 25.7, 24.7; IR (film) 3499, 2935, 1732 cm^{-1}. MS (ESI) 479.2191 (479.2198 calcd for $C_{30}H_{32}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding triol (**VI-S3**) through reduction with $LiAlH_4$ using General Procedure B. This procedure afforded 17 mg (52%) of **VI-S3**. The enantiopurity of the triol was determined to be 93% ee by chiral HPLC analysis (chiracel AD 0.46 cm x 25 cm, 10% isopropanol/ hexanes, 0.2 mL/min, RT= 16.2 and 24.5 min).

(–)-(*E*)-(2*S*,3*S*)-2-benzyl-5-phenylpent-4-ene-1,2,3-triol (VI-S3). $[\alpha]^{23}_D$ –9.7 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.43 (m, 2 H), 7.38–7.30 (m, 5 H), 7.29–

7.21 (m, 3 H), 6.72 (m, 1 H), 6.47–6.41 (m, 1 H), 4.41 (d, *J* = 9.0 Hz, 1 H), 3.66–3.60 (m, 2 H), 3.02 (d, *J* = 17.5 Hz, 1 H), 2.74 (d, *J* = 17.5 Hz, 1 H), 2.63 (s, 1 H), 2.51 (s, 1 H), 2.20 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 136.2, 133.6, 130.6, 128.7, 128.5, 128.4, 128.0, 127.0, 126.8, 126.7, 75.4, 65.9, 40.0; IR (film) 3401, 2927 cm^{-1}. MS (ESI) 307.1305 (307.1310 calcd for $C_{18}H_{20}O_3$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2',3'-dihydroxy-3'-phenylpent-4-enoate (VI-34). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2-(allyloxy)acetate (**VI-30**) (54 mg, 0.20 mmol) with benzaldehyde (40 μL, 0.39 mmol, 2.0 equiv) was conducted according to General Procedure A using diisopropylethylamine as base to afford 65 mg (87%) of the title compound as a white solid, m.p. 138–140 °C. The diastereoselectivity of the transformation could not be determined prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –21.4 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 4 H), 7.27–7.26 (m, 3 H), 7.22–7.19 (m, 1 H), 7.18–7.14 (m, 2 H), 5.56–5.47 (m, 1 H), 5.10–5.05 (m, 1 H), 5.00–4.97 (m, 2 H), 4.17 (d, *J* = 6.5 Hz, 1 H), 3.22 (s, 1 H), 2.82–2.76 (m, 1 H), 2.31–2.26 (m, 1 H), 2.20–2.17 (m, 1 H), 2.01–1.98 (m, 1 H), 1.92–1.88 (m, 1 H), 1.85–1.81 (m, 2 H), 1.67–1.59 (m, 1 H), 1.58–1.50 (m, 1 H), 1.49–1.35 (m, 2 H), 1.18 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 143.3, 138.6, 131.6, 128.7, 128.0, 127.9, 127.8, 127.6, 127.0, 118.9, 80.6, 79.9, 78.7, 50.1, 40.0, 33.6, 32.3, 25.7, 24.6; IR (film) 3450, 2934, 1722 cm^{-1}. MS (ESI) 403.1883 (403.1885 calcd for $C_{24}H_{28}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding triol (**VI-S4**) through reduction with $LiAlH_4$ using General Procedure B. This procedure afforded 17 mg (52%) of **VI-S4**. The enantiopurity of the triol was determined to be 90% ee by chiral HPLC analysis (chiracel AD 0.46 cm x 25 cm, 10% isopropanol/ hexanes, 0.8 mL/min, RT= 15.4 and 20.1 min).

(+)-(1*S*,2*S*)-2-Allyl-1-phenylpropane-1,2,3-triol (VI-S4). $[\alpha]^{23}_{D}$ +5.3 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.44 (m, 2 H), 7.38–7.35 (m, 2 H), 7.34–7.30 (m, 1 H), 5.86–5.78 (m, 1 H), 5.12–5.10 (m, 1 H), 5.08–5.03 (m, 1 H), 4.86 (s, 1 H), 3.64–3.63 (m, 2 H), 2.80–2.78 (m, 2 H), 2.33–2.28 (m, 2 H), 2.00–1.96 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 133.0, 128.2, 128.1, 127.6, 119.0, 77.5, 75.3, 66.3, 37.8; IR (film) 3401, 2927 cm^{-1}. MS (ESI) 231.0994 (231.0997 calcd for $C_{12}H_{16}O_3$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-allyl-2',3'-dihydroxydodecanoate (VI-35). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VI-30**) (41 mg, 0.15 mmol) with decanal (56 μL, 0.30 mmol, 2.0 equiv) was conducted according to General Procedure A using diisopropylethylamine as base to afford 51 mg (79%) of the title compound as a clear oil. The diastereoselectivity of the transformation could not be determined prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with 8:1 dr following purification. $[\alpha]^{23}_{D}$ –12.2 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 2 H), 7.26–7.23 (m, 3 H), 5.67–5.58 (m, 1 H), 5.09–5.00

(m, 2 H), 5.02–4.98 (m, 1 H), 3.10 (s, 1 H), 3.09–3.06 (m, 1 H), 2.75–2.70 (m, 1 H), 2.45–2.41 (m, 1 H), 2.33–2.27 (m, 1 H), 2.20–2.17 (m, 1 H), 1.98–1.96 (m, 1 H), 1.90–1.87 (m, 1 H), 1.83–1.80 (m, 1 H), 1.62–1.48 (m, 3 H), 1.44–1.35 (m, 2 H), 1.33–1.20 (m, 10 H), 1.18–1.07 (m, 3 H), 1.04–0.96 (m, 1 H), 0.91–0.86 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 143.2, 132.0, 128.9, 127.3, 127.1, 118.9, 80.6, 79.6, 78.8, 75.3, 50.0, 39.5, 33.9, 32.2, 31.9, 31.8, 30.2, 29.6, 29.3, 26.0, 25.6, 24.6, 22.7, 14.1; IR (film) 3514, 2926, 1727 cm^{-1}. MS (ESI) 453.2993 (453.2981 calcd for $C_{27}H_{42}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VI-41**) using General Procedure D. This procedure afforded 19 mg (67%) of **VI-41**. The enantiopurity was determined to be 75% ee by ^{19}F NMR analysis.

(–)-(1*S*,2'*S*,3'*S*)-2'-Allyl-2',3'-dihydroxydodecyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VI-41). $[\alpha]^{23}_D$ –22.3 (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.52 (m, 2 H), 7.42–7.26 (m, 3 H), 5.86–5.74 (m, 1 H), 5.17–5.07 (m, 2 H), 4.42–4.33 (m, 1 H), 4.30–4.23 (m, 1 H), 3.54 (s, 3 H), 3.47–3.44 (m, 1 H), 2.43–2.36 (m, 1 H), 2.28–2.27 (m, 1 H), 2.18–2.12 (m, 1 H), 1.99–1.94 (m, 1 H), 1.55–1.30 (m, 3 H), 1.26–1.19 (m, 13 H), 0.88 (t, *J* = 6.4 Hz, 3 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –72.6; IR (film) 3401, 2925, 1752 cm^{-1}. MS (ESI) 497.2473 (497.2491 calcd for $C_{25}H_{37}F_3O_3$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'3'-dihydroxy-3'-dimethylpent-4'-enoate (VI-36). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VI-30**) (47 mg, 0.17 mmol) with isobutyraldehyde (31 μL, 0.34 mmol, 2.0 equiv) was conducted according to General Procedure A using diisopropylethylamine as base to afford 45 mg (76%) of the title compound as a clear oil. The diastereoselectivity of the transformation could not be determined prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –10.5 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2 H), 7.25–7.23 (m, 3 H), 5.61–5.53 (m, 1 H), 5.08–4.96 (m, 2 H), 4.95–4.94 (m, 1 H), 3.06 (s, 1 H), 2.99 (dd, *J* = 3.0, 9.0 Hz, 1 H), 2.74–2.69 (m, 1 H), 2.37–2.28 (m, 2 H), 2.21–2.18 (m, 1 H), 1.98–1.95 (m, 1 H), 1.90–1.86 (m, 1 H), 1.82–1.80 (m, 1 H), 1.64–1.58 (m, 2 H), 1.53–1.48 (m, 1 H), 1.43–1.34 (m, 2 H), 0.78 (d, *J* = 7.0 Hz, 3 H), 0.74 (d, *J* = 9.5 Hz, 1 H), 0.66 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 143.2, 131.8, 128.8, 127.5, 127.0, 119.0, 80.1, 78.8, 78.3, 50.0, 40.2, 33.7, 32.2, 28.7, 25.7, 24.6, 21.5, 16.0; IR (film) 3514, 2935, 1731 cm^{-1}. MS (ESI) 369.2033 (369.2042 calcd for $C_{21}H_{30}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VI-S5**) using General Procedure D. This procedure afforded 6 mg (43%) of **VI-S5**. The enantiopurity was determined to be 89% ee by ^{19}F NMR analysis.

(–)-(1*S*,2'*S*,3'*S*)-2'-Allyl-2',3'-dihydroxy-3'-dimethyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VI-S5). $[\alpha]^{23}_{D}$ –15.1 (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.71–7.68 (m, 1 H), 7.58–7.56 (m, 1 H), 7.52–7.44 (m, 3 H), 5.95–5.85 (m, 1 H), 5.26–5.25 (m, 1 H), 5.12–5.01 (m, 2 H), 4.38–4.30 (m, 2 H), 3.61 (s, 3 H), 2.82–2.78 (m, 1 H), 2.49–2.34 (m, 1 H), 2.32–2.13 (m, 1 H), 0.88–0.81 (m, 6 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –72.5; IR (film) 3436, 2957, 1750 cm^{-1}. MS (ESI) 413.1542 (413.1552 calcd for $C_{19}H_{23}F_3O_6$, M + Na^+).

(–)-(*E*)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-allyl-2',3'-dihydroxy-5'-phenylpent-4'-enoate (VI-37). The reaction of (-)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VI-30**) (47 mg, 0.17 mmol) with cinnamaldehyde (43 μL, 0.34 mmol, 2.0 equiv) was conducted according to General Procedure A using diisopropylethylamine as base to afford 59 mg (86%) of the title compound as a clear oil. The diastereoselectivity of the transformation could not be determined prior to purification prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_{D}$ –39.6 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 5 H), 7.35–7.32 (m, 3 H), 7.30–7.28 (m, 2 H), 6.42 (d, *J* = 15.5 Hz, 1 H), 6.01 (dd, *J* = 7.5, 16.0 Hz, 1 H), 5.67–5.60 (m, 1 H), 5.13–5.07 (m, 3 H), 3.84–3.81 (m, 1 H), 3.26 (s, 1 H), 2.85–2.79 (m, 1 H), 2.42–2.37 (m, 1 H), 2.32–2.28 (m, 1 H), 2.27–2.23 (m, 1 H), 2.06–2.03 (m, 1 H), 1.96–1.93 (m, 1 H), 1.89–1.85 (m, 1 H), 1.67–1.56 (m, 2 H), 1.55–1.40 (m, 2 H), 1.06 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 143.2, 136.3, 133.5, 131.6, 128.8, 128.5, 127.9, 127.5, 127.1, 126.7, 125.9, 119.0, 79.7, 78.7, 50.0, 39.7, 33.9, 32.3, 25.7, 24.6 (one carbon signal is absent due to incidental

equivalence); IR (film) 3498, 2934, 1731 cm^{-1}. MS (ESI) 429.2036 (429.2042 calcd for $C_{26}H_{30}O_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding diol (**VI-S6**) through reduction with $LiAlH_4$ followed by treatment with benzoyl chloride using General Procedure C. This procedure afforded 6 mg (32%) of **VI-S6**. The enantiopurity was determined to be 95% ee by chiral HPLC analysis (chiracel AD 0.46 cm x 25 cm, 5% isopropanol/ hexanes, 0.2 mL/min, RT= 58.6 and 80.7 min).

(–)-(*E*)-(2*S*,3*S*)-2-Allyl-2,3-dihydroxy-5-phenylpent-4-enyl benzoate (VI-S6). $[\alpha]^{23}_D$ – 15.7 (*c* 0.10, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2 H), 7.51–7.41 (m, 6 H), 7.39–7.25 (m, 2 H), 6.81 (d, *J* = 16.0 Hz, 1 H), 6.44 (dd, *J* = 8.0, 8.5 Hz, 1 H), 6.02–5.96 (m, 1 H), 5.86–5.84 (m, 1 H), 5.25–5.17 (m, 2 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 11.5 Hz, 1 H), 2.71 (s, 1 H), 2.63–2.59 (m, 2 H), 2.52–2.48 (m, 1 H); IR (film) 3402, 2921, 1719 cm^{-1}. MS (ESI) 361.1420 (361.1416 calcd for $C_{21}H_{22}O_4$, M + Na^+).

(±)-(2*S*,3*R*,4*S*)-Methyl-2-allyl-2,3-dihydroxy-4-methylhexanoate (VI-44). The reaction of methyl 2-(allyloxy)acetate (**VI-48**) (131 mg, 1.0 mmol) with (*S*)-2-methylbutanal[11] (1.5 mL, 2.0 mmol, 2.0 equiv) was conducted according to General Procedure A using diisopropylethylamine as base to afford 139 mg (64%) of the title

compound as a colorless oil. ^{1}H NMR analysis of the crude reaction mixture indicated that the product was formed as a 2:1 mixture of diastereomers; the isolated product was obtained with 2:1 dr following purification. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79–5.64 (m, 1 H), 5.16–5.07 (m, 2 H), 3.84–3.76 (m, 3.66 H), 3.72–3.67 (m, 0.33 H), 3.52–3.48 (m, 1 H), 2.48–2.39 (m, 2 H), 2.18 (dd, *J*= 3.9, 10.9 Hz, 1 H), 1.82–1.66 (m, 2 H), 1.52–1.30 (m, 2 H), 1.16–1.07 (m, 0.66 H), 1.03 (d, *J*= 1.33 Hz, 1 H), 0.96–0.87 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 131.8, 119.3, 80.9, 78.6, 76.0, 53.0, 40.4, 35.8, 35.1, 28.3, 22.2, 17.5, 12.7, 11.9; IR (film) 3501, 2961, 1738 cm^{-1}. MS (ESI) 239.1268 (239.1259 calcd for $C_{11}H_{20}O_4$, M + Na^+).

(+)-(1*S*,2*R*,2'*S*,3'*R*,4'*S*)-2-Phenylcyclohexyl-2'-allyl-2',3'-dihydroxy-4'-methylhexanoate (VI-45). The reaction of (+)-(1*S*,2*R*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VI-50**) (98 mg, 0.36 mmol) with (*S*)-2-methylbutanal (0.65 mL, 0.71 mmol, 2.0 equiv) was conducted according to General Procedure A using diisopropylethylamine as base to afford 104 mg (81%) of the title compound as a white solid, mp 59–61 °C. ^{1}H NMR analysis of the crude reaction mixture indicated that the product was formed as a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ +17.8 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2 H), 7.25–7.22 (m, 3 H), 5.61–5.52 (m, 1 H), 5.08–4.96 (m, 3 H), 3.16 (dd, *J* = 2.5, 9.0, Hz, 1 H), 3.12 (s, 1 H), 2.75–2.69 (m, 1 H), 2.30–2.29 (m, 2 H), 2.20–2.17 (m, 1 H), 1.98–1.95 (m, 1 H), 1.88–1.86 (m, 1 H), 1.82–1.79 (m, 1 H), 1.63–1.49 (m, 2 H), 1.48–1.32 (m, 4 H), 1.18–1.08 (m, 2 H), 0.80 (t, *J* = 7.5 Hz,

3 H), 0.67 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 143.2, 131.8, 128.7, 127.5, 127.0, 119.0, 80.3, 78.7, 76.2, 50.0, 40.1, 35.0, 33.8, 32.2, 28.2, 25.7, 24.6, 12.9, 11.8; IR (film) 3512, 2935, 1735 cm^{-1}. MS (ESI) 383.2183 (383.2198 calcd for $C_{22}H_{32}O_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*,4'*S*)-2-Phenylcyclohexyl-2'-allyl-2',3'-dihydroxy-4'-methylhexanoate (VI-52). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VI-30**) (42 mg, 0.15 mmol), and (*S*)-2-methylbutanal[6] (0.31 mL, 0.60 mmol, 2.0 equiv) was conducted according to general procedure A using diisopropylethylamine as base to afford 44 mg (81%) of the title compound as a yellow oil. ^{1}H NMR analysis of the crude reaction mixture indicated that the product was formed at a >20:1 mixture of diastereomers; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –13.6 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2 H), 7.25–7.22 (m, 3 H), 5.61–4.96 (m, 2 H), 4.99–4.94 (m, 1 H), 3.11 (s, 1 H), 3.03–3.00 (m, 1 H), 2.74–2.69 (m, 1 H), 2.40–2.29 (m, 2 H), 2.21–2.18 (m, 1 H), 1.98–1.94 (m, 1 H), 1.88–1.86 (m, 1 H), 1.82–1.79 (m, 1 H), 1.63–1.47 (m, 2 H), 1.46–1.32 (m, 4 H), 0.78 (d, J = 7.0 Hz, 3 H), 0.79–0.77 (m, 3 H), 0.76–0.72 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 131.9, 128.9, 127.5, 127.0, 119.0, 80.1, 78.9, 78.6, 50.0, 40.4, 35.6, 33.8, 32.2, 25.7, 24.6, 22.4, 18.8, 17.3, 11.5; IR (film) 3504, 2935, 1731 cm^{-1}. MS (ESI) 383.2198 (383.2198 calcd for $C_{22}H_{32}O_4$, M + Na^+).

Hydrolysis of 2-phenylcyclohexyl ester VI-28

Ester **(VI-28)** was converted to carboxylic acid **(VI-42)** via protection of the 1,2-diol as an acetonide followed by hydrolysis using NaOMe in wet ethanol at 80 °C.

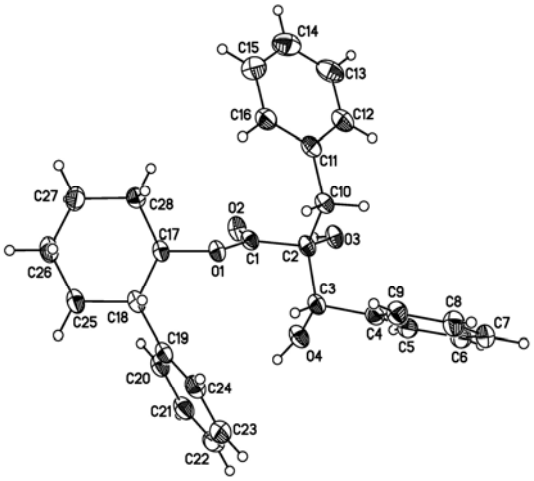
(+)-(4*R*,5*S*)-4-Benzyl-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylic acid (VI-42). A flame-dried round-bottom flask was charged with ester (**VI-28**) (86 mg, 0.20 mmol), camphorsulfonic acid (5.0 mg, 0.02 mmol) and dry acetone (2.0 mL, 0.1 M). Neat 2,2-dimethoxypropane (0.27 mL, 2.21 mmol) was added dropwise, and the resulting solution was stirred at room temperature until consumption of the starting material was complete 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 85 mg (90%) of (1*R*,2*S*,2'*R*,3'*S*)-(2-phenylcyclohexyl)-4'-benzyl-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 8 H), 7.20–7.10 (m, 5 H), 7.03–7.01 (m, 2 H), 5.36–5.31 (m, 1 H), 4.69 (s, 1 H), 2.90–2.85 (m, 1 H), 2.42 (d, *J* = 14.0 Hz, 1 H), 2.15 (d, *J* = 13.5 Hz, 1 H), 2.01–1.93 (m, 2 H), 1.86–1.84 (m, 1 H), 1.79–1.76 (m, 1 H), 1.64 (s, 3 H), 1.52–1.38 (m, 4 H), 1.18 (s, 3 H).

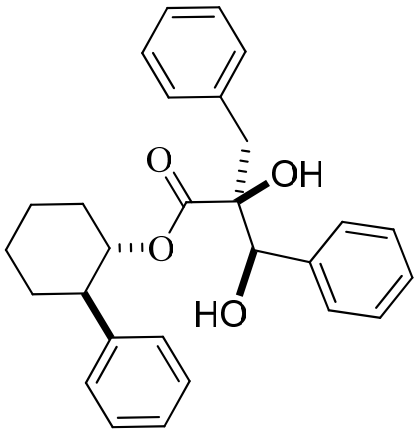
A portion of (1*R*,2*S*,2'*R*,3'*S*)-2-phenylcyclohexyl-4-benzyl-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate (25 mg, 0.05 mmol) was dissolved in wet EtOH (0.5 mL). A solution of NaOMe in MeOH (0.5 mL, 2.0 mmol, 4 M) was added dropwise, and the mixture was heated to 80 °C until consumption of the starting material was complete as judged by TLC analysis. The reaction mixture was cooled to rt, 1 M HCl (0.1 mL, 0.1 mmol) was added, and the mixture was concentrated *in vacuo*. The crude residue was

extracted with Et_2O (2 x 1 mL). The layers were separated, the organic layer was discarded, and the aqueous extracts were acidified to pH 1 with 4 M HCl and extracted with CH_2Cl_2 (3 x 2 mL). The dichloromethane layers were combined, washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 16 mg (97%) of the title compound as an orange oil. $[\alpha]^{23}_D$ +54.5 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.61 (m, 2 H), 7.45–7.37 (m, 3 H), 7.18–7.15 (m, 3 H), 7.11–7.08 (m, 2 H), 6.28 (s, br, 1 H), 5.43 (s, 1 H), 2.55 (d, *J* = 13.6 Hz, 1 H), 2.46 (d, *J* = 13.6 Hz, 1 H), 1.79 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 135.8, 135.0, 130.0, 128.4, 128.1, 127.3, 126.8, 109.9, 86.9, 82.0, 53.4, 41.0, 28.0, 25.2; IR (film) 3386, 2918, 1721 cm^{-1}. MS (ESI) 335.1257 (335.1259 calcd for $C_{29}H_{20}O_4$, M + Na^+).

Assignment of Stereochemistry

Stereochemical Assignment of (VI-28). Stereochemical assignment of **VI-28** was accomplished by single-crystal x-ray analysis of product that had been recrystallized from dichloromethane/hexanes. The ORTEP of **VI-28** indicated this material had the ***1R,2S,2'R,3'S*** stereochemical configuration.





Stereochemical Assignment of VI-51. 2-Phenylcyclohexyl ester **(VI-45)** was converted to known methyl ester **(VI-51)** using the sequence shown below. The relative stereochemistry of (**VI-51**) was confirmed based on comparison of NMR data to that previously reported in the literature, and the absolute stereochemistry was confirmed by optical rotation.

(–)-(3'S,4*S*,5*S*)-Methyl-4-allyl-5-sec-butyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (VI-51). A flame-dried flask was charged with 2-phenylcyclohexyl ester **VI-45** (360 mg, 1.0 mmol), camphorsulfonic acid (23 mg, 0.01 mmol) and dry acetone (10 mL). Neat 2,2-dimethoxypropane (1.35 mL, 11 mmol) was added dropwise, and the resulting mixture was stirred at rt until consumption of the starting material was complete 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 340 mg (85%) of (1*S*,2*R*,3'*S*,4'*S*,5'*S*)-2-phenylcyclohexyl-4'-allyl-5'-sec-butyl-2',2'-dimethyl-1,3-dioxolane-4-carboxylate. $[\alpha]^{23}_{D}$ +5.8 (*c* 0.10, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 3 H), 7.19–7.15 (m, 2 H), 5.68–5.58 (m, 1 H), 5.16–5.10 (m, 1 H), 5.02–4.98 (m, 2 H), 3.57 (d, *J*= 8.0 Hz, 1 H), 2.75–2.69 (m, 1 H), 2.39–2.34 (m, 1 H), 2.23–2.14 (m, 2 H), 1.95–1.91 (m, 1 H), 1.86–1.84 (m, 1 H), 1.78–1.75 (m, 1 H), 1.51–1.39 (m, 4 H), 1.38 (s, 3 H), 1.34–1.24 (m, 2 H), 1.23 (s, 3 H), 1.06–0.96 (m, 1 H), 0.89–0.85 (m, 3 H), 0.70 (t, *J*= 7.6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 143.0, 133.2, 128.4, 127.4, 126.5, 117.9, 108.2, 84.5, 84.4, 49.6, 37.5, 34.9, 34.0, 32.2, 27.7, 25.6, 24.9, 24.7, 15.7, 11.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2935, 1732 cm^{-1}. MS (ESI) 423.2501 (423.2511 calcd for $C_{25}H_{36}O_4$, M + Na^+).

A flame dried two-neck flask fitted with a reflux condenser was charged with (1*S*,2*R*,3'*S*,4'*S*,5'*S*)-2-phenylcyclohexyl-4'-allyl-5'-sec-butyl-2',2'-dimethyl-1,3-dioxolane-4-carboxylate (340 mg, 0.85 mmol) in wet ethanol (6 mL). Sodium methoxide in methanol (8.5 mL, 4 M) was added, and the mixture was heated to 80 °C until the starting material had been completely consumed as judged by TLC analysis (ca 4 h). The reaction mixture was cooled to rt, quenched with 1 M HCl and concentrated *in vacuo*. The crude residue was extracted with Et_2O (3 x 3 mL). The layers were separated, the organic layer was discarded, and the aqueous extracts were acidified to pH 1 with 4 M HCl and extracted with CH_2Cl_2 (3 x 3 mL). The dichloromethane layers were combined, washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford the crude carboxylic acid. A portion of the crude

product (25 mg, 0.10 mmol) was treated with trimethylsilyl diazomethane (1.5 mL, 2.0 M in Et_2O), and stirred at rt until the starting material had been completely consumed as judged by TLC analysis (ca 15 min). The reaction mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford 20.9 mg (82%) of the title compound as a colorless oil. $[\alpha]^{23}_D$ –49.5 (*c* 0.1, CH_2Cl_2); lit $[\alpha]^{23}_D$ –54.97 (*c* 3.8, CH_2Cl_2).[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89–5.81 (m, 1 H), 5.14–5.11 (m, 2 H), 3.92 (d, *J* = 9.0 Hz, 1 H), 3.75 (s, 3 H), 2.69–2.61 (m, 1 H), 2.39–2.33 (m, 1 H), 1.78–1.73 (m, 1 H), 1.57–1.51 (m, 1 H), 1.47 (s, 3 H), 1.44 (s, 3 H), 1.06–1.04 (m, 1 H), 1.03 (m, 3 H), 0.90–0.86 (m, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.2, 133.2, 118.6, 108.8, 85.0, 84.9, 52.4, 37.1, 34.0, 27.9, 25.2, 16.2, 10.9; IR (film) 1740 cm^{-1}. MS (ESI) 279.1571 (279.1572 calcd for $C_{14}H_{24}O_4$, M + Na^+).

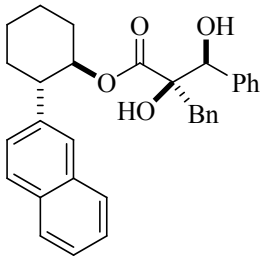
Stereochemical Analysis of Diol VI-53. Diol **VI-52** was converted to derivative (**VI-53**) via protection of the 1,2-diol as an acetonide followed by reduction of the ester with $LiAlH_4$.

(+)-(3'*S*,4*R*,5*S*)-4-Allyl-5-sec-butyl-2,2-dimethyl-1,3-dioxolan-4-ylmethanol (VI-53). A flame-dried flask was charged with diol **VI-52** (45.9 mg, 0.13 mmol, 1.0 equiv), camphorsulfonic acid (3.0 mg, 0.01 mmol), and dry acetone (1.3 mL). Neat 2,2-dimethoxypropane (170 μL, 1.4 mmol) was added dropwise, and the resulting solution was stirred at rt until the starting material had been completely consumed 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 43 mg (84%) of (1*R*,2*S*,3'*S*,4'*R*,5'*S*)-2-(phenylcyclohexyl)-4-allyl-5-sec-butyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.23 (m, 2 H), 7.19–7.13 (m, 3 H), 5.76–5.66 (m, 1 H), 5.12–5.05 (m, 1 H), 5.04–4.94 (m, 2 H), 3.58 (d, *J* = 10 Hz, 1 H), 2.75–2.68 (m, 1 H), 2.41–2.35 (m, 1 H), 2.21–2.16 (m, 3 H), 1.94–1.90 (m, 1 H), 1.86–1.84 (m, 1 H), 1.79–1.75 (m, 1 H), 1.59–1.40 (m, 7 H), 1.24 (s, 3 H), 1.12–1.02 (m, 2 H), 0.81–0.74 (m, 3 H), 0.37–0.35 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 143.0, 133.4, 128.4, 127.5, 126.5, 117.9, 108.4, 84.8, 84.1, 49.7, 36.9, 34.8, 33.2, 32.2, 27.7, 26.4, 25.8, 24.9, 24.7, 14.4, 10.1; IR (film) 2935, 1733 cm^{-1}. MS (ESI) 423.2498 (423.2511 calcd for $C_{25}H_{36}O_4$, M + Na^+).

A flame-dried flask was charged with (1*R*,2*S*,3'*S*,4'*R*,5'*S*)-2-(phenylcyclohexyl)-4-allyl-5-sec-butyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (43 mg, 0.1 mmol) and THF (1.1 mL, 0.1 M) and cooled to 0 °C. A solution of $LiAlH_4$ (0.21 mL, 2 equiv, 1.0 M in THF) was added, and the reaction mixture was allowed to warm to rt and was stirred until the starting material had been completely consumed as judged by TLC analysis. The reaction mixture was cooled to 0 °C and quenched with H_2O (1 mL/mmol substrate). The crude residue was diluted with Et_2O (2 mL/mmol substrate), 10 M NaOH was added (1 mL/mmol substrate), then H_2O (0.5 mL/mmol substrate) was added. The phases were separated, the inorganic precipitate was washed with ether (3 x 2 mL), and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 12 mg (51%) of the title compound as a yellow oil. $[\alpha]^{23}_{D}$ +49.6 (*c* 0.03, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97–5.87 (m, 1 H), 5.14–5.07 (m, 2 H), 3.88 (d, *J* = 10.0 Hz, 1 H),

3.79–3.76 (m, 1 H), 3.43–3.89 (m, 1 H), 2.53–2.49 (m, 1 H), 2.09–2.04 (m, 1 H), 1.87–1.84 (m, 1 H), 1.80–1.73 (m, 1 H), 1.71–164 (m, 1 H), 1.47 (s, 3 H), 1.38 (s, 3 H), 1.31–1.22 (m, 1 H), 0.93–0.88 (m, 6 H).

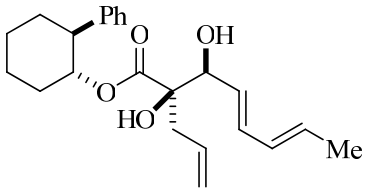


(1*R*,2*S*,2'*R*,3'*S*)-2-(Naphthalen-2-yl)cyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-phenylpropanoate (VI-57). The reaction of 1*R*,2*S*)-2-(Naphthalen-2-yl)cyclohexyl-2-benzyloxyacetate (**VI-56**) (44 mg, 0.12 mmol) with benzaldehyde (18 μL, 0.18 mmol, 1.5 equiv) was conducted according to General Procedure A using triethylamine as base to afford 47 mg (83%) of the title compound. The diastereoselectivity of the transformation could not be determined prior to purification through ^{1}H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.80 (m, 2 H), 7.75–7.74 (m, 2 H), 7.44–7.41 (m, 2 H), 7.39–7.36 (m, 1 H), 7.19–7.13 (m, 8 H), 6.98–6.96 (m, 2 H), 5.07–5.02 (m, 1 H), 4.04–4.03 (m, 1 H), 3.20 (s, 1 H), 3.03–2.97 (m, 1 H), 2.75 (d, *J* = 14 Hz, 1 H), 2.39 (d, *J*= 13.5 Hz, 1 H), 2.06–1.98 (m, 2 H), 1.88–1.81 (m, 2 H), 1.74–1.66 (m, 1 H), 1.48–1.39 (m, 3 H), 1.12–1.10 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 140.5, 138.7, 135.4, 133.4, 132.4, 130.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.4, 126.6, 126.4, 126.2, 125.8, 125.7, 80.4, 79.2, 77.5, 50.1, 41.1,

34.0, 32.2, 25.7, 24.7 (one carbon signal is absent due to incidental equivalence); IR (film) 3513, 2934, 1731 cm^{-1}. MS (ESI) 503.2187 (503.2198 calcd for $C_{32}H_{32}O_4$, M + Na^+).

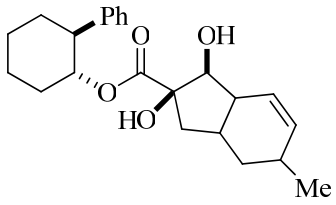
The enantiopurity of the title compound was assessed by conversion to the corresponding triol (**VI-58**) through reduction with $LiAlH_4$ using General Procedure B. The enantiopurity of the triol was determined to be 94% ee by chiral HPLC analysis (chiracel OD-H 0.46 cm x 25 cm, 10% isopropanol/ hexanes, 0.2 mL/min, RT= 35.3 and 43.2 min).

Tandem Wittig/Aldol/Diels-Alder Reactions



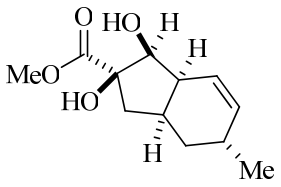
(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-allyl-2',3'-dihydroxyocta-4',6'-dienoate (VI-66). The reaction of (1*R*,2*S*)-2-phenylcyclohexyl-2-benzyloxyacetate (**VI-30**) (106 mg, 0.38 mmol) with hexa-2,4-dienal (64 μL, 0.58 mmol, 1.5 equiv) was conducted according to General Procedure A using diisopropylethylamine as base to afford 85 mg (60%) of the title compound. The diastereoselectivity of the transformation could not be determined prior to purification through ^1H NMR analysis of the crude reaction mixture due to signal overlap with boron-containing byproducts; the isolated product was obtained with 7:1 dr following purification. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.33 (m,

2 H), 7.27–7.24 (m, 3 H), 6.02–5.93 (m, 2 H), 5.74–5.68 (m, 1 H), 5.62–5.54 (m, 1 H), 5.25–5.20 (m, 1 H), 5.07–5.01 (m, 3 H), 3.62 (t, *J*= 7.5 Hz, 1 H), 3.12 (s, 1 H), 2.77–2.72 (m, 1 H), 2.31–2.27 2.22–2.17 (m, 2 H), 2.00–1.97 (m, 1 H), 1.91–1.86 (m, 1 H), 1.84–1.81 (m, 1 H), 1.76 (d, *J*= 6.5 Hz, 3 H), 1.64–1.49 (m, 3 H), 1.47–1.37 (m, 2 H), 0.92 (d, *J*= 7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 143.2, 134.0, 131.7, 130.7, 130.6, 128.7, 127.5, 127.0, 126.6, 118.9, 79.6, 78.5, 76.5, 50.0, 39.6, 33.9, 32.3, 25.7, 24.6, 18.1; IR (film) 3391, 2926, 1727 cm^{-1}. MS (ESI) 393.2032 (393.2042 calcd for $C_{23}H_{30}O_4$, M + Na^+).



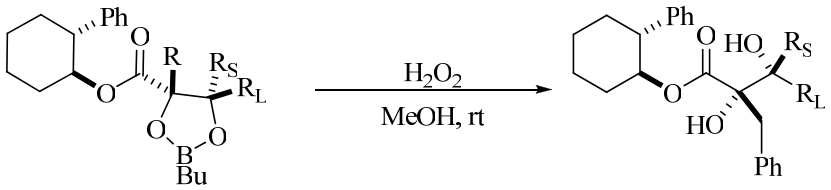
(1*R*,2*S*,2'*S*,3'*R*)-2-Phenylcyclohexyl-1',2'-dihydroxy-7'-methyl-2',3',3a',4',5',7a'-hexahydro-1H-indene-2'-carboxylate (VI-70). Compound **VI-66** (45 mg, 0.12 mmol) was heated in diglyme (1.5 mL, 0.1 M) at 150 °C for 12 h. The reaction was cooled to rt, concentrated and purified via flash chromatography on silica gel to afford 42 mg (92%) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 3 H), 7.26–7.19 (m, 1 H), 7.17–7.15 (m, 1 H), 5.67–5.58 (m, 2 H), 5.07–5.01 (m, 1 H), 3.21 (s, br, 1 H), 3.03–3.00 (m, 1 H), 2.75–2.68 (m, 1 H), 2.27–2.21 (m, 1 H), 2.19–2.10 (m, 2 H), 2.08–2.03 (m, 1 H), 1.98–1.96 (m, 1 H), 1.93–1.90 (m, 1 H), 1.84–1.81 (m, 1 H), 1.73–1.69 (m, 2 H), 1.68–1.65 (m, 1 H), 1.61–1.55 (m, 2 H), 1.54–1.48 (m, 2 H), 1.43–1.34 (m, 2 H), 1.04 (d, *J*= 7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 143.0, 134.7, 128.6, 127.6, 126.8, 126.2, 81.5, 80.7, 78.0, 50.4, 42.7, 40.8, 38.3, 34.0, 32.2, 31.5, 30.6, 25.7, 24.7,

21.6; IR (film) 3412, 2926, 1723 cm^{-1}. MS (ESI) 393.2039 (393.2042 calcd for $C_{23}H_{30}O_4$, $M + Na^+$).



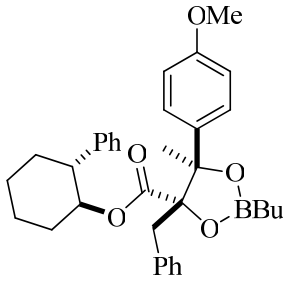
(1*S*,2*R*,3a*S*,5*R*,7a*R*)-Methyl-1,2-dihydroxy-5-methyl-2,3,3a,4,5,7a-hexahydro-1H-indene-2-carboxylate (VI-71). ^1H NMR (500 MHz, $CDCl_3$) δ 5.96–6.93 (m, 1 H), 5.58–5.56 (m, 1 H), 4.00 (t, *J*= 10.5 Hz, 1 H), 3.51 (s, 1 H), 3.16 (s, 3 H), 2.42–2.38 (m, 1 H), 2.12–2.08 (m, 1 H), 2.02–1.99 (m, 1 H), 1.87–1.84 (m, 2 H), 1.78–1.74 (m, 1 H), 1.37–1.34 (m, 1 H), 0.81–0.77 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 134.5, 126.5, 81.8, 80.8, 52.0, 43.9, 41.7, 38.4, 31.7, 30.6, 21.2.

Tandem Wittig/Aldol Reaction with Ketones



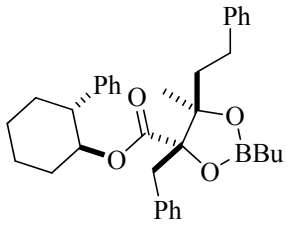
General Procedure E: Method to Cleave Boronate Ester from Tandem Products. To a flask was added the boronate ester (1 equiv) in methanol (0.1 M). H_2O_2 (1 mL/mmol substrate) was added dropwise, and the reaction was allowed to stir at rt until the starting material had been completely consumed as judged by TLC analysis. The mixture was diluted with ether (10 mL/mmol substrate) and water (5 mL/mmol substrate), then was transferred to a separatory funnel. The layers were separated, and the organic layer was

washed with a saturated aqueous solution of $FeSO_4$ (4 x 5 mL/mmol substrate) until a red-orange aqueous phase no longer persisted in order to quench any remaining peroxide. *Caution! This procedure is exothermic. The $FeSO_4$ solution should be added via glass pipette SLOWLY DROPWISE.* The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.



(+)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-5'-butyl-3'-(*p*-methoxyphenyl)-3'-methyl-4',6'-dioxa-5'-borolane-4'-carboxylate (VI-77). The reaction of (–)-(1*S*,2*R*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VI-75**) (56 mg, 0.17 mmol) mmol) with 4-methoxyacetophenone (39 mg, 0.35 mmol) using triethylamine as base was conducted according to General Procedure A to afford 71mg (76%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_D$ +45.8 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 4 H), 7.22–7.19 (m, 1 H), 7.16–7.10 (m, 3 H), 7.09–7.08 (m, 2 H), 6.99–6.89 (m, 2 H), 6.80–6.79 (m, 2 H), 5.10–5.04 (m, 1 H), 3.82 (s, 3 H), 2.82–2.77 (m, 1 H),

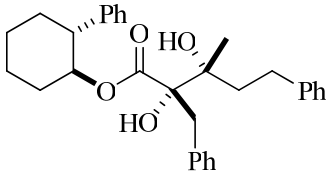
1.97–1.93 (m, 1 H), 1.83–1.80 (m, 1 H), 1.73–1.68 (m, 2 H), 1.55–1.46 (m, 4 H), 1.45–1.29 (m, 5 H), 1.00 (t, *J*= 6.0 Hz, 3 H), 0.92 (t, *J*= 7.5 Hz, 3 H), 0.88 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 158.8, 143.6, 136.4, 136.0, 133.7, 130.2, 128.8, 127.7, 127.5, 127.1, 127.0, 126.5, 113.1, 90.7, 87.0, 78.3, 55.2, 49.6, 42.9, 35.5, 31.6, 26.1, 25.8, 25.7, 25.4, 24.6, 13.9; IR (film) 2932, 1743 cm^{-1}. MS (ESI) 563.2953 (563.2945 calcd for $C_{34}H_{41}BO_5$, M + Na^+).



(–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-5'-butyl-3'-methyl-3'-phenethyl-4',6'-dioxa-5'-borolane-4'-carboxylate (VI-79). The reaction of (–)-(1*S*,2*R*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VI-75**) (53 mg, 0.17 mmol) with 4-phenylbutan-2-one (37 μL, 37 mg, 0.25 mmol) using diisopropyl ethylamine as base was conducted according to General Procedure A to afford 64 mg (74%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_D$ –14.6 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.34 (m, 2 H), 7.29–7.26 (m, 4 H), 7.24–7.20 (m, 9 H), 4.90–4.84 (m, 1 H), 2.98 (d, *J*= 14 Hz, 1 H), 2.90 (d, *J*= 14 Hz, 1 H), 2.72–2.61 (m, 2 H), 2.43–2.40 (m, 1 H), 1.97–1.85 (m, 3 H), 1.81–1.72 (m, 1 H), 1.63–1.58 (m, 1 H), 1.54–1.22 (m, 10 H), 1.09–0.98 (m, 1 H), 0.95–0.81 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

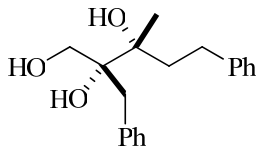
178.5, 169.5, 143.6, 135.8, 130.3, 128.7, 128.5, 128.4, 128.0, 127.6, 126.8, 126.7, 126.0, 78.6, 49.7, 39.7, 37.5, 34.7, 31.8, 30.0, 26.0, 25.7, 25.4, 24.6, 20.9, 13.9 (three carbon signals are absent due to incidental equivalence); IR (film) 2935, 1740 cm^{-1}. MS (ESI) 561.3144 (561.3152 calcd for $C_{35}H_{43}BO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester using General Procedure E then C. This procedure afforded 6 mg (60%) of # as a 4:1 mixture of diastereomers. The enantiopurity was determined to be 96% ee by ^{19}F NMR analysis.

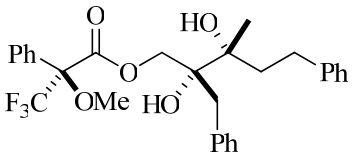


(+)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-methyl-5'-phenylpentanoate (VI-84). The reaction of (–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-5'-butyl-3'-methyl-3'-phenethyl-4',6'-dioxa-5'-borolane-4'-carboxylate (**VI-79**) (56 mg, 0.10 mmol) with H_2O_2 (0.1 mL) was conducted according to General Procedure B to afford 28 mg (58%) of the title compound as a colorless oil. $[\alpha]^{23}_D$ +14.5 (*c* 0.10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2 H), 7.23–7.20 (m, 6 H), 7.19–7.13 (m, 7 H), 5.01–4.95 (m, 1 H), 3.43 (s, 1 H), 3.15 (d, *J*= 13.6 Hz, 1 H), 3.04 (d, *J*= 14 Hz, 1 H), 2.79–2.72 (m, 1 H), 2.40–2.36 (m, 2 H), 1.93–1.85 (m, 2 H), 1.82–1.72 (m, 3 H), 1.70–1.64 (m, 1 H), 1.54 (s, 1 H), 1.48–1.45 (m, 1 H), 1.40–1.27 (m, 1 H), 1.98–1.06 (m, 1 H), 0.88–0.83 (m, 1 H), 0.82 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 142.9, 142.6, 136.3, 130.6, 129.2, 128.3, 128.2, 127.8, 127.3, 127.1, 126.7, 126.6, 82.3, 80.1,

75.3, 49.8, 37.8, 37.6, 35.0, 32.0, 29.4, 25.6, 24.6, 19.4; IR (film) 3393, 2935, 1718 cm^{-1}. MS (ESI) 495.2516 (495.2511 calcd for $C_{31}H_{36}O_4$, M + Na^+).

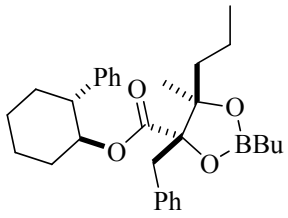


(–)-(2'*R*,3'*R*)-2-benzyl-3-methyl-5-phenylpentane-1,2,3-triol. The reaction of (–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-methyl-5'-phenylpentanoate (**VI-84**) (28 mg, 0.06 mmol) was conducted according to General Procedure C to afford 10 mg (54%) of the title compound as a white foam. $[\alpha]^{23}_D$ –25.2 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 4 H), 7.25–7.23 (m, 5 H), 7.22–7.18 (m, 1 H), 3.86–3.82 (m, 1 H), 3.55–3.51 (m, 1 H), 3.06 (s, 1 H), 2.98–2.92 (m, 1 H), 2.91–2.88 (m, 2 H), 2.76–2.71 (m, 1 H), 2.65–2.62 (m, 1 H), 2.24–2.18 (m, 1 H), 1.82–1.78 (m, 1 H), 1.55 (s, 1 H), 1.36 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 136.9, 130.4, 130.3, 128.5, 128.4, 126.8, 125.8, 66.0, 39.8, 38.6, 29.8, 21.1 (one carbon signal is absent due to incidental equivalence); IR (film) 3400, 2931 cm^{-1}. MS (ESI) 323.1623 (323.1619 calcd for $C_{19}H_{24}O_3$, M + Na^+).



(–)-(1*S*,2'R,3'*R*)-2'-benzyl-2',3'-dihydroxy-3'-methyl-5'-phenylpentyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VI-86). $[\alpha]^{23}_D$ –18.0 (*c* 0.10, CH_2Cl_2). ^{19}F

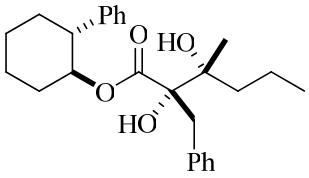
NMR (376 MHz, $(CD_3)_2CO$) δ –76.3; MS (ESI) 539.2034 (539.2021 calcd for $C_{29}H_{31}F_3O_5$, M + Na^+).



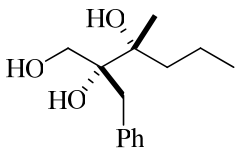
(–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-5'-butyl-3'-methyl-3'-propyl-4',6'-dioxa-5'-borolane-4'-carboxylate (VI-80). The reaction of (–)-(1*S*,2*R*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VI-75**) (53 mg, 0.17 mmol) with pentan-2-one (26 μL, 21 mg, 0.25 mmol) using diisopropyl ethylamine as base was conducted according to General Procedure A to afford 58 mg (73%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts. $[\alpha]^{23}_D$ –22.5 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 5 H), 7.21–7.17 (m, 5 H), 4.84–4.76 (m, 1 H), 3.01–2.98 (m, 1 H), 2.87 (d, *J*= 14 Hz, 1 H), 2.71–2.64 (m, 1 H), 1.92–1.83 (m, 3 H), 1.76–1.71 (m, 3 H), 1.56–1.47 (m, 4 H), 1.45–1.18 (m, 6 H), 1.12–1.00 (m, 2 H), 0.96–0.89 (m, 3 H), 0.88–0.83 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 143.5, 136.4, 136.0, 130.3, 128.6, 128.0, 127.5, 126.8, 126.7, 89.8, 85.0, 78.7, 49.7, 39.7, 37.4, 34.5, 31.8, 26.0, 25.7, 25.4, 24.6, 21.1, 16.9, 14.5, 13.6; IR (film) 2931, 1751 cm^{-1}. MS (ESI) 499.2999 (499.2996 calcd for $C_{30}H_{41}BO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester using General Procedure E, then C. This procedure afforded

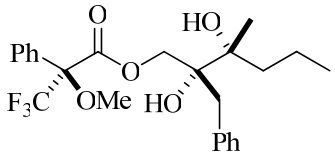
2 mg (50%) of # as a 4:1 mixture of diastereomers. The enantiopurity was determined to be 96% ee by ^{19}F NMR analysis.



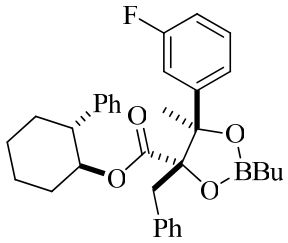
(+)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-2',3'-dihydroxy-3'-methylhexanoate (VI-83). The reaction of (–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-5'-butyl-3'-methyl-3'-phenethyl-4',6'-dioxa-5'-borolane-4'-carboxylate (**VI-80**) (69 mg, 0.13 mmol) with H_2O_2 (0.2 mL) was conducted according to General Procedure B to afford 37 mg (69%) of the title compound as a colorless oil. $[\alpha]^{23}_D$ +27.3 (*c* 0.10, CH_2Cl_2). ^1H NMR (^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2 H), 7.25–7.24 (m, 1 H), 7.23–7.17 (m, 7 H), 4.98–4.91 (m, 1 H), 3.38 (s, 1 H), 3.17 (d, *J*= 13.6 Hz, 1 H), 3.01 (d, *J*= 13.6 Hz, 1 H), 2.82–2.75 (m, 1 H), 1.97–1.92 (m, 1 H), 1.87–1.75 (m, 3 H), 1.54–1.45 (m, 1 H), 1.44–1.22 (m, 6 H), 1.05–0.93 (m, 1 H), 0.90–0.86 (m, 1 H), 0.78–0.74 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 143.0, 136.5, 130.6, 129.1, 127.8, 127.2, 127.1, 126.6, 82.4, 80.2, 75.4, 49.8, 38.7, 37.6, 34.9, 32.0, 25.6, 24.6, 19.2, 16.3, 14.5; IR (film) 3375, 2933, 1717 cm^{-1}. MS (ESI) 433.2352 (433.2355 calcd for $C_{26}H_{34}O_4$, $M + Na^+$).



(–)-(2'*R*,3'*R*)-2-benzyl-3-methylhexane-1,2,3-triol. The isolated product was obtained with 3:1 dr following purification. $[\alpha]^{23}_{D}$ –14.1 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5 H), 7.25–7.21 (m, 5 H), 3.85–3.79 (m, 1 H), 3.73 (s, 1 H), 3.51–3.46 (m, 1 H), 2.99–2.95 (m, 2 H), 2.69 (s, 1 H), 2.68–2.59 (m, 1 H), 1.91–1.81 (m, 2 H), 1.62–1.43 (m, 4 H), 1.35–1.21 (m, 6 H), 0.98 (t, *J*= 8.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.4, 130.3, 128.5, 128.4, 126.7, 66.0, 39.8, 38.6, 21.1 16.4, 14.8 (one carbon signal is absent due to incidental equivalence); IR (film) 3404, 2929 cm^{-1}. MS (ESI) 261.1464 (261.1467 calcd for $C_{14}H_{22}O_3$, M + Na^+).



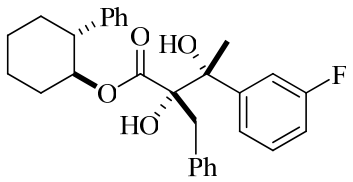
(–)-(1*S*,2'R,3'*R*)-2'-benzyl-2',3'-dihydroxy-3'-methylhexyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate. $[\alpha]^{23}_{D}$ –5.2 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2 H), 7.44–7.40 (m, 3 H), 7.29–7.25 (m, 7 H), 7.18–7.15 (m, 3 H), 4.24 (d, *J*= 11.6 Hz, 1 H), 4.11 (d, *J*= 12 Hz, 1 H), 3.51 (s, 3 H), 3.03–3.00 (m, 1 H), 2.78–2.73 (m, 1 H), 2.53 (s, 1 H), 2.14 (s, 1 H), 1.64–1.58 (m, 1 H), 1.51–1.40 (m, 3 H), 1.35–1.29 (m, 1 H), 1.28–1.23 (m, 2 H), 1.15–1.13 (m, 3 H), 0.90 (t, *J*= 7.2 Hz, 3 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –72.3, –72.2; IR (film) 3360, 2919 cm^{-1}. MS (ESI) 477.1869 (477.1865 calcd for $C_{24}H_{29}F_3O_5$, M + Na^+).



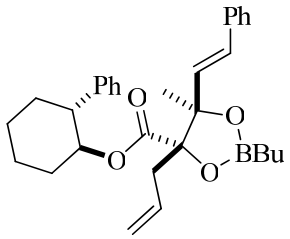
(+)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-5'-butyl-3'-(*m*-fluorophenyl)-3'-methyl-4',6'-dioxa-5'-borolane-4'-carboxylate (VI-81). The reaction of (–)-(1*S*,2*R*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VI-75**) (41 mg, 0.13 mmol) with 3-fluoroacetophenone (31 μL, 35 mg, 0.25 mmol) using triethylamine as base was conducted according to General Procedure A to afford 39 mg (58%) of the title compound as a yellow oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_{D}$ +17.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.35 (m, 4 H), 7.34–7.26 (m, 2 H), 7.25–7.23 (m, 1 H), 7.22–7.13 (m, 3 H), 7.10–7.05 (m, 2 H), 6.99–6.95 (m, 2 H), 6.80–6.79 (m, 2 H), 5.10–5.04 (m, 1 H), 3.82 (s, 3 H), 2.82–2.77 (m, 1 H), 1.97–1.93 (m, 1 H), 1.83–1.80 (m, 1 H), 1.73–1.68 (m, 1 H), 1.55–1.46 (m, 2 H), 1.45–1.29 (m, 4 H), 1.00 (t, *J*= 6.0 Hz, 2 H), 0.92 (t, *J*= 7.5 Hz, 3 H), 0.88 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 143.4, 135.4, 130.2, 129.2, 129.4, 128.9, 127.8, 127.6, 127.0, 126.7, 123.2, 122.2, 121.6, 114.4 (t, *J*= 25.6 Hz), 90.4, 78.5, 49.6, 42.9, 35.5, 31.8, 26.0, 25.9, 25.7, 25.4, 24.6, 13.9 (two carbon signals are absent due to incidental equivalence); IR (film) 2932, 1749 cm^{-1}. MS (ESI) 551.2744 (551.2745 calcd for $C_{33}H_{38}BFO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester using General Procedure E, then C. This procedure afforded

2 mg (30%) of **#** as a 20:1 mixture of diastereomers. The enantiopurity was determined to be 92% ee by ^{19}F NMR analysis.



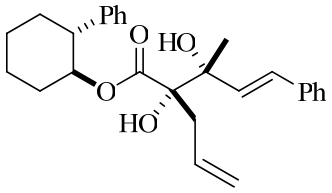
(–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-3'-(*m*-fluorophenyl)-2',3'-dihydroxybutanoate. The reaction of (–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-5'-butyl-3'-(*m*-fluorophenyl)-3'-methyl-4',6'-dioxa-5'-borolane-4'-carboxylate (**VI-81**) (56 mg, 0.11 mmol) with H_2O_2 (0.1 mL) was conducted according to General Procedure B to afford 29 mg (60%) of the title compound as a white foam. $[\alpha]^{23}_D$ –15.6 (*c* 0.10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2 H), 7.35–7.30 (m, 1 H), 7.27–7.22 (m, 3 H), 7.20–7.12 (m, 4 H), 7.09–7.03 (m, 1 H), 6.87–6.83 (m, 1 H), 6.64–6.61 (m, 1 H), 6.45–6.42 (m, 1 H), 4.58–4.51 (m, 1 H), 3.30 (s, 1 H), 3.25 (d, *J*= 14 Hz, 1 H), 3.11 (d, *J*= 14 Hz, 1 H), 2.78 (s, 1 H), 2.70–2.67 (m, 1 H), 1.92–1.86 (m, 1 H), 1.71–1.60 (m, 3 H), 1.55–1.49 (m, 2 H), 1.44 (s, 2 H), 1.31–1.21 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 142.8, 136.1, 130.4, 129.4, 128.9, 127.9, 127.5, 126.7, 121.3, 113.9, 113.7, 113.5, 113.2, 82.1, 81.4, 49.5, 38.5, 34.0, 30.9, 25.5, 24.6, 23.2 (one carbon signal is absent due to incidental equivalence); IR (film) 3393, 2935, 1718 cm^{-1}. MS (ESI) 495.2516 (495.2511 calcd for $C_{29}H_{31}FO_4$, M + Na^+).



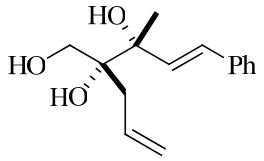
(+)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-allyl-5'-butyl-3'-methyl-3'-styryl-4',6'-dioxa-5'-borolane-4'-carboxylate (VI-82). The reaction of (–)-(1*S*,2*R*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VI-78**) (55 mg, 0.2 mmol) with 4-phenylbut-3-en-2-one (44 mg, 0.3 mmol) using diisopropylethylamine as base was conducted according to General Procedure A to afford 54 mg (55%) of the title compound as a yellow oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 7:1 dr following purification. $[\alpha]^{23}_{D}$ +39.4 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, 5 H), 7.31–7.24 (m, 3 H), 7.24–7.15 (m, 2 H), 6.54 (d, *J*= 16 Hz, 1 H), 5.82 (d, *J*= 16 Hz, 1 H), 5.63–5.55 (m, 1 H), 5.09–4.99 (m, 3 H), 2.79–2.73 (m, 1 H), 2.39–2.34 (m, 1 H), 2.26–2.23 (m, 1 H), 2.17–2.12 (m, 1 H), 1.99–1.94 (m, 1 H), 1.89–1.78 (m, 2 H), 1.62–1.56 (m, 1 H), 1.55–1.49 (m, 2 H), 1.48–1.41 (m, 2 H), 1.40–1.26 (m, 3 H), 0.98–0.87 (m, 6 H), 0.50 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 143.4, 136.6, 131.6, 128.8, 128.7, 128.6, 127.7, 127.6, 127.0, 126.5, 119.3, 88.8, 84.7, 78.2, 49.8, 41.4, 34.5, 32.3, 25.9, 25.7, 25.3, 24.6, 23.8, 13.9 (two carbon signals are absent due to incidental equivalence); IR (film) 2930, 1750 cm^{-1}. MS (ESI) 509.2835 (509.2839 calcd for $C_{31}H_{39}BO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester using General Procedure E, then C. This procedure afforded

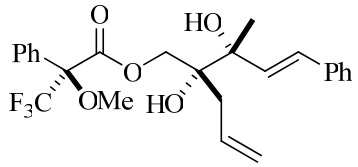
2 mg (30%) of # as a 7:1 mixture of diastereomers. The enantiopurity was determined to be 79% ee by ^{19}F NMR analysis.



(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-allyl-2',3'-dihydroxy-3'-methyl-5'-phenylpent-4'-enoate. The reaction of (–)-(1*S*,2*R*,2'*S*,3'*R*)-2-Phenylcyclohexyl-2'-allyl-5'-butyl-3'-methyl-3'-styryl-4',6'-dioxa-5'-borolane-4'-carboxylate (**VI-82**) (48 mg, 0.1 mmol) with H_2O_2 (0.1 mL) was conducted according to General Procedure B to afford 37 mg (87%) of the title compound as a white foam. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2 H), 7.29–7.26 (m, 4 H), 7.25–7.17 (m, 4 H), 6.30 (d, *J*= 15.5 Hz, 1 H), 5.97 (d, *J*= 16 Hz, 1 H), 5.47–5.39 (m, 1 H), 5.12–5.06 (m, 2 H), 5.03–4.98 (m, 2 H), 3.43 (s, 1 H), 2.80–2.74 (m, 1 H), 2.58–2.53 (m, 1 H), 2.51 (s, 1 H), 2.46–2.42 (m, 1 H), 2.20–2.12 (m, 1 H), 1.98–1.92 (m, 1 H), 1.87–1.80 (m, 1 H), 1.79–1.74 (m, 1 H), 1.52–1.42 (m, 1 H), 1.39–1.31 (m, 2 H), 0.88 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 142.8, 137.2, 132.1, 131.7, 129.1, 128.4, 127.2, 127.1, 126.6, 119.2, 80.8, 79.3, 75.5, 49.7, 37.6, 34.9, 32.2, 25.6, 24.6, 22.7 (two carbon signals are absent due to incidental equivalence); MS (ESI) 443.2198 (443.2198 calcd for $C_{27}H_{32}O_4$, M + Na^+).



(–)-(2'*R*,3'*R*)-2-allyl-3-methyl-5-phenylpent-4-ene-1,2,3-triol. $[\alpha]^{23}_{D}$ –21.8 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.40 (m, 2 H), 7.34–7.29 (m, 2 H), 7.25–7.23 (m, 1 H), 6.68 (d, *J*= 16 Hz, 1 H), 6.46 (d, *J*= 16 Hz, 1 H), 5.99–5.91 (m, 1 H), 5.17–5.12 (m, 2 H), 3.85–3.82 (m, 1 H), 3.73–3.69 (m, 1 H), 2.93 (s, 1 H), 2.82 (s, 1 H), 2.48–2.44 (m, 1 H), 2.36–2.31 (m, 2 H), 1.46 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 133.9, 132.4, 129.2, 128.6, 127.7, 126.7, 118.8, 78.1, 65.8, 38.4, 31.5, 23.3; IR (film) 3368, 2918 cm^{-1}. MS (ESI) 271.1308 (271.1310 calcd for $C_{15}H_{20}O_3$, M + Na^+).



(–)-(1*S*,2'R,3'*R*)-2'-allyl-2',3'-dihydroxy-3'-methyl-5'-phenylpent-4'-enyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate. $[\alpha]^{23}_{D}$ –35.9 (*c* 0.10, CH_2Cl_2). ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –72.5; MS (ESI) 487.1700 (487.1708 calcd for $C_{25}H_{27}F_3O_5$, M + Na^+).

X-ray Data for VI-28

Table 1. Crystal data and structure refinement for ncga.

Identification code	ncga
Empirical formula	C28 H30 O4
Formula weight	430.52
Temperature	85(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P1
Unit cell dimensions	a = 10.5410(7) A alpha = 88.484(1) deg.
	b = 10.6705(7) A beta = 84.284(1) deg.
	c = 10.8608(7) A gamma = 75.633(1) deg.
Volume	1177.51(13) A^3
Z, Calculated density	2, 1.214 Mg/m^3
Absorption coefficient	0.080 mm^-1
F(000)	460
Crystal size	0.32 x 0.22 x 0.16 mm
Theta range for data collection	1.88 to 28.32 deg.
Limiting indices	-14<=h<=14, -14<=k<=14, -14<=l<=14
Reflections collected / unique	54483 / 5855 [R(int) = 0.0269]
Completeness to theta = 28.32	99.8 %

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9873 and 0.9749
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5855 / 3 / 593
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0305, wR2 = 0.0780
R indices (all data)	R1 = 0.0317, wR2 = 0.0790
Absolute structure parameter	0(10)
Largest diff. peak and hole	0.264 and -0.152 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic

displacement parameters (A^2 x 10^3) for ncga.

U(eq) is defined as one third of the trace of the orthogonalized

Uij tensor.

	x	y	z	U(eq)
O(1)	1311(1)	1413(1)	5064(1)	22(1)
O(2)	828(1)	-466(1)	4644(1)	29(1)
O(3)	1754(1)	-469(1)	2311(1)	26(1)
O(4)	3909(1)	-485(1)	3593(1)	30(1)
C(1)	1250(2)	456(2)	4325(1)	22(1)
C(2)	1808(2)	632(1)	2989(1)	22(1)
C(3)	3261(2)	690(2)	3010(1)	23(1)
C(4)	3918(2)	811(2)	1720(2)	24(1)
C(5)	4474(2)	-282(2)	993(2)	27(1)
C(6)	5052(2)	-159(2)	-196(2)	31(1)
C(7)	5104(2)	1044(2)	-663(2)	32(1)
C(8)	4564(2)	2138(2)	54(2)	33(1)
C(9)	3965(2)	2022(2)	1242(2)	28(1)

C(10)	978(2)	1853(2)	2392(1)	23(1)
C(11)	-461(2)	1878(2)	2452(2)	25(1)
C(12)	-930(2)	1178(2)	1606(2)	32(1)
C(13)	-2262(2)	1194(2)	1679(2)	41(1)
C(14)	-3130(2)	1898(2)	2594(2)	45(1)
C(15)	-2682(2)	2601(2)	3431(2)	40(1)
C(16)	-1355(2)	2597(2)	3360(2)	30(1)
C(17)	906(2)	1300(2)	6388(1)	22(1)
C(18)	1951(2)	1675(2)	7079(1)	23(1)
C(19)	3302(2)	800(2)	6729(1)	24(1)
C(20)	3596(2)	-510(2)	7045(2)	28(1)
C(21)	4837(2)	-1309(2)	6725(2)	34(1)
C(22)	5801(2)	-820(2)	6070(2)	39(1)
C(23)	5524(2)	483(2)	5739(2)	38(1)
C(24)	4279(2)	1286(2)	6068(2)	31(1)
C(25)	1519(2)	1707(2)	8481(2)	28(1)
C(26)	182(2)	2669(2)	8753(2)	31(1)
C(27)	-863(2)	2291(2)	8065(2)	32(1)
C(28)	-461(2)	2189(2)	6670(2)	27(1)

O(5)	1842(1)	6312(1)	3096(1)	22(1)
O(6)	2364(1)	4191(1)	3582(1)	26(1)
O(7)	1327(1)	4589(1)	5876(1)	23(1)
O(8)	-767(1)	5709(1)	4512(1)	27(1)
C(29)	1915(1)	5309(1)	3866(1)	20(1)
C(30)	1320(1)	5732(1)	5183(1)	19(1)
C(31)	-119(2)	6526(2)	5106(1)	21(1)
C(32)	-807(2)	6920(2)	6380(1)	22(1)
C(33)	-881(2)	8139(2)	6849(2)	27(1)
C(34)	-1463(2)	8472(2)	8044(2)	32(1)
C(35)	-1983(2)	7601(2)	8766(2)	32(1)
C(36)	-1942(2)	6397(2)	8293(2)	32(1)
C(37)	-1356(2)	6057(2)	7105(2)	27(1)
C(38)	2132(2)	6520(2)	5789(1)	21(1)
C(39)	3556(2)	5824(2)	5863(1)	22(1)
C(40)	3913(2)	4875(2)	6761(2)	26(1)
C(41)	5228(2)	4269(2)	6865(2)	32(1)
C(42)	6201(2)	4619(2)	6081(2)	38(1)
C(43)	5861(2)	5557(2)	5184(2)	38(1)

C(44)	4546(2)	6158(2)	5069(2)	29(1)
C(45)	2264(2)	6027(1)	1782(1)	22(1)
C(46)	1231(2)	6917(2)	1052(1)	22(1)
C(47)	-133(2)	6715(2)	1398(1)	25(1)
C(48)	-438(2)	5546(2)	1163(2)	30(1)
C(49)	-1703(2)	5384(2)	1470(2)	37(1)
C(50)	-2675(2)	6385(2)	2015(2)	41(1)
C(51)	-2392(2)	7549(2)	2275(2)	38(1)
C(52)	-1118(2)	7704(2)	1972(2)	30(1)
C(53)	1689(2)	6742(2)	-339(2)	27(1)
C(54)	3030(2)	7041(2)	-623(2)	29(1)
C(55)	4063(2)	6158(2)	113(2)	31(1)
C(56)	3633(2)	6244(2)	1504(2)	26(1)

Table 3. Bond lengths [A] and angles [deg] for ncga.

O(1)-C(1)	1.3336(18)
O(1)-C(17)	1.4688(18)
O(2)-C(1)	1.206(2)
O(3)-C(2)	1.4180(18)
O(4)-C(3)	1.4350(19)
C(1)-C(2)	1.535(2)
C(2)-C(10)	1.545(2)
C(2)-C(3)	1.551(2)
C(3)-C(4)	1.516(2)
C(4)-C(9)	1.390(2)
C(4)-C(5)	1.395(2)
C(5)-C(6)	1.390(2)
C(6)-C(7)	1.380(3)
C(7)-C(8)	1.387(3)
C(8)-C(9)	1.395(2)
C(10)-C(11)	1.506(2)
C(11)-C(16)	1.395(2)

C(11)-C(12)	1.398(2)
C(12)-C(13)	1.394(3)
C(13)-C(14)	1.381(3)
C(14)-C(15)	1.382(3)
C(15)-C(16)	1.392(3)
C(17)-C(28)	1.523(2)
C(17)-C(18)	1.528(2)
C(18)-C(19)	1.516(2)
C(18)-C(25)	1.544(2)
C(19)-C(24)	1.394(2)
C(19)-C(20)	1.396(2)
C(20)-C(21)	1.389(3)
C(21)-C(22)	1.382(3)
C(22)-C(23)	1.393(3)
C(23)-C(24)	1.396(3)
C(25)-C(26)	1.530(2)
C(26)-C(27)	1.527(3)
C(27)-C(28)	1.531(2)
O(5)-C(29)	1.3328(18)

O(5)-C(45)	1.4678(17)
O(6)-C(29)	1.2053(19)
O(7)-C(30)	1.4155(18)
O(8)-C(31)	1.4334(19)
C(29)-C(30)	1.536(2)
C(30)-C(38)	1.540(2)
C(30)-C(31)	1.552(2)
C(31)-C(32)	1.515(2)
C(32)-C(33)	1.391(2)
C(32)-C(37)	1.392(2)
C(33)-C(34)	1.394(2)
C(34)-C(35)	1.381(3)
C(35)-C(36)	1.386(3)
C(36)-C(37)	1.390(2)
C(38)-C(39)	1.510(2)
C(39)-C(44)	1.396(2)
C(39)-C(40)	1.396(2)
C(40)-C(41)	1.391(2)
C(41)-C(42)	1.385(3)

C(42)-C(43)	1.386(3)
C(43)-C(44)	1.392(3)
C(45)-C(56)	1.518(2)
C(45)-C(46)	1.528(2)
C(46)-C(47)	1.515(2)
C(46)-C(53)	1.541(2)
C(47)-C(52)	1.394(2)
C(47)-C(48)	1.398(2)
C(48)-C(49)	1.394(3)
C(49)-C(50)	1.382(3)
C(50)-C(51)	1.390(3)
C(51)-C(52)	1.400(3)
C(53)-C(54)	1.526(2)
C(54)-C(55)	1.529(3)
C(55)-C(56)	1.532(2)

C(1)-O(1)-C(17)	117.53(12)
O(2)-C(1)-O(1)	125.23(15)
O(2)-C(1)-C(2)	122.31(14)

O(1)-C(1)-C(2)	112.45(13)
O(3)-C(2)-C(1)	107.30(12)
O(3)-C(2)-C(10)	108.76(12)
C(1)-C(2)-C(10)	111.13(13)
O(3)-C(2)-C(3)	109.63(12)
C(1)-C(2)-C(3)	108.05(12)
C(10)-C(2)-C(3)	111.86(13)
O(4)-C(3)-C(4)	110.81(13)
O(4)-C(3)-C(2)	106.00(13)
C(4)-C(3)-C(2)	112.03(12)
C(9)-C(4)-C(5)	118.97(15)
C(9)-C(4)-C(3)	120.20(14)
C(5)-C(4)-C(3)	120.82(15)
C(6)-C(5)-C(4)	120.38(16)
C(7)-C(6)-C(5)	120.39(16)
C(6)-C(7)-C(8)	119.78(16)
C(7)-C(8)-C(9)	120.08(17)
C(4)-C(9)-C(8)	120.39(16)
C(11)-C(10)-C(2)	113.20(13)

C(16)-C(11)-C(12)	118.58(16)
C(16)-C(11)-C(10)	120.47(14)
C(12)-C(11)-C(10)	120.95(15)
C(13)-C(12)-C(11)	120.51(18)
C(14)-C(13)-C(12)	120.12(18)
C(13)-C(14)-C(15)	120.00(19)
C(14)-C(15)-C(16)	120.2(2)
C(15)-C(16)-C(11)	120.56(17)
O(1)-C(17)-C(28)	108.22(12)
O(1)-C(17)-C(18)	106.16(12)
C(28)-C(17)-C(18)	113.11(13)
C(19)-C(18)-C(17)	111.23(12)
C(19)-C(18)-C(25)	113.85(13)
C(17)-C(18)-C(25)	109.05(13)
C(24)-C(19)-C(20)	118.40(16)
C(24)-C(19)-C(18)	120.51(15)
C(20)-C(19)-C(18)	121.08(15)
C(21)-C(20)-C(19)	120.98(17)
C(22)-C(21)-C(20)	120.28(18)

C(21)-C(22)-C(23)	119.61(18)
C(22)-C(23)-C(24)	119.99(19)
C(19)-C(24)-C(23)	120.73(18)
C(26)-C(25)-C(18)	110.11(13)
C(27)-C(26)-C(25)	110.74(14)
C(26)-C(27)-C(28)	111.30(15)
C(17)-C(28)-C(27)	111.34(14)
C(29)-O(5)-C(45)	117.33(11)
O(6)-C(29)-O(5)	125.20(14)
O(6)-C(29)-C(30)	122.72(13)
O(5)-C(29)-C(30)	112.06(12)
O(7)-C(30)-C(29)	106.81(12)
O(7)-C(30)-C(38)	109.34(12)
C(29)-C(30)-C(38)	111.62(12)
O(7)-C(30)-C(31)	109.69(12)
C(29)-C(30)-C(31)	107.89(12)
C(38)-C(30)-C(31)	111.37(12)
O(8)-C(31)-C(32)	110.58(12)
O(8)-C(31)-C(30)	106.34(12)

C(32)-C(31)-C(30)	111.36(12)
C(33)-C(32)-C(37)	119.12(15)
C(33)-C(32)-C(31)	120.52(14)
C(37)-C(32)-C(31)	120.36(14)
C(32)-C(33)-C(34)	120.13(16)
C(35)-C(34)-C(33)	120.42(17)
C(34)-C(35)-C(36)	119.71(16)
C(35)-C(36)-C(37)	120.14(17)
C(36)-C(37)-C(32)	120.45(16)
C(39)-C(38)-C(30)	114.44(12)
C(44)-C(39)-C(40)	118.75(15)
C(44)-C(39)-C(38)	120.49(14)
C(40)-C(39)-C(38)	120.70(14)
C(41)-C(40)-C(39)	120.88(16)
C(42)-C(41)-C(40)	119.84(18)
C(41)-C(42)-C(43)	119.87(17)
C(42)-C(43)-C(44)	120.47(18)
C(43)-C(44)-C(39)	120.18(17)
O(5)-C(45)-C(56)	108.16(12)

O(5)-C(45)-C(46)	106.42(11)
C(56)-C(45)-C(46)	113.58(13)
C(47)-C(46)-C(45)	112.05(12)
C(47)-C(46)-C(53)	113.69(13)
C(45)-C(46)-C(53)	108.60(13)
C(52)-C(47)-C(48)	118.37(16)
C(52)-C(47)-C(46)	120.02(15)
C(48)-C(47)-C(46)	121.60(15)
C(49)-C(48)-C(47)	120.81(18)
C(50)-C(49)-C(48)	120.08(18)
C(49)-C(50)-C(51)	120.19(18)
C(50)-C(51)-C(52)	119.51(19)
C(47)-C(52)-C(51)	121.00(18)
C(54)-C(53)-C(46)	110.45(13)
C(53)-C(54)-C(55)	111.16(14)
C(54)-C(55)-C(56)	111.27(14)
C(45)-C(56)-C(55)	111.25(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for ncga.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	30(1)	19(1)	17(1)	-1(1)	-4(1)	-5(1)
O(2)	42(1)	23(1)	23(1)	0(1)	-3(1)	-12(1)
O(3)	37(1)	21(1)	21(1)	-3(1)	-5(1)	-9(1)
O(4)	36(1)	26(1)	25(1)	1(1)	-10(1)	-2(1)
C(1)	26(1)	18(1)	20(1)	0(1)	-6(1)	-3(1)
C(2)	29(1)	19(1)	18(1)	-2(1)	-6(1)	-6(1)
C(3)	28(1)	22(1)	20(1)	-2(1)	-6(1)	-4(1)
C(4)	23(1)	26(1)	22(1)	-4(1)	-6(1)	-5(1)
C(5)	25(1)	26(1)	27(1)	-6(1)	-4(1)	-3(1)
C(6)	26(1)	36(1)	27(1)	-11(1)	-4(1)	-1(1)
C(7)	29(1)	43(1)	21(1)	-2(1)	-2(1)	-6(1)
C(8)	37(1)	33(1)	28(1)	3(1)	-2(1)	-8(1)
C(9)	32(1)	25(1)	26(1)	-4(1)	-3(1)	-6(1)

C(10)	28(1)	21(1)	21(1)	2(1)	-6(1)	-6(1)
C(11)	30(1)	23(1)	24(1)	5(1)	-9(1)	-8(1)
C(12)	38(1)	30(1)	30(1)	-1(1)	-13(1)	-8(1)
C(13)	41(1)	40(1)	48(1)	0(1)	-23(1)	-16(1)
C(14)	32(1)	51(1)	56(1)	5(1)	-14(1)	-15(1)
C(15)	32(1)	44(1)	41(1)	1(1)	-3(1)	-6(1)
C(16)	31(1)	31(1)	28(1)	0(1)	-7(1)	-7(1)
C(17)	29(1)	21(1)	17(1)	0(1)	-3(1)	-5(1)
C(18)	31(1)	19(1)	19(1)	0(1)	-6(1)	-5(1)
C(19)	30(1)	25(1)	18(1)	-1(1)	-7(1)	-5(1)
C(20)	35(1)	25(1)	22(1)	1(1)	-7(1)	-3(1)
C(21)	39(1)	32(1)	28(1)	-3(1)	-12(1)	2(1)
C(22)	30(1)	51(1)	34(1)	-11(1)	-10(1)	1(1)
C(23)	34(1)	55(1)	30(1)	-5(1)	-4(1)	-16(1)
C(24)	37(1)	36(1)	25(1)	-1(1)	-7(1)	-14(1)
C(25)	38(1)	26(1)	19(1)	-1(1)	-6(1)	-2(1)
C(26)	40(1)	28(1)	22(1)	-4(1)	-4(1)	-2(1)
C(27)	35(1)	33(1)	25(1)	-3(1)	1(1)	-4(1)
C(28)	28(1)	28(1)	24(1)	-2(1)	-4(1)	-4(1)

O(5)	30(1)	19(1)	16(1)	-1(1)	-1(1)	-7(1)
O(6)	34(1)	21(1)	22(1)	-1(1)	-2(1)	-5(1)
O(7)	28(1)	20(1)	21(1)	2(1)	-3(1)	-6(1)
O(8)	28(1)	36(1)	21(1)	1(1)	-7(1)	-13(1)
C(29)	20(1)	21(1)	19(1)	0(1)	-4(1)	-6(1)
C(30)	21(1)	20(1)	17(1)	2(1)	-3(1)	-6(1)
C(31)	21(1)	24(1)	19(1)	1(1)	-3(1)	-5(1)
C(32)	19(1)	26(1)	20(1)	1(1)	-3(1)	-2(1)
C(33)	23(1)	27(1)	30(1)	-2(1)	-2(1)	-3(1)
C(34)	29(1)	34(1)	32(1)	-10(1)	-3(1)	-2(1)
C(35)	25(1)	44(1)	22(1)	-4(1)	-1(1)	2(1)
C(36)	28(1)	40(1)	26(1)	5(1)	1(1)	-5(1)
C(37)	26(1)	29(1)	25(1)	1(1)	-1(1)	-5(1)
C(38)	21(1)	22(1)	21(1)	-2(1)	-4(1)	-4(1)
C(39)	22(1)	24(1)	20(1)	-5(1)	-3(1)	-6(1)
C(40)	26(1)	29(1)	23(1)	-1(1)	-5(1)	-6(1)
C(41)	31(1)	33(1)	34(1)	-3(1)	-13(1)	-3(1)
C(42)	22(1)	45(1)	44(1)	-10(1)	-8(1)	-2(1)
C(43)	25(1)	50(1)	39(1)	-7(1)	2(1)	-12(1)

C(44)	27(1)	34(1)	27(1)	0(1)	-2(1)	-11(1)
C(45)	29(1)	20(1)	15(1)	-2(1)	1(1)	-6(1)
C(46)	30(1)	20(1)	17(1)	-1(1)	-3(1)	-7(1)
C(47)	32(1)	27(1)	18(1)	3(1)	-7(1)	-9(1)
C(48)	39(1)	31(1)	24(1)	4(1)	-10(1)	-14(1)
C(49)	45(1)	46(1)	28(1)	12(1)	-15(1)	-25(1)
C(50)	34(1)	66(1)	29(1)	14(1)	-10(1)	-22(1)
C(51)	32(1)	53(1)	25(1)	4(1)	-4(1)	-5(1)
C(52)	32(1)	35(1)	22(1)	1(1)	-4(1)	-6(1)
C(53)	39(1)	27(1)	17(1)	-2(1)	-3(1)	-11(1)
C(54)	39(1)	28(1)	20(1)	-1(1)	1(1)	-10(1)
C(55)	34(1)	32(1)	24(1)	-1(1)	6(1)	-7(1)
C(56)	27(1)	29(1)	22(1)	1(1)	1(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for ncga.

	x	y	z	U(eq)
H(3A)	1600(30)	-1000(30)	2820(30)	47(7)
H(4A)	4290(30)	-350(30)	4190(30)	52(8)
H(3B)	3296	1445	3520	28
H(5A)	4459	-1116	1313	32
H(6A)	5414	-908	-690	37
H(7A)	5509	1123	-1473	38
H(8A)	4601	2967	-264	39
H(9A)	3588	2774	1727	34
H(10A)	1076	2628	2817	28
H(10B)	1323	1900	1515	28
H(12A)	-337	688	978	39
H(13A)	-2573	720	1097	49
H(14A)	-4036	1899	2648	54
H(15A)	-3281	3089	4057	48
H(16A)	-1056	3088	3935	36

H(17A)	884	386	6590	27
H(18A)	1980	2574	6819	28
H(20A)	2938	-860	7484	33
H(21A)	5023	-2196	6958	41
H(22A)	6647	-1369	5848	47
H(23A)	6183	825	5289	46
H(24A)	4095	2174	5838	37
H(25A)	1458	834	8767	34
H(25B)	2182	1965	8936	34
H(26A)	-84	2686	9654	38
H(26B)	253	3547	8494	38
H(27A)	-1709	2947	8222	39
H(27B)	-994	1450	8382	39
H(28A)	-1106	1850	6262	32
H(28B)	-471	3060	6329	32
H(7B)	1510(30)	3990(30)	5390(20)	39(6)
H(8B)	-1020(30)	6040(30)	3850(30)	58(8)
H(31A)	-122	7317	4591	25
H(33A)	-533	8746	6355	33

H(34A)	-1502	9302	8363	39
H(35A)	-2368	7828	9584	39
H(36A)	-2314	5802	8781	38
H(37A)	-1330	5230	6785	32
H(38A)	2096	7331	5314	25
H(38B)	1719	6761	6637	25
H(40A)	3248	4640	7308	31
H(41A)	5457	3616	7472	39
H(42A)	7101	4216	6158	45
H(43A)	6530	5792	4643	45
H(44A)	4321	6796	4448	34
H(45A)	2289	5104	1612	26
H(46A)	1206	7828	1272	27
H(48A)	226	4854	789	36
H(49A)	-1897	4586	1305	44
H(50A)	-3540	6276	2213	49
H(51A)	-3058	8235	2656	45
H(52A)	-921	8496	2160	36
H(53A)	1746	5841	-584	32

H(53B)	1038	7328	-824	32
H(54A)	2960	7955	-414	35
H(54B)	3309	6924	-1519	35
H(55A)	4908	6409	-49	37
H(55B)	4205	5253	-164	37
H(56A)	4266	5587	1946	32
H(56B)	3641	7108	1810	32

Table 6. Hydrogen bonds for ncga [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3A)...O(2)	0.82(3)	2.10(3)	2.6231(17)	122(2)
O(7)-H(7B)...O(6)	0.81(3)	2.11(3)	2.6205(16)	121(2)

Symmetry transformations used to generate equivalent atoms:

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[1] Reproduced in part with permission from "Asymmetric, Tandem Wittig Rearrangement/Aldol Reactions" Giampietro, N. C.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12556–12557. Copyright 2009 American Chemical Society.

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Chapter VII

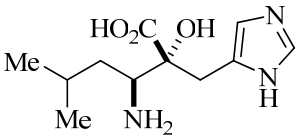
Asymmetric, Tandem Wittig Rearrangement/Mannich Reactions

The previous chapter described asymmetric, tandem Wittig rearrangement/aldol reactions between aldehydes and *O*-allyl or *O*-benzyl glycolate esters of *trans*-2-phenylcyclohexanol.[1] The transformations proceed through *Z*-boron ester enolates, and afford *syn*-α-alkyl-α,β-dihydroxy esters with up to 95% ee and >20:1 *syn*:*anti* selectivity after cleavage of the 2-phenylcyclohexanol chiral auxiliary. Based on these results, it seemed likely that the development of a related Wittig rearrangement/Mannich reaction sequence could provide an efficient means of preparing α-alkyl-α-hydroxy-β-amino esters with a high degree of stereocontrol. In this chapter, our preliminary studies in this area will be described, which have led to the first asymmetric Mannich reactions of ester enolates that afford both *syn*- and *anti*-α-alkyl-α-hydroxy-β-amino esters with both high dr and ee.[2] These are also the first examples of asymmetric Mannich reactions that proceed via tetrasubstituted enolboronate intermediates.

VII.1 Biological Significance and Common Methods of Synthesis

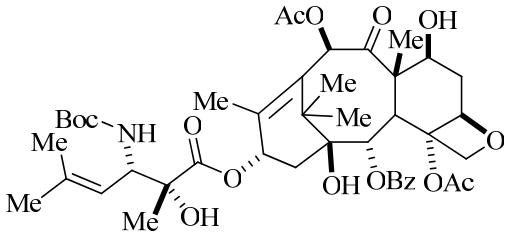
Asymmetric Mannich reactions provide a highly convergent and efficient means to access enantiomerically enriched β-amino acid derivatives.[3,4] Methods for the construction of these molecules is important in that these types compounds have been used as intermediates in the synthesis of taxol analogs,[5] and are displayed in natural products such as leuhistin **VII-1**, which is known to be a potent aminopeptidase inhibitor (Figure VII-1).[6]

Figure VII-1. Biologically Significant α-Alkyl-α-Hydroxy-β-Amino Acid-Containing Compounds



VII-1

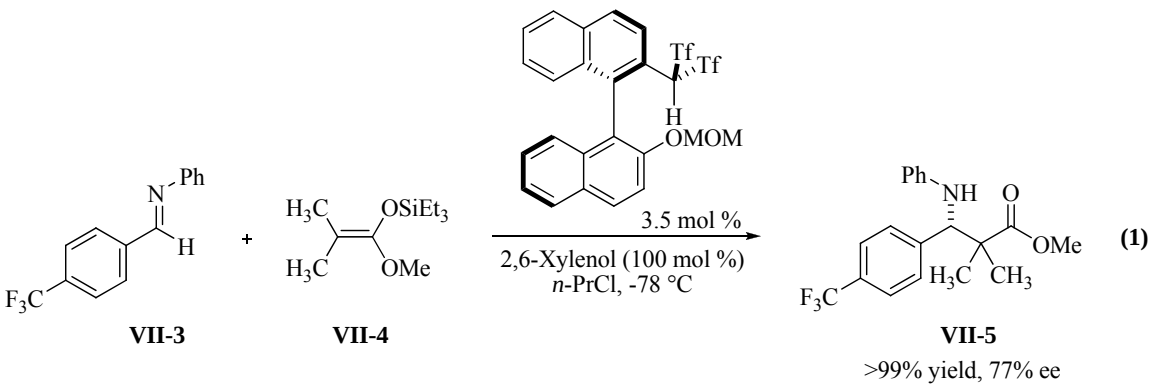
Leuhistin



VII-2

C2' Substituted Taxoid

Both Leuhistin **VII-1** and the C2'-substituted taxoid **VII-2** shown in Figure VII-1 contain a quaternary stereocenter substituted with a nitrogen atom adjacent to the carbonyl group. In some instances asymmetric Mannich reactions have proven effective for the generation of β-amino acids that contain a quaternary stereocenter.[7] For example, Yamamoto has reported a chiral Brønsted acid-catalyzed enantioselective Mannich reaction of *N*-phenyl aldimines **VII-3** with silyl ketene acetals **VII-4**, which provides good yields of products **VII-5** (eq 1).[8] However, levels of enantioselectivity are moderate, and the silane coupling partner is limited to **VII-4** as shown, or a trimethylsilyl derivative.



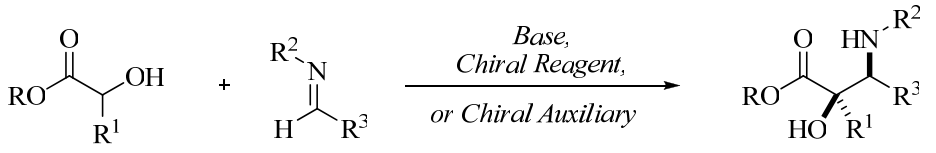
VII-3 **VII-4** **VII-5**

>99% yield, 77% ee

(1)

In principle, related asymmetric Mannich reactions of α-alkyl-α-hydroxy esters **VII-6** could provide efficient access to α-alkyl-α-hydroxy-β-amino acids **VII-7** (Scheme VII-1). However, in practice, the transformation illustrated in Scheme VII-1 is difficult to achieve, and the direct asymmetric synthesis of **VII-7** via ester enolate Mannich reactions has not been described. This may be due to the fact that deprotonation of α-alkyl-α-hydroxy esters typically leads to formation of *E* and *Z* ester enolate mixtures,[9] which are transformed to stereoisomeric amino alcohol products in the Mannich reactions.

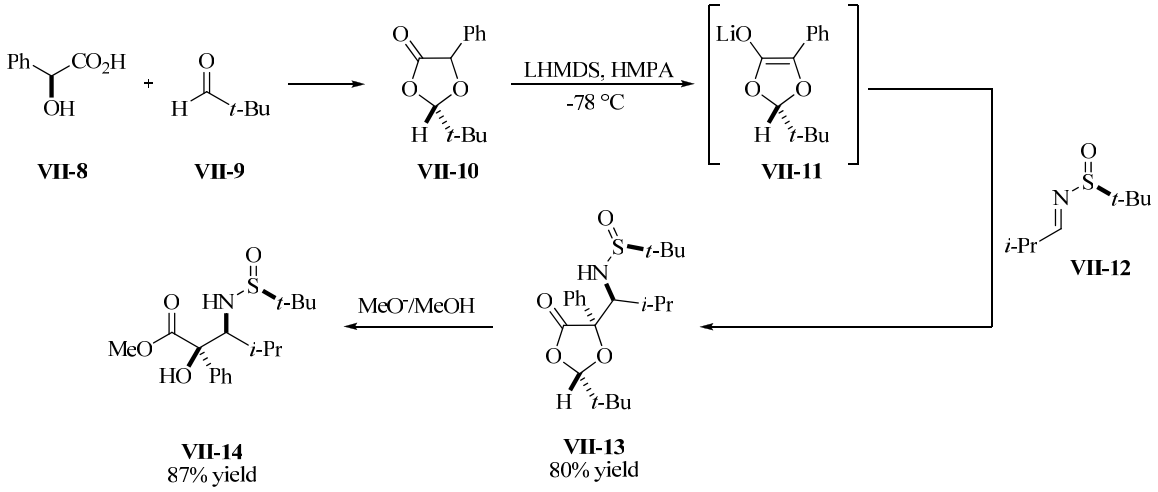
Scheme VII-1. Synthesis of α-Alkyl-α-Hydroxy-β-Amino Acids via Asymmetric Mannich Reactions of α-Alkyl-α-Hydroxy-β-Amino Esters



VII-6 **VII-7**

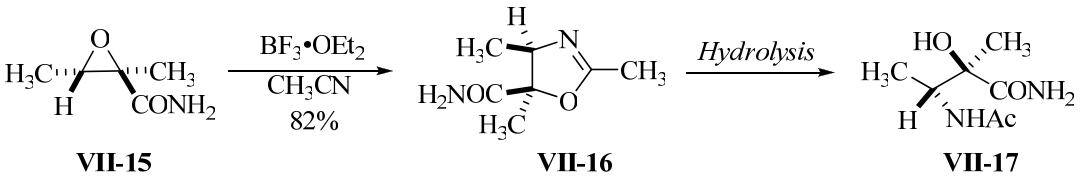
To avoid this problem, asymmetric Mannich reactions of chiral lactone enolates derived from enantiopure 1,3-dioxolan-4-ones have been developed.[10] For example, the 1,4-dioxolanone **VII-10** can be generated from acetalization of chiral α–hydroxy acids **VII-8** with aldehydes **VII-9** or ketones (Figure VII-2). Formation of the lithium enolate **VII-11** followed by reaction with *tert*-butylsulfinyl imine **VII-12** provides the *syn*-product **VII-13** in 80% yield. Subsequent methanolysis provides the methyl ester **VII-14** in 87% yield. However, the enantiopurity of **VII-14** was not reported. Although these reactions do provide access to compounds related to **VII-14**, formation of mixtures of *syn*:*anti* amino alcohol stereoisomers remains problematic in many examples.

Figure VII-2. Mannich Reaction of Chiral Lactone Enolate



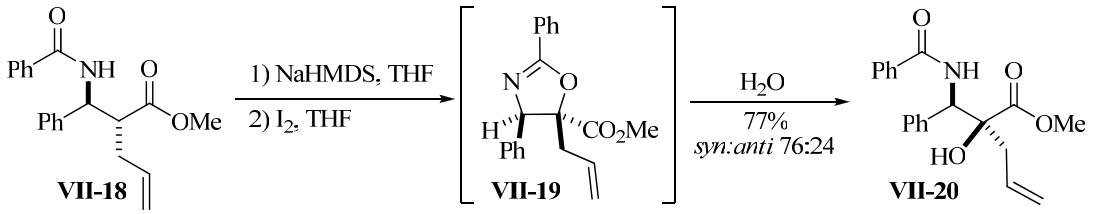
Several alternative approaches to the synthesis of α-alkyl-α-hydroxy-β-amino esters have also been explored, but either lack the convergence of a Mannich-based strategy,[11] or suffer from limited stereocontrol.[12,13] The BF_3•OEt_2 catalyzed oxirane ring

opening of glycidic amides **VII-15** with acetonitrile has been accomplished, giving rise to 2-oxazolines **VII-16** which can be subsequently hydrolyzed to the corresponding α-alkyl-α-hydroxy-β-amino derivatives **VII-16** (eq 2).[11a]



(2)

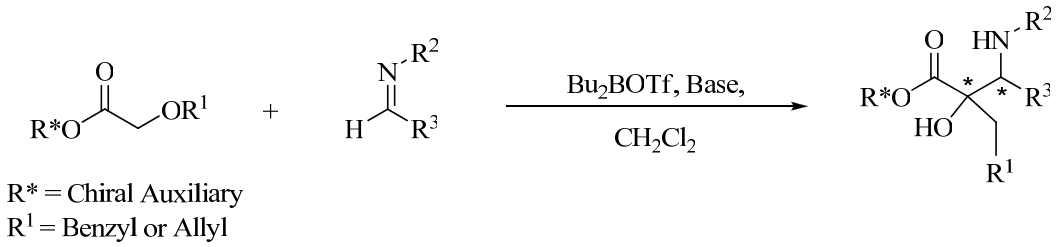
Another non-convergent method involves iodination of **VII-18** (prepared in four steps from 3-aminobutanoic acid), which effects spontaneous formation of *cis*-isoxazoline **VII-19** (eq 3). Hydrolysis of **VII-19** affords α-alkyl-α-hydroxy-β-amino acid **VII-20** in 77% yield and 76:24 *syn:anti* selectivity.



(3)

We felt the development of a Wittig rearrangement/Mannich reaction sequence would provide a simple and efficient means of preparing α-alkyl-α-hydroxy-β-amino esters with a high degree of stereocontrol (Scheme VII-2). The reaction of *O*-benzyl or *O*-allyl glycolate esters with simple imine coupling partners would allow for the preparation of a wide variety of α-alkyl-α-hydroxy-β-amino esters in a one-flask transformation.

Scheme VII-2. Proposed Asymmetric, Tandem Wittig/Mannich Reaction



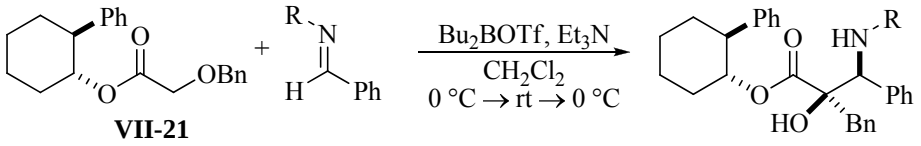
R* = Chiral Auxiliary
R^1 = Benzyl or Allyl

VII.2 Substrate Synthesis and Screening of Imine Coupling Partner

The *O*-benzyl and *O*-allyl glycolate esters used in these studies were prepared as previously described in Chapter VI. Imines examined were synthesized via reaction of the appropriate aldehyde with amines. In our initial efforts to effect tandem asymmetric Wittig rearrangement/Mannich reactions we examined the coupling of *O*-benzyl glycolate ester **VII-21** with several different imines derived from benzaldehyde. As shown in Table VII-1, the nature of the *N*-substituents had a large effect on reactivity and selectivity. Imines bearing strongly electron-withdrawing *N*-substituents such as tosyl or phosphoryl failed to undergo the Mannich reaction with the boron enolate generated after the Wittig rearrangement (Entries 4–5). Improved reactivity was observed with *N*-aryl imines, but diastereoselectivity was modest providing products **VII-23** and **VII-24** in 4:1 and 11:1 dr respectively (Entries 2–3). However, use of the *N*-benzyl imine provided satisfactory results (Entry 1).[14] The tandem Wittig/Mannich product **VII-22** was formed in 71% yield and with >20:1 diastereoselectivity. The relative stereochemistry of **VII-22** was confirmed by nOe analysis upon conversion to **VII-25** (Figure VII-3). The absolute

stereochemistry of **VII-22** was determined by X-ray crystallographic analysis (Figure VII-4).[15]

Table VII-1. Imine Substituent Effects[a]



Entry	R	Yield (%)[b]	dr[c]	*ee*[d]	Product
1	Bn	71	>20:1	96%	**VII-22**
2	PMP	85	4:1	58%	**VII-23**
3	Ph	71	11:1	83%	**VII-24**
4	Ts	0[e]	-	-	-
5	$P(O)Ph_2$	0[e]	-	-	-

[a] Conditions: 1.0 equiv **VII-21**, 3.2 equiv Bu_2BOTf, 4.0 equiv Et_3N, CH_2Cl_2 (0.1 M), 0 °C, 5 min, warm to rt for 15 min, cool to 0 °C, add imine. [b] Isolated yield (average of two or more runs). [c] Diastereomeric ratio of isolated material (determined by ^1H NMR analysis). The dr of the crude product could not be determined due to signal overlap with boron-containing byproducts. [d] Enantiomeric excess was determined by HPLC or Mosher ester analysis after transesterification to the methyl ester or reduction to the amino-diol. [e] The imine failed to undergo Mannich reaction.

Figure VII-3. Proof of Relative Stereochemistry

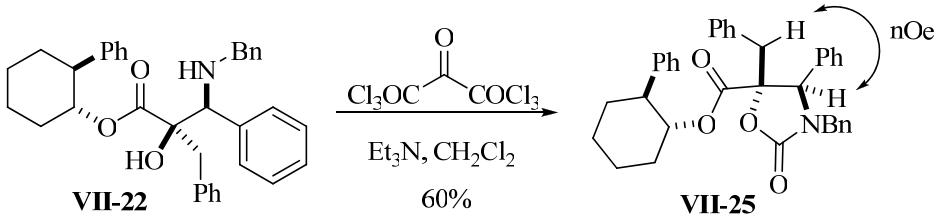
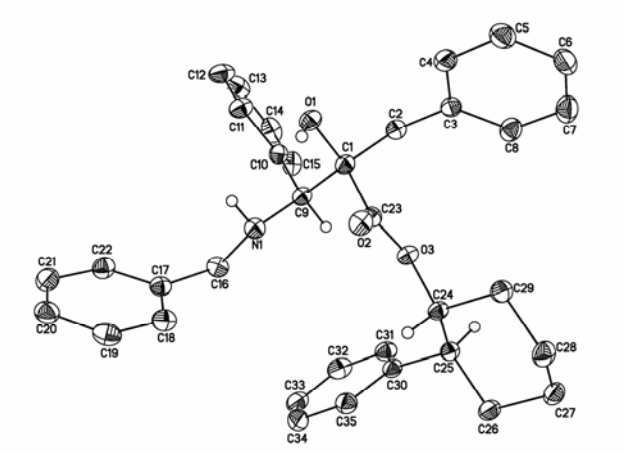


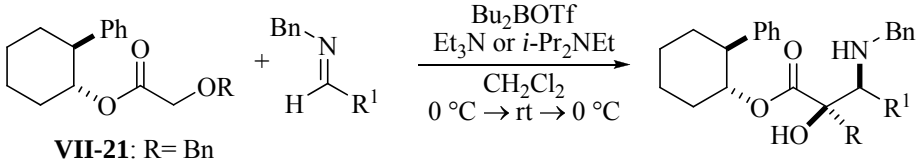
Figure VII-4. X-ray Crystal Structure of *Syn*-Amino Alcohol



VII.3 Scope of Tandem Wittig/Mannich Reaction Using Imines

As shown in Table VII-2, tandem asymmetric Wittig rearrangement/Mannich reactions between *O*-benzyl- and *O*-alkyl-2-phenycyclohexyl glycolate esters **VII-21** and **VII-26** and a range of *N*-benzyl imines derived from aromatic aldehydes proceed in good yield and with excellent stereoselectivity. In all cases products were formed with at least 20:1 dr, and enantiomerically enriched amino-diols were obtained in 90–96% ee after reduction with $LiAlH_4$. The *N*-benzyl imine prepared from cyclohexane carboxaldehyde was also transformed with high stereoselectivity, but in slightly lower yield (Entry 4). However, *N*-benzyl imines derived from unbranched aliphatic aldehydes gave complex mixtures of products.

Table VII-2. Asymmetric Wittig/Mannich Reactions with *N*-Benzyl Imines

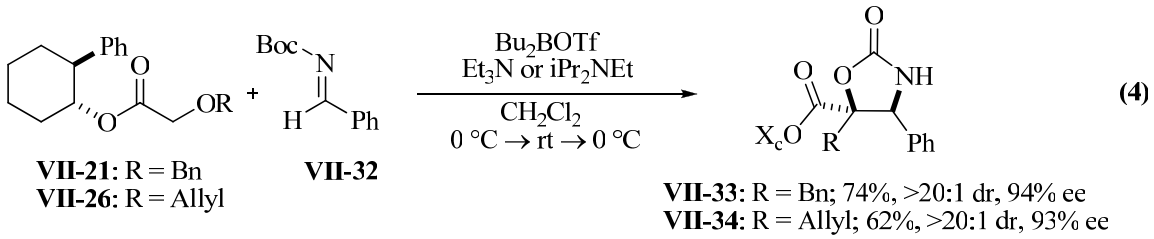


VII-21: R= Bn
VII-26: R= Allyl

Entry	R	R^1	Product	Yield (%)[b]	dr[c]	*ee*[d]
1	Bn	Ph	**VII-22**	71	>20:1	96%
2	Bn	PMP	**VII-27**	85	20:1	90%
3	Bn	2-furyl	**VII-28**	70	20:1	90%
4	Bn	Cy	**VII-29**	54	>20:1	93%
5	Allyl	Ph	**VII-30**	63	>20:1	94%
6	Allyl	*p*-F-Ph	**VII-31**	69	>20:1	94%

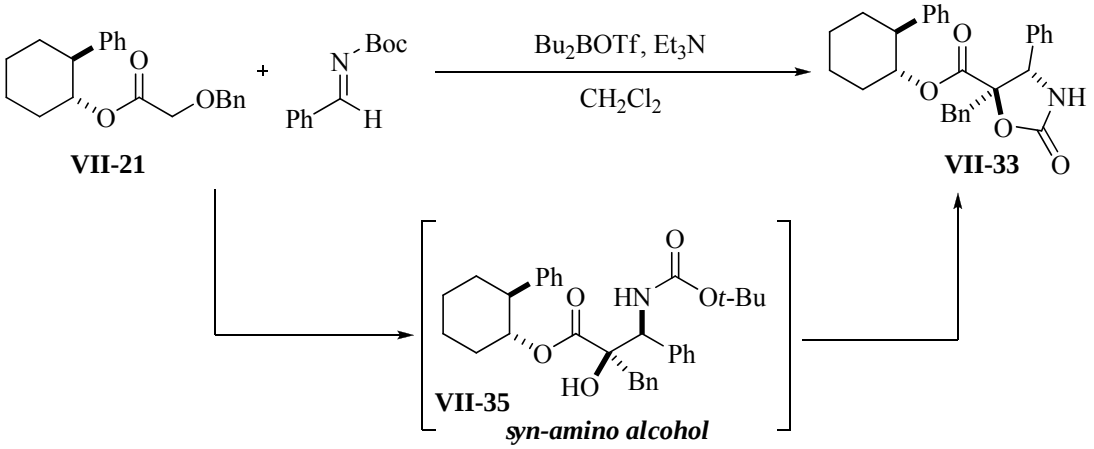
[a] Conditions: 1.0 equiv **VII-21** or **VII-26**, 3.2 equiv Bu_2BOTf, 4.0 equiv Et_3N (R =Bn) or 4.0 equiv $i Pr_2NEt$ (R = allyl), CH_2Cl_2 (0.1 M), 0 °C, 5 min, warm to rt for 15-20 min, cool to 0 °C, add imine. [b] Isolated yield (average of two or more runs). [c] Diastereomeric ratio of isolated material (determined by ^1H NMR analysis). The dr of the crude product could not be determined due to signal overlap with boron-containing byproducts. [d] Enantiomeric excess was determined by HPLC or Mosher ester analysis after transesterification to the methyl ester or reduction to the amino-diol.

Although imines bearing strong electron-withdrawing groups failed to undergo Mannich reaction (Table VII-1, Entries 4–5), use of *N*-Boc imine **VII-32** as an electrophile in the tandem reaction with **VII-21** generated isoxazolidin-2-one **VII-33** in 74% yield and >20:1 dr (94% ee after reduction) (eq 4). Compound **VII-33** is likely derived from the corresponding *syn*-amino alkoxy borane intermediate **VII-35** (Figure VII-5). A similar result was obtained for the coupling of **VII-32** with *O*-allyl glycolate ester **VII-26** to give **VII-34** (eq 4).



(4)

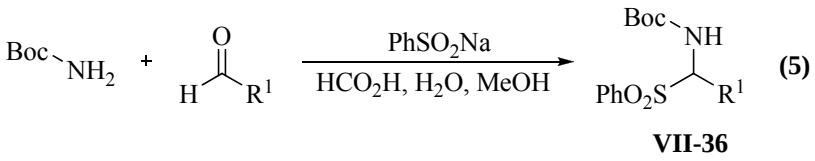
Figure VII-5. Oxazolidin-2-one Derived from *syn*-Amino Alcohol Intermediate



VII.4 Sulfonylamines as Imine Surrogates in Tandem Wittig/Mannich Reaction

Reactions of *N*-Boc imines or enamides derived from aliphatic aldehydes failed to afford the desired amino alcohol products. However, we were pleased to discover that transformations of *N*-Boc-2-(phenylsulfonyl)amines **VII-36** bearing either aliphatic or aromatic R^1 groups proceeded in moderate to good yields with excellent stereocontrol (Table VII-3). The sulfones used in these reactions were easily accessed in a one-flask procedure as outlined in Equation 5. In contrast to reactions of imine electrophiles, which

afforded *syn*-amino alcohols (or oxazolidinones), use of sulfones **VII-36** led to the formation of *anti*-amino alcohol products **VII-37**–**VII-39**.

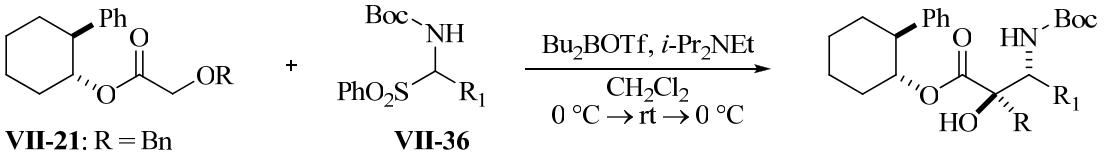


(5)

VII-36

R^1	Yield
Ph	73%
i-Bu	54%
Cy	94%

Table VII-3. Asymmetric Wittig/Mannich Reactions with *N*-Boc-2-(phenylsulfonyl)amines



VII-21: R = Bn
VII-26: R = Allyl

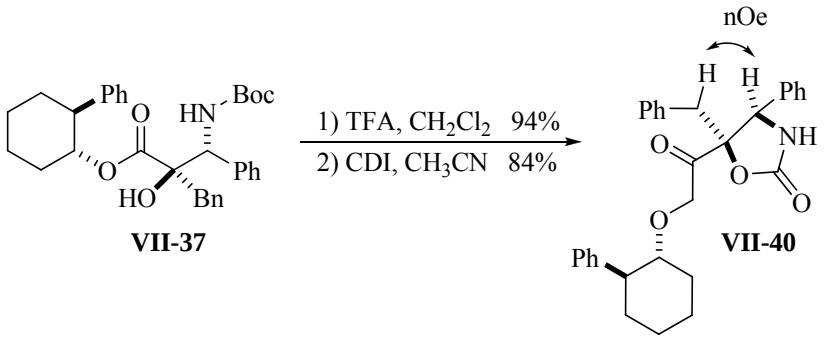
VII-36

Entry	R	R^1	Product	Yield (%)[b]	dr[c]	*ee*[d]
1	Bn	Ph	**VII-37**	58	>20:1	96%
2	Bn	*i*-Bu	**VII-38**	75	20:1	91%
3	Allyl	Cy	**VII-39**	60	20:1	90%

[a] Conditions: 1.0 equiv **VII-21** or **VII-26**, 3.2 equiv Bu_2BOTf, 4.0 equiv *i*-Pr_2NEt, CH_2Cl_2 (0.1 M), 0 °C, 5 min, warm to rt for 20 min, cool to 0 °C, add **VII-36**. [b] Isolated yield (average of two or more runs). [c] Diastereomeric ratio of isolated material (determined by ^1H NMR analysis). The dr of the crude product could not be determined due to signal overlap with boron-containing byproducts. [d] Enantiomeric excess was determined by HPLC or Mosher ester analysis after reduction to the corresponding amino-diol.

In order to confirm the relative stereochemistry of **VII-37** amino alcohol **VII-37** was converted to derivative **VII-40** via deprotection of the Boc group followed by conversion to the oxazolidin-2-one **VII-40** with CDI. The relative stereochemistry of **VII-40** was assigned based on the nOe signals depicted in Figure VII-6.

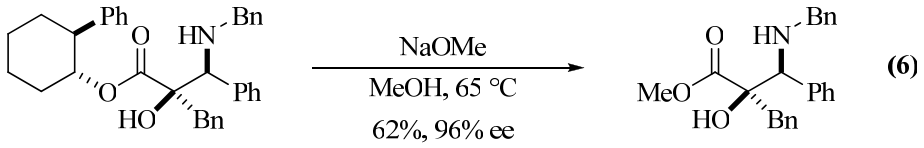
Figure VII-6. Assignment of *Anti*-Amino Alcohol Relative Stereochemistry



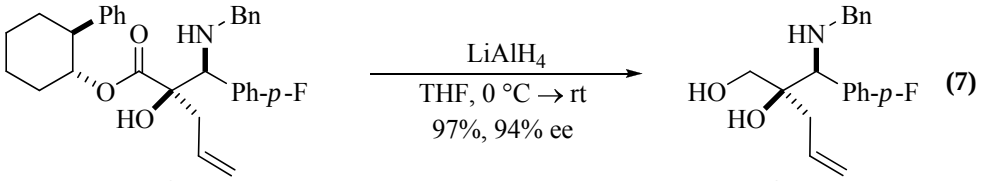
VII-37 **VII-40**

VII.5 Chiral Auxiliary Cleavage

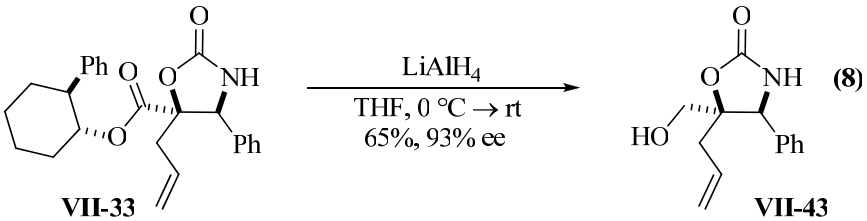
Cleavage of the chiral auxiliary from the amino alcohol products was accomplished either through methanolysis or reduction. For example, treatment of **VII-22** with NaOMe/MeOH provided methyl ester **VII-41** in 62% yield (eq 6). Alternatively, reduction of **VII-31** with $LiAlH_4$ generated amino-diol **VII-42** in 97% yield (eq 7). Selective reduction of cyclic carbamate **VII-33** and Boc-protected amino alcohol **VII-37** also proceeded smoothly (eq 8–9).



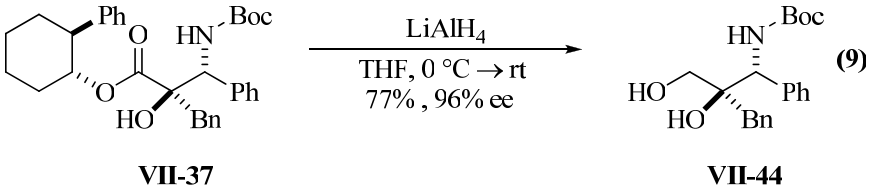
VII-22 **VII-41** **(6)**



VII-31 **VII-42** **(7)**



VII-33 **VII-43** **(8)**



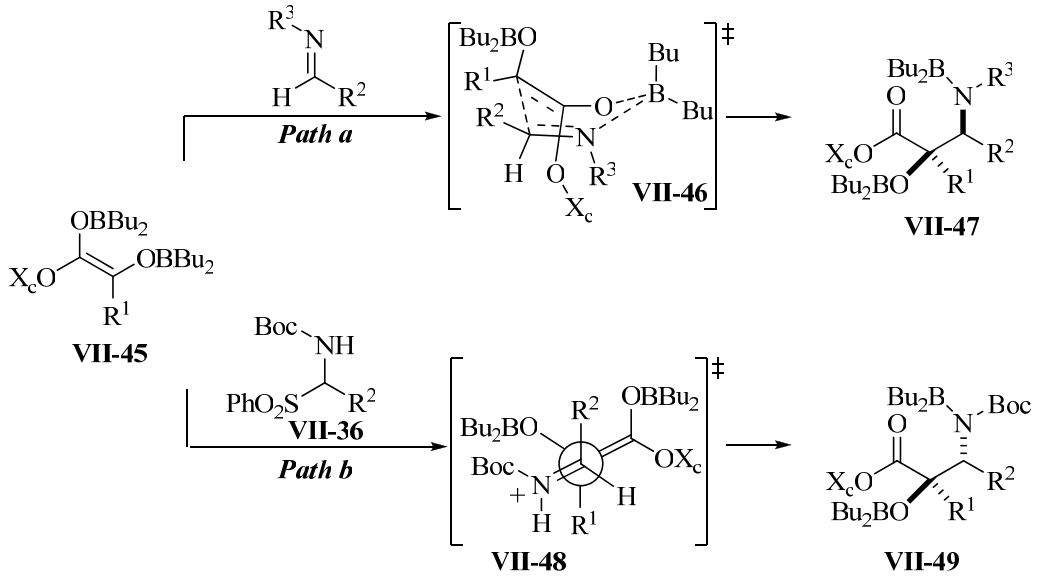
VII-37 **VII-44** **(9)**

VII.6 Mechanism of Tandem Wittig/Mannich Reaction

The mechanism of the tandem reactions likely occurs via an initial ester enolate Wittig-rearrangement followed by a second enolization to yield **VII-45** (Scheme VII-3).[16,17] The relative stereochemistry of the amino-alcohol product is set during the subsequent Mannich reaction, and is dependent on the nature of the electrophile. In reactions involving *N*-benzyl or *N*-Boc imine electrophiles the Mannich reactions occur via boat-like transition state **VII-46** to afford the *syn*-amino alcohol products **VII-47** and oxazolidin-2-ones (Scheme VII-3, Path a).[18]

In contrast, reactions of *N*-Boc-2-(phenylsulfonyl)amines **VII-36** likely involve intermediate *N*-Boc iminium ions (Scheme VII-5, Path b). The Mannich reactions between **VII-45** and the electrophilic iminium ions likely occur via open transition states such as **VII-48** in which R^2 is positioned to avoid gauche interactions with R^1. This gives rise to the observed *anti*-amino alcohol products.

Scheme VII-3. Stereochemical Hypothesis



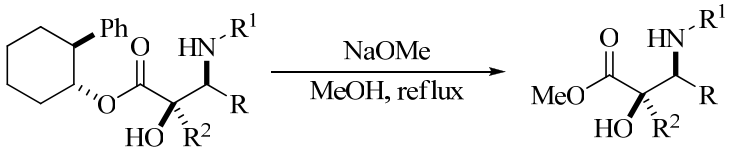
VIII.7 Summary and Conclusions

In conclusion, we have developed a new, highly stereoselective synthesis of enantiomerically enriched α-alkyl-α-hydroxy-β-amino esters via tandem asymmetric Wittig rearrangement/Mannich reactions. This method provides access to a range of *syn*- and *anti*-amino alcohol products from simple starting materials, and further illustrates the utility of Wittig rearrangements for stereoselective generation of enolates derived from α-alkyl-α-hydroxy esters.

VII.7 Experimental

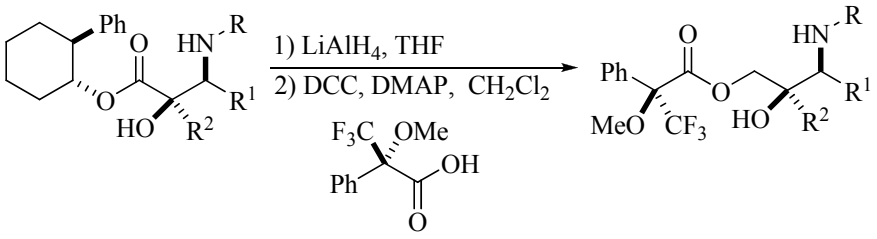
General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. Dibutylboron triflate (1.0 M solution in dichloromethane) was purchased from Aldrich Chemical Co. and was used as obtained. All imines and α-amido sulfones were prepared from aldehydes obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.). Aldehydes were purified by distillation from crushed anhydrous Ca_2SO_4. Triethylamine and diisopropylethylamine were obtained from Aldrich Chemical Co. and were purified by distillation from CaH_2. Phosphate buffer solution (pH 7) and 2-(benzyloxy)acetyl chloride were obtained from commercial sources and were used as obtained. *N*-(benzylidene)benzylamine,[19] *N*-(4-methoxybenzylidene)benzylamine, *N*-(furylidene)benzylamine, *N*-(4-fluorophenylmethylidine)benzylamine, *N*-*tert*-butoxycarbonyl-α-(phenylsulfonyl)benzylamine,[20] *N*-(*tert*-butoxycarbonyl)benzylamine, *N*-*tert*-butoxycarbonyl-3-methyl-1-(phenylsulfonyl)butylcarbamate,[21] *N*-*tert*-butoxycarbonyl-α-cyclohexyl(phenylsulfonyl)methylcarbamate, *N*-(benzylidene)-4-methoxyaniline,[22] *N*-benzylideneaniline, *N*-(cyclohexylmethylidene)benzylamine,[23] (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate,[1a] and (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate were prepared according to published procedures. Methylene chloride, tetrahydrofuran, and ether were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis. The yields reported in the Supporting Information describe the result of a single experiment, Thus, the yields reported in the Supporting Information may differ from those shown in this Chapter.

General Procedure A: Tandem Wittig rearrangement/Mannich reactions. A flame-dried flask was cooled under a stream of nitrogen and charged with a 1 M solution of dibutylboron triflate in dichloromethane (3.2 equiv). The pale yellow solution was cooled to 0 °C, and triethylamine or diisopropylethylamine (4.0 equiv) was added dropwise to afford a colorless solution. The ester substrate (1 equiv) was then added dropwise, and the reaction mixture was warmed to rt, stirred for 15 min (with triethylamine as base) or 20 min (with diisopropylethylamine as base), and then cooled to 0 °C. A solution of the imine (1.5 or 2 equiv) or α-amido sulfone (2 equiv) in CH_2Cl_2 (0.1 mL/mmol substrate) was added dropwise, and the reaction mixture was warmed to rt and stirred for 3–12 h. The reaction vessel was then opened to air, and pH 7 buffer (1 mL/mmol substrate), and methanol (2 mL/mmol substrate) were added. The resulting mixture was cooled to 0 °C, 30% aqueous H_2O_2 (2 mL/mmol substrate) was added slowly, and the reaction mixture was warmed to rt and stirred for 1 h. The mixture was diluted with ether (10 mL/mmol substrate) and water (5 mL/mmol substrate), then was transferred to a separatory funnel. The layers were separated, and the organic layer was washed with a saturated aqueous solution of $FeSO_4$ (4 x 5 mL/mmol substrate) until a red-orange aqueous phase no longer persisted in order to quench any remaining peroxide. *Caution! This procedure is exothermic. The $FeSO_4$ solution should be added via glass pipette SLOWLY DROPWISE.* The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.



General Procedure B: Method to Assess Enantiopurity of Products via Conversion to Methyl Esters. In order to assess the enantiomeric purity of the products formed in the tandem Wittig-rearrangement/Mannich reactions, the 2-phenylcyclohexyl esters were converted to the corresponding methyl esters using the following procedure. The glycolate ester (1.0 equiv) was dissolved in methanol (0.1 M) and added to a flame-dried 2-neck flask fitted with a reflux condenser under nitrogen. A solution of NaOMe (4.0 M in MeOH) was added, and the reaction mixture was heated to reflux and stirred until the starting material had been completely consumed as judged by TLC analysis (ca. 2 h). The reaction mixture was cooled to rt, quenched with 1 M HCl (1 mL/mmol substrate) and concentrated *in vacuo*. The crude residue was diluted with H_2O (1 mL/mmol substrate), and extracted with Et_2O (3 x 2 mL/mmol substrate). The phases were separated, and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude methyl ester product was purified by flash chromatography on silica gel. The enantiopurity was subsequently determined by chiral HPLC analysis.

For purposes of comparison, racemic amino-alcohol methyl esters were prepared from the corresponding *O*-benzyl or *O*-allyl methyl esters,[1b] using a procedure identical to that described above.



General Procedure C: Method to Assess Enantiopurity of Products via Reduction to Triol and Conversion to Mosher Ester. In order to assess the enantiomeric purity of the products formed in the tandem Wittig-rearrangement/Mannich reactions, the 2-phenylcyclohexyl esters were converted to the corresponding Mosher esters using the following procedure. The glycolate ester (1.0 equiv) was dissolved in THF (0.1 M) and cooled to 0 °C. A solution of $LiAlH_4$ (2 equiv/mmol substrate, 1.0 M in THF) was added, the reaction mixture was warmed to rt, and stirred until the starting material had been completely consumed as judged by TLC analysis. The reaction mixture was cooled to 0 °C and quenched with H_2O (1 mL/mmol substrate). The crude residue was diluted with Et_2O (2 mL/mmol substrate), 10 M NaOH was added (1 mL/mmol substrate), then H_2O (0.5 mL/mmol substrate) was added. The phases were separated, the inorganic precipitate was washed with ether (3 x 2 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude triol product was purified by flash chromatography on silica gel.

A solution of the triol in CH_2Cl_2 (0.2 M), DCC (1.1 equiv), DMAP (0.2 equiv) and (–)-(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (1.1 equiv) were combined and stirred at room temperature until the triol had been completely consumed as judged by TLC analysis. The reaction mixture was diluted with CH_2Cl_2, filtered through a cotton plug, and concentrated *in vacuo*. The crude product was purified by flash

chromatography on silica gel. The enantiopurity was subsequently determined by ^{19}F NMR analysis.

For purposes of comparison, racemic amino-alcohol Mosher esters were prepared from the corresponding *O*-benzyl or *O*-allyl methyl esters, using a procedure identical to that described above.

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-3'-benzylamino-2'-hydroxy-3'-phenylpropanoate (VII-22). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (47 mg, 0.14 mmol) with *N*-(benzylidene)benzylamine (42 mg, 0.22 mmol) was conducted according to General Procedure A using triethylamine as base to afford 54 mg (72%) of the title compound as a white foam. The diastereoselectivity of the transformation could not be determined through ^1H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –36.8 (*c* 0.20, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.24 (m, 8 H), 7.21–7.14 (m, 6 H), 7.13–7.11 (m, 3 H), 7.08–7.05 (m, 3 H), 4.81–4.76 (m, 1 H), 3.48 (s, 1 H), 3.30 (s, 1 H), 3.03 (d, *J* = 13.5 Hz, 1 H), 2.86–2.80 (m, 2 H), 2.60 (d, *J* = 13.0 Hz, 1 H), 2.53 (d, *J* = 13.5 Hz, 1 H), 2.06–2.03 (m, 1 H), 1.95–1.92 (m, 1 H), 1.80–1.77 (m, 2 H), 1.64–1.54 (m, 2 H), 1.44–1.36 (m, 2 H), 1.26–1.23 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 143.5, 140.8, 138.9, 136.1, 130.4, 128.7, 128.6, 128.1, 128.0, 127.9, 127.7, 127.5, 126.7, 126.5, 80.3, 80.1, 68.1, 50.4, 49.9, 42.4, 34.0, 31.9, 25.8, 24.6 (two carbon signals are absent due to incidental equivalence); IR (film) 3494, 2931, 1725 cm^{-1}. MS (ESI) 520.2835 (520.2852 calcd for $C_{35}H_{37}NO_3$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding methyl ester (**VII-41**) through reaction with NaOMe using General Procedure B. This procedure afforded 27 mg (62%) of **VII-21**. The enantiopurity of the methyl ester was determined to be 96% ee by chiral HPLC analysis (chiracel AD 0.46 cm x 15 cm, 10% isopropanol/ hexanes, 0.5 mL/min, RT= 23.9 and 28.4 min).

(+)-(2*R*,3*S*)-Methyl-2-benzyl-3-benzylamino-2-hydroxy-3-phenylpropanoate (VII-41). $[\alpha]^{23}_{D}$ +30.9 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.37 (m, 3 H), 7.37–7.27 (m, 4 H), 7.24–7.16 (m, 6 H), 7.01–7.00 (m, 2 H), 3.90 (s, 1 H), 3.72 (s, br, 1 H), 3.69 (s, 3 H), 3.46 (s, 1 H), 3.37 (d, *J* = 13.5 Hz, 1 H), 2.78 (d, *J* = 13.0 Hz, 1 H), 2.40–2.37 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 140.2, 138.4, 135.6, 128.8, 129.3, 128.4, 128.3, 128.1, 128.0, 127.8, 126.9, 126.7, 81.7, 65.9, 52.5, 50.1, 43.2; IR (film) 3502, 3029, 1738 cm^{-1}. MS (ESI) 376.1898 (376.1913 calcd for $C_{24}H_{25}NO_3$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-2'-hydroxy-3'-(*p*-methoxyphenylamino)-3'-phenylpropanoate (VII-23). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (67 mg, 0.21 mmol) with *N*-(benzylidene)-4-methoxyaniline (66 mg, 0.31 mmol) was conducted according to General Procedure A using triethylamine as base to afford 97 mg (87%) of the title compound as a white foam. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal

overlap with boron-containing byproducts; the isolated product was obtained with 4:1 dr following purification. $[\alpha]^{23}_{D}$ –35.9 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.08 (m, 12 H), 7.04–7.02 (m, 3 H), 6.56–6.54 (m, 2 H), 6.13–6.11 (m, 2 H), 4.96–4.90 (m, 1 H), 3.40 (s, br, 1 H), 4.13–4.11 (m, 1 H), 3.68 (s, 3 H), 3.31 (s, 1 H), 2.85–2.78 (m, 2 H), 2.68–2.65 (m, 1 H), 2.00–1.90 (m, 2 H), 1.80–1.73 (m, 2 H), 1.54–1.44 (m, 2 H), 1.40–1.23 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 151.8, 142.6, 140.1, 138.2, 135.4, 130.4, 128.6, 128.5, 128.0, 127.9, 127.4, 127.0, 126.8, 126.8, 115.6, 114.3, 79.6, 79.5, 62.9, 55.6, 49.5, 42.7, 34.8, 31.9, 25.7, 24.6; IR (film) 3378, 2931, 1733 cm^{-1}. MS (ESI) 558.2617 (558.2620 calcd for $C_{35}H_{37}NO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding methyl ester (**VII-S1**) through reaction with NaOMe using General Procedure B. The enantiopurity of the methyl ester was determined to be 58% ee by chiral HPLC analysis (chiracel AD 0.46 cm x 15 cm, 10% isopropanol/ hexanes, 1.0 mL/min, RT= 19.3 and 31.9 min).

(–)-(2*R*,3*S*)-Methyl-2-benzyl-2-hydroxy-3-(*p*-methoxyphenylamino)-3-phenylpropanoate (VII-S1). $[\alpha]^{23}_{D}$ –4.6 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 2 H), 7.36–7.31 (m, 2 H), 7.28–7.17 (m, 4 H), 7.07–7.04 (m, 2 H), 6.68–6.63 (m, 2 H), 6.55–6.52 (m, 2 H), 4.78 (s, 1 H), 4.59 (s, 1 H), 3.71 (s, 3 H), 3.67 (s, 3 H), 3.41 (s, 1 H), 3.01 (d, *J* = 13.2 Hz, 1 H), 2.52 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 140.3, 138.1, 135.3, 129.8, 128.9, 128.2, 128.1, 127.8, 126.9, 115.7, 114.6, 81.1, 63.6, 55.6, 53.0, 43.4, 27.0; IR (film) 3503, 2931, 1735 cm^{-1}. MS (ESI) 414.1673 (414.1681 calcd for $C_{24}H_{25}NO_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-2'-hydroxy-3'-phenylamino-3'-phenylpropanoate (VII-24). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (45 mg, 0.14 mmol) with *N*-benzylideneaniline (37 mg, 0.21 mmol) was conducted according to General Procedure A using triethylamine as base to afford 47 mg (67%) of the title compound as a white foam. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 11:1 dr following purification. $[\alpha]^{23}_{D}$ –63.8 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.16 (m, 8 H), 7.15–7.12 (m, 2 H), 7.10–7.07 (m, 2 H), 7.05–6.99 (m, 3 H), 6.98–6.93 (m, 2 H), 6.59–6.53 (m, 1 H), 6.21–6.20 (m, 2 H), 4.96–4.91 (m, 1 H), 4.67 (d, *J*= 10.5 Hz, 1 H), 4.20 (d, *J*= 10.0 Hz, 1 H), 3.29 (s, 1 H), 2.86 (s, 1 H), 2.84–2.79 (m, 1 H), 2.70–2.67 (m, 1 H), 1.99–1.91 (m, 2 H), 1.79–1.74 (m, 2 H), 1.53–1.43 (m, 1 H), 1.40–1.33 (m, 2 H), 1.30–1.22 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 145.9, 142.5, 138.0, 135.2, 130.4, 128.7, 128.6, 128.0, 127.9, 127.5, 127.0, 126.9, 126.8, 117.2, 114.3, 79.6, 79.5, 62.9, 49.5, 42.6, 34.7, 31.9, 25.7, 24.6 (one carbon signal is absent due to incidental equivalence); IR (film) 3396, 2924, 1717 cm^{-1}. MS (ESI) 528.2524 (528.2515 calcd for $C_{34}H_{35}NO_3$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S2**) using General Procedure C. This procedure afforded 17 mg (57%) of **VII-S2**. The enantiopurity was determined to be 83% ee by ^{19}F NMR analysis.

(–)-(1*S*,2'*R*,3'*S*)-2'-Benzyl-3'-benzylamino-3'-furan-2-yl-2-hydroxy-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S2). $[\alpha]^{23}_{D}$ –30.6 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2 H), 7.40–7.36 (m, 1 H), 7.34–7.29 (m, 3 H), 7.28–7.23 (m, 7 H), 7.07–6.97 (m, 2 H), 6.99–6.97 (m, 1 H), 6.67–6.62 (m, 2 H), 6.50–6.48 (m, 2 H), 4.89–4.86 (m, 1 H), 4.57–4.55 (m, 1 H), 4.41–4.38 (m, 1 H), 3.92–3.90 (m, 1 H), 3.57 (s, 3 H), 2.77 (d, *J*= 14.0 Hz, 1 H), 2.56–2.53 (m, 1 H), 1.54 (s, 1 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –70.9; IR (film) 3402, 2924, 1750 cm^{-1}. MS (ESI) 572.2034 (572.2025 calcd for $C_{31}H_{30}F_3NO_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-3'-benzylamino-2'-hydroxy-3'-*p*-methoxyphenylpropanoate (VII-27). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (56 mg, 0.17 mmol) with *N*-(4-methoxybenzylidene)benzylamine (58 mg, 0.26 mmol) was conducted according to General Procedure A using triethylamine as base to afford 87 mg (93%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_{D}$ –32.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 5 H), 7.20–7.09 (m, 9 H), 7.08–7.04 (m, 1 H), 6.98–6.96 (m, 2 H), 6.82–6.80 (m, 2 H), 4.81–4.76 (m, 1 H), 3.80 (s, 3 H), 3.45 (s, 1 H), 3.26 (s, 1 H), 3.04 (d, *J* = 13.5 Hz, 1 H), 2.85–2.79 (m, 2 H), 2.60 (d, *J* = 13.5 Hz, 1 H), 2.55 (d, *J* = 14.0 Hz, 1 H), 2.06–2.03 (m, 1 H), 1.94–1.92 (m, 1 H), 1.79–1.73 (m, 2 H), 1.63–

1.54 (m, 1 H), 1.44–1.35 (m, 2 H), 1.31–1.20 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 158.9, 143.5, 140.8, 136.2, 130.9, 130.4, 129.7, 128.6, 128.0, 127.9, 127.7, 127.5, 126.7, 126.5, 126.4, 113.5, 80.4, 80.0, 67.4, 55.2, 50.4, 49.8, 42.3, 34.0, 31.9, 25.9, 24.6; IR (film) 3494, 2934, 1725 cm^{-1}. MS (ESI) 572.2778 (572.2777 calcd for $C_{36}H_{39}NO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding methyl ester (**VII-S3**) through reaction with NaOMe using General Procedure B. This procedure afforded 20 mg (55%) of **VII-S3**. The enantiopurity of the methyl ester was determined to be 90% ee by chiral HPLC analysis (chiracel AD 0.46 cm x 15 cm, 5% isopropanol/ hexanes, 0.2 mL/min, RT= 86.5 and 95.7 min).

(+)-(2*R*,3*S*)-Methyl-2-benzyl-3-benzylamino-2-hydroxy-3-(4-methoxyphenyl)propanoate (VII-S3). $[\alpha]^{23}_D$ +28.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, 2 H), 7.28–7.27 (m, 2 H), 7.23–7.20 (m, 2 H), 7.19–7.15 (m, 4 H), 7.01–6.99 (m, 2 H), 6.95–6.93 (m, 2 H), 3.88 (s, 1 H), 3.84 (s, 3 H), 3.71 (s, 1 H), 3.68 (s, 3 H), 3.64 (s, 1 H), 3.45–3.34 (m, 2 H), 2.75 (d, *J* = 13.2 Hz, 1 H), 2.39 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 159.2, 140.3, 135.8, 130.5, 130.3, 129.8, 128.4, 128.0, 126.8, 126.7, 113.7, 81.8, 65.3, 55.2, 52.4, 50.0, 43.2 (one carbon signal is absent due to incidental equivalence); IR (film) 3498, 3035, 1730 cm^{-1}. MS (ESI) 428.1845 (428.1838 calcd for $C_{25}H_{27}NO_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-3'-benzylamino-2'-furan-2-yl-2'-hydroxypropanoate (VII-28). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (52 mg, 0.16 mmol) with *N*-(furylidene)benzylamine, (45 mg, 0.24 mmol) was conducted according to General Procedure A using triethylamine as base to afford 56 mg (68%) of the title compound as a white foam. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_{D}$ –9.5 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 1 H), 7.31–7.23 (m, 3 H), 7.22–7.18 (m, 7 H), 7.17–7.09 (m, 4 H), 7.05–7.02 (m, 1 H), 6.30–6.29 (m, 1 H), 6.09–6.07 (m, 1 H), 4.85–4.80 (m, 1 H), 3.49 (s, 1 H), 3.45 (s, 1 H), 3.12 (d, *J* = 13.0 Hz, 1 H), 2.93 (d, *J* = 14.0 Hz, 1 H), 2.83–2.78 (m, 1 H), 2.69–2.65 (m, 2 H), 2.07–2.04 (m, 1 H), 1.94–1.90 (m, 1 H), 1.81–1.76 (m, 2 H), 1.60–1.47 (m, 2 H), 1.47–1.33 (m, 2 H), 1.32–1.24 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 153.0, 143.3, 141.9, 140.5, 135.8, 130.4, 128.6, 128.0, 127.9, 127.8, 127.4, 126.6, 126.5, 110.0, 108.7, 79.9, 79.8, 61.9, 50.6, 49.7, 41.8, 34.3, 31.9, 25.8, 24.6 (two carbon signals are absent due to incidental equivalence); IR (film) 3420, 2935, 1728 cm^{-1}. MS (ESI) 510.2639 (510.2644 calcd for $C_{33}H_{35}NO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S4**) using General Procedure C. This procedure afforded 6 mg (43%) of **VII-S4**. The enantiopurity was determined to be 90% ee by ^{19}F NMR analysis.

(–)-(1*S*,2'*R*,3'*S*)-2'-Benzyl-3'-benzylamino-3'-furan-2-yl-2-hydroxy-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S4). $[\alpha]^{23}_{D}$ –11.6 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.53 (m, 2 H), 7.44–7.43 (m, 1 H), 7.42–7.33 (m, 3 H), 7.29–7.27 (m, 2 H), 7.25–7.18 (m, 6 H), 7.14–7.12 (m, 2 H), 6.37–6.36 (m, 1 H), 6.04–6.03 (m, 1 H), 4.37–4.35 (m, 1 H), 3.90–3.85 (m, 3 H), 3.70–3.69 (m, 1 H), 3.45 (s, 3 H), 3.41–3.39 (m, 2 H), 2.75–2.72 (m, 1 H), 2.61–2.58 (m, 1 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –71.5; IR (film) 3376, 2936, 1751 cm^{-1}. MS (ESI) 576.1972 (576.1974 calcd for $C_{31}H_{30}F_3NO_5$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-3'-benzylamino-3'-cyclohexyl-2'-hydroxypropanoate (VII-29). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (43 mg, 0.13 mmol) with *N*-(cyclohexylmethylidene)benzylamine (54 mg, 0.27 mmol, 2 equiv) was conducted according to General Procedure A using triethylamine as base to afford 46 mg (66%) of the title compound as a yellow oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_{D}$ –4.6 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.35 (m, 2 H), 7.30–7.27 (m, 2 H), 7.25–7.19 (m, 6 H), 7.18–7.14 (m, 5 H), 4.58–4.53 (m, 1 H), 4.08 (s, 1 H), 3.03 (d, *J* = 13.5 Hz, 1 H), 2.95 (d, *J* = 14.0 Hz, 1 H), 2.86 (d, *J* = 12.5 Hz, 1 H), 2.71–2.64 (m, 2 H), 2.20 (s, 1 H), 1.89–1.86 (m, 1 H), 1.78–1.64 (m, 6 H), 1.62–1.60 (m, 3 H), 1.42–1.40 (m, 1 H), 1.35–1.25 (m, 3

H), 1.22–1.10 (m, 3 H), 1.06–0.88 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 143.5, 141.1, 136.9, 130.3, 128.5, 128.2, 128.1, 127.9, 126.8, 126.7, 126.4, 79.6, 79.4, 67.5, 53.9, 49.7, 41.4, 38.8, 33.3, 32.5, 31.6, 27.0, 26.7, 26.3, 25.7, 24.5; IR (film) 3382, 2924, 1724 cm^{-1}. MS (ESI) 526.3333 (526.3321 calcd for $C_{35}H_{43}NO_3$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S5**) using General Procedure C. This procedure afforded 15 mg (71%) of **VII-S5**. The enantiopurity was determined to be 93% ee by ^{19}F NMR analysis.

(+)-(1*S*,2'*R*,3'*S*)-2'-Benzyl-3'-benzylamino-3'-cyclohexyl-2'-hydroxypropyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S5). $[\alpha]^{23}_D$ +42.8 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2 H), 7.43–7.39 (m, 4 H), 7.34–7.29 (m, 4 H), 7.24–7.20 (m, 3 H), 7.15–7.13 (m, 2 H), 4.11–4.09 (m, 1 H), 3.88–3.80 (m, 2 H), 3.63–3.59 (m, 2 H), 3.53 (s, 3 H), 2.84–2.80 (m, 1 H), 2.64–2.61 (m, 2 H), 1.75–1.67 (m, 6 H), 1.30–1.22 (m, 6 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –71.0; IR (film) 3358, 2932, 1754 cm^{-1}. MS (ESI) 570.2850 (570.2831 calcd for $C_{33}H_{38}F_3NO_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-3'-benzylamino-2'-hydroxy-3'-phenylpent-4-enoate (VII-30). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VII-26**) (46 mg, 0.17 mmol) with *N*-(benzylidene)benzylamine (49 mg, 0.25 mmol) was conducted according to General Procedure A using diisopropylethylamine as base to afford 78 mg (70%) of the title compound as a white foam. The diastereoselectivity of the

transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –36.7 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.21 (m, 7 H), 7.21–7.14 (m, 3 H), 7.10–7.08 (m, 2 H), 7.07–7.04 (m, 3 H), 5.44–5.37 (m, 1 H), 4.96–4.90 (m, 3 H), 3.38–3.36 (m, 2 H), 3.10 (d, *J* = 13.5 Hz, 1 H), 2.83–2.77 (m, 1 H), 2.71 (d, *J* = 13.5 Hz, 1 H), 2.40–2.32 (m, 2 H), 1.96–1.93 (m, 1 H), 1.89–1.79 (m, 3 H), 1.67–1.49 (m, 3 H), 1.42–1.33 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 143.4, 140.6, 138.8, 131.9, 128.6, 128.1, 128.0, 127.9, 127.5, 127.4, 126.7, 126.6, 118.8, 79.8, 79.3, 67.6, 50.5, 49.7, 41.4, 34.1, 32.2, 25.8, 24.6 (one carbon signal is absent due to incidental equivalence); IR (film) 3494, 2935, 1727 cm^{-1}. MS (ESI) 492.2903 (492.2515 calcd for $C_{31}H_{35}NO_3$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S6**) using General Procedure C. This procedure afforded 16 mg (41%) of **VII-S6**. The enantiopurity was determined to be 94% ee by ^{19}F NMR analysis.

(+)-(2*S*,3'*R*,4'*S*)-3'-Allyl-4'-benzylamino-4'-phenyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate VII-S6). $[\alpha]^{23}_D$ +11.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.56 (m, 2 H), 7.44–7.40 (m, 3 H), 7.37–7.29 (m, 5 H), 7.27–7.23 (m, 4 H), 7.15–7.13 (m, 1 H), 5.86–5.75 (m, 1 H), 5.10–5.08 (m, 1 H), 5.01–4.95 (m, 1 H), 4.55 (d, *J* = 11.2 Hz, 1 H), 3.90 (d, *J* = 11.6 Hz, 1 H), 3.75 (s, 1 H), 3.64 (d, *J* = 13.2 Hz, 1 H), 3.51

(s, 3 H), 3.38 (d, J = 13.2 Hz, 1 H), 3.23 (s, br, 1 H), 2.20–2.15 (m, 2 H), 1.97–1.92 (m, 1 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –71.4; IR (film) 3397, 2949, 1752 cm^{-1}. MS (ESI) 514.2204 (514.2205 calcd for $C_{29}H_{30}F_3NO_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-3'-benzylamino-3'-(*p*-fluorophenyl)-2'-hydroxypent-4-enoate (VII-31). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VII-26**) (49 mg, 0.18 mmol) with *N*-(4-fluorophenylmethylidine)benzylamine (57 mg, 0.27 mmol) was conducted according to General Procedure A using diisopropylethylamine as base to afford 59 mg (68%) of the title compound as a white foam. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_D$ –25.8 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.20 (m, 5 H), 7.19–7.14 (m, 2 H), 7.09–7.05 (m, 3 H), 6.98–6.91 (m, 4 H), 5.44–5.36 (m, 1 H), 4.98–4.91 (m, 3 H), 3.36–3.32 (m, 2 H), 3.09 (d, J = 13.0 Hz, 1 H), 2.82–2.76 (m, 1 H), 2.72 (d, J = 13.0 Hz, 1 H), 2.38–2.32 (m, 2 H), 1.96–1.93 (m, 1 H), 1.89–1.79 (m, 3 H), 1.65–1.59 (m, 2 H), 1.57–1.48 (m, 1 H), 1.42–1.33 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 163.4, 161.0, 143.4, 140.4, 134.5, 134.4, 131.7, 130.1, 128.6, 128.0, 127.4, 126.7, 118.9, 115.0 (d, J= 26.6 Hz), 79.7, 79.5, 67.9, 50.4, 49.7, 41.4, 34.1, 32.2, 25.8, 24.6; IR (film) 3366, 2931, 1730 cm^{-1}. MS (ESI) 488.2595 (488.2601 calcd for $C_{31}H_{34}FNO_3$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S7**) using General Procedure C. This procedure afforded 27 mg (50%) of **VII-S7**. The enantiopurity was determined to be 94% ee by ^{19}F NMR analysis.

(+)-(2*S*,3'*R*,4'*S*)-3'-Allyl-4'-benzylamino-4'-(*p*-fluorophenyl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S7). $[\alpha]^{23}_{D}$ +5.0 (*c* 0.10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2 H), 7.45–7.36 (m, 3 H), 7.31–7.24 (m, 3 H), 7.21–7.16 (m, 3 H), 7.11–7.07 (m, 1 H), 7.02–6.95 (m, 2 H), 5.82–5.71 (m, 1 H), 5.10–5.09 (m, 1 H), 5.00–4.96 (m, 1 H), 4.54 (t, *J* = 11.6 Hz, 1 H), 4.04 (d, *J* = 11.2 Hz, 0.5 H), 3.90 (d, *J* = 14.5 Hz, 0.5 H), 3.72 (s, 1 H), 3.61–3.56 (m, 2 H), 3.50 (s, 3 H), 3.39–3.32 (m, 1 H), 2.19–2.11 (m, 1 H), 1.98–1.85 (m, 2 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –71.3; IR (film) 3386, 2929, 1750 cm^{-1}. MS (ESI) 532.2110 (532.2111 calcd for $C_{29}H_{29}F_4NO_4$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-benzyl-2'-oxo-3'-phenyloxazolidine-5'-carboxylate (VII-33). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (56 mg, 0.18 mmol) with *N*-(*tert*-butoxycarbonyl)benzylamine (55 mg, 0.27 mmol) was conducted according to General Procedure A using triethylamine as base to afford 52 mg (97%) of the title compound as a white foam. The diastereoselectivity of the transformation could not be determined through ^1H NMR analysis of the crude reaction mixture prior to purification due to signal

overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_{D}$ –64.0 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 7 H), 7.23–7.14 (m, 4 H), 7.12–7.08 (m, 2 H), 7.00–6.98 (m, 2 H), 5.16–5.11 (m, 1 H), 5.03 (s, 1 H), 3.69 (s, 1 H), 2.85–2.80 (m, 1 H), 2.45 (d, *J*= 15.0 Hz, 1 H), 2.33 (d, *J* = 15.0 Hz, 1 H), 2.00–1.98 (m, 1 H), 1.84–1.78 (m, 3 H), 1.56–1.48 (m, 1 H), 1.45–1.32 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 158.1, 143.1, 135.8, 134.1, 129.9, 129.1, 128.9, 128.8, 128.0, 127.4, 127.2, 127.1, 86.5, 62.1, 50.4, 39.4, 34.8, 31.9, 25.7, 24.7 (two carbon signals are absent due to incidental equivalence); IR (film) 3270, 2935, 1766 cm^{-1}. MS (ESI) 478.2001 (478.1994 calcd for $C_{29}H_{29}NO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S8**) using General Procedure C. This procedure afforded 16 mg (64%) of **VII-S8**. The enantiopurity was determined to be 94% ee by ^{19}F NMR analysis.

(+)-(2*S*,4'*R*,5'*S*)-4'-Benzyl-4'-oxo-5'-phenyloxazolidine-5'-carboxylate-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S8). $[\alpha]^{23}_{D}$ +8.5 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.56 (m, 2 H), 7.48–7.30 (m, 7 H), 7.25–7.15 (m, 4 H), 7.03–7.00 (m, 2 H), 5.31 (s, 1 H), 4.79 (s, 1 H), 4.28 (d, *J* = 11.6 Hz, 1 H), 4.17 (d, *J* = 12.0 Hz, 1 H), 3.56 (s, 3 H), 2.59 (d, *J* = 14.8 Hz, 1 H), 2.12 (d, *J* = 14.4 Hz, 1 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –71.1; IR (film) 3387, 2921, 1760 cm^{-1}. MS (ESI) 522.1497 (522.1504 calcd for $C_{27}H_{24}F_3NO_5$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-allyl-2'-oxo-3'-phenyloxazolidine (VII-34). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(allyloxy)acetate (**VII-26**) (47 mg, 0.17 mmol) with *N*-(*tert*-butoxycarbonyl)benzylamine (53 mg, 0.26 mmol) was conducted according to General Procedure A using diisopropylethylamine as base to afford 45 mg (62%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_{D}$ –6.1 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 7 H), 7.22–7.17 (m, 1 H), 6.99–6.97 (m, 2 H), 5.42–5.32 (m, 1 H), 5.26–5.20 (m, 1 H), 5.09 (s, 1 H), 4.91–4.83 (m, 2 H), 3.95 (s, 1 H), 2.86–2.80 (m, 1 H), 2.19–2.16 (m, 1 H), 2.06–2.00 (m, 1 H), 1.99–1.89 (m, 2 H), 1.85–1.81 (m, 1 H), 1.75–1.63 (m, 1 H), 1.60–1.34 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 143.0, 135.7, 130.0, 129.1, 128.8, 127.5, 127.1, 126.6, 119.8, 86.1, 77.8, 61.7, 50.1, 38.1, 34.6, 32.1, 25.7, 24.7 (two carbon signals are absent due to incidental equivalence); IR (film) 3295, 2934, 1766 cm^{-1}. MS (ESI) 428.1829 (428.1838 calcd for $C_{25}H_{27}NO_4$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S9**) using General Procedure C. This procedure afforded 71 mg (53%) of **VII-S9**. The enantiopurity was determined to be 93% ee by ^{19}F NMR analysis.

(+)-(2*S*,4'*R*,5'*S*)-4'-Allyl-4'-oxo-5'-phenyloxazolidine-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S9). $[\alpha]^{23}_{D}$ +9.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.56 (m, 2 H), 7.47–7.44 (m, 3 H), 7.41–7.35 (m, 3 H), 7.16–7.14 (m, 2 H), 5.62–5.55 (m, 1 H), 5.35 (s, 1 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 4.91–4.88 (m, 1 H), 4.74 (s, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 3.58 (s, 3 H), 2.10–2.06 (m, 1 H), 1.72–1.67 (m, 1 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –71.3; IR (film) 3273, 2926, 1760 cm^{-1}. MS (ESI) 472.1336 (472.1348 calcd for $C_{23}H_{22}F_3NO_5$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-3'-[(*tert*-butoxycarbonyl)amino]-2'-hydroxy-3'-phenylpropanoate (VII-37). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (53 mg, 0.16 mmol) with *N*-*tert*-butoxycarbonyl-α-(phenylsulfonyl)benzylamine (85 mg, 0.25 mmol) was conducted according to General Procedure A using diisopropylethylamine as base to afford 50 mg (58%) of the title compound as a white solid, m.p. 160–162 °C. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with >20:1 dr following purification. $[\alpha]^{23}_{D}$ –8.0 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.38 (m, 1 H), 7.31–7.27 (m, 3 H), 7.22–7.21 (m, 3 H), 7.15–7.13 (m, 5 H), 7.08–7.06 (m, 2 H), 6.43–6.41 (m, 1 H), 5.49–5.46 (m, 1 H), 4.89–4.84 (m, 1 H), 4.65–4.63 (m, 1 H), 3.12–3.08 (m, 1 H), 3.03–3.00 (m, 1 H), 2.98 (s, 1 H), 2.92–2.86 (m, 1 H), 2.03–2.00 (m, 1 H), 1.91–1.88 (m, 1 H), 1.81–1.63 (m, 1 H), 1.58 (s, 1 H), 1.53 (s, 9 H), 1.45–1.35 (m, 2 H), 1.30–1.21 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 154.7, 143.1, 137.5, 135.2, 130.6, 129.2, 127.9,

127.8, 127.6, 127.5, 127.4, 126.9, 80.9, 79.5, 60.0, 49.2, 33.8, 31.8, 28.5, 24.5 (four carbon signals are absent due to incidental equivalence); IR (film) 3429, 2934, 1718 cm^{-1}. MS (ESI) 552.2718 (552.2726 calcd for $C_{33}H_{39}NO_5$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S10**) using General Procedure C. This procedure afforded 21.3 mg (51%) of **VII-S10**. The enantiopurity was determined to be 96% ee by ^{19}F NMR analysis.

(–)-(1*S*,2'*R*,3'*R*)-2'-Benzyl-3'-[(*tert*-butoxycarbonyl)amino]-2'-hydroxy-3'-phenylpropyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S10). $[\alpha]^{23}_D$ –26.0 (*c* 0.20, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.66 (m, 2 H), 7.52–7.46 (m, 3 H), 7.36–7.29 (m, 5 H), 7.21–7.16 (m, 3 H), 6.84–6.81 (m, 2 H), 5.58–5.55 (m, 1 H), 4.82–4.80 (m, 1 H), 4.23 (d, *J* = 11.2 Hz, 1 H), 3.70 (s, 3 H), 3.67–3.60 (m, 1 H), 2.72–2.69 (m, 1 H), 2.39–2.36 (m, 1 H), 1.54 (s, 1 H), 1.40 (s, 9 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –70.9; IR (film) 3432, 2932, 1752 cm^{-1}. MS (ESI) 596.2254 (596.2236 calcd for $C_{31}H_{34}F_3NO_6$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-3'-[(*tert*-butoxycarbonyl)amino]-2'-hydroxy-5'-methylhexanoate (VII-38). The reaction of (–)-(1*R*,2*S*)-2-

phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-21**) (49 mg, 0.15 mmol) with *N-tert*-butoxycarbonyl-3-methyl-1-(phenylsulfonyl)butylcarbamate (75 mg, 0.23 mmol) was conducted according to General Procedure A using diisopropylethylamine as base to afford 62 mg (81%) of the title compound as a white foam. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_D$ –6.8 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.35 (m, 3 H), 7.30–7.26 (m, 2 H), 7.25–7.19 (m, 5 H), 4.94–4.88 (m, 1 H), 3.92–3.90 (m, 1 H), 3.58–3.54 (m, 1 H), 3.27–3.20 (m, 1 H), 3.12 (d, *J* = 13.5 Hz, 1 H), 2.92 (d, *J* = 14.0 Hz, 1 H), 2.88–2.83 (m, 1 H), 2.06–2.03 (m, 1 H), 1.99–1.97 (m, 1 H), 1.86–1.82 (m, 1 H), 1.81–1.77 (m, 1 H), 1.57–1.54 (m, 2 H), 1.53 (s, 9 H), 1.41–1.37 (m, 5 H), 0.74–0.72 (m, 3 H), 0.67–0.66 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 155.8, 143.4, 135.8, 130.6, 129.4, 127.8, 127.3, 126.7, 80.2, 79.6, 78.9, 54.7, 49.7, 41.6, 37.8, 34.6, 32.2, 28.5, 28.4, 25.6, 24.7, 23.3, 20.9 (one carbon signal is absent due to incidental equivalence); IR (film) 3420, 2923, 1718 cm^{-1}. MS (ESI) 532.3027 (532.3039 calcd for $C_{31}H_{43}NO_5$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S11**) using General Procedure C. This procedure afforded 12.2 mg (53%) of **VII-S11**. The enantiopurity was determined to be 91% ee by ^{19}F NMR analysis.

(–)-(1*S*,2'*R*,3'*R*)-2'-Benzyl-3'-[(*tert*-butoxycarbonyl)amino]-2'-hydroxy-5'-methylhexyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S11). $[\alpha]^{23}_D$ –28.0

(*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2 H), 7.41–7.40 (m, 3 H), 7.20–7.19 (m, 3 H), 7.04–7.03 (m, 2 H), 4.48–4.42 (m, 1 H), 4.09–4.05 (m, 1 H), 3.90–3.87 (m, 1 H), 3.71–3.63 (m, 1 H), 3.57 (s, 3 H), 3.52 (s, 1 H), 2.91 (s, 1 H), 2.80–2.76 (m, 1 H), 2.69–2.65 (m, 1 H), 1.50 (s, 2 H), 1.39 (s, 9 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.78 (d, *J* = 6.4 Hz, 3 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –70.9; IR (film) 3420, 2958, 1751 cm^{-1}. MS (ESI) 576.2545 (576.2549 calcd for $C_{29}H_{38}F_3NO_6$, M + Na^+).

(–)-(1*R*,2*S*,2'*R*,3'*R*)-2-Phenylcyclohexyl-3'-[(*tert*-butoxycarbonyl)amino]-3'-cyclohexyl-2'-hydroxypent-4-enoate (VII-39). The reaction of (–)-(1*R*,2*S*)-2-phenylcyclohexyl-2'-(benzyloxy)acetate (**VII-26**) (44 mg, 0.16 mmol) with *N*-*tert*-butoxycarbonyl-α-cyclohexyl(phenylsulfonyl)methylcarbamate (85 mg, 0.24 mmol) was conducted according to General Procedure A using diisopropylethylamine as base to afford 49 mg (63%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through ^{1}H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 20:1 dr following purification. $[\alpha]^{23}_D$ –21.4 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 2 H), 7.29–7.24 (m, 2 H), 7.20–7.16 (m, 1 H), 5.52–5.46 (m, 1 H), 5.08–5.02 (m, 3 H), 4.89–4.83 (m, 1 H), 4.61 (d, *J* = 11.0 Hz, 1 H), 3.22 (s, 1 H), 2.80–2.75 (m, 1 H), 2.52–2.48 (m, 1 H), 2.35–2.25 (m, 3 H), 1.98–1.95 (m, 1 H), 1.89–1.86 (m, 1 H), 1.82–1.79 (m, 2 H), 1.72–1.70 (m, 1 H), 1.66–1.60 (m, 2 H), 1.54 (s, 9 H), 1.44–1.38 (m, 7 H), 1.38–1.26 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 155.6, 143.3, 131.4, 129.0, 127.6, 127.2, 119.8, 80.5,

78.9, 60.2, 49.5, 42.3, 36.9, 33.9, 32.0, 31.3, 28.5, 26.2, 25.9, 25.7, 25.3, 24.5; IR (film) 3420, 2923, 1718 cm^{-1}. MS (ESI) 508.3029 (508.3039 calcd for $C_{29}H_{43}NO_5$, M + Na^+).

The enantiopurity of the title compound was assessed by conversion to the corresponding Mosher ester (**VII-S12**) using General Procedure C. This procedure afforded 13.4 mg (67%) of **VII-S12**. The enantiopurity was determined to be 90% ee by ^{19}F NMR analysis.

(–)-(1*S*,2'*R*,3'*R*)-3'-[(*tert*-Butoxycarbonyl)amino]-3'-cyclohexyl-2'-hydroxypent-4'-enyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (VII-S12). $[\alpha]^{23}_D$ –48.0 (*c* 0.20, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.52 (m, 2 H), 7.44–7.40 (m, 3 H), 5.75–5.65 (m, 1 H), 5.19–5.12 (m, 1 H), 4.91–4.88 (m, 1 H), 4.23–4.11 (m, 1 H), 3.56 (s, 3 H), 3.53–3.50 (m, 1 H), 2.31–2.29 (m, 2 H), 2.04 (s, 1 H), 1.88–1.81 (m, 1 H), 1.74–1.71 (m, 3 H), 1.68–1.61 (m, 1 H), 1.40 (s, 9 H), 1.23–1.14 (m, 4 H), 1.13–1.04 (m, 2 H), 1.00–0.88 (m, 1 H), 0.86–0.84 (m, 1 H); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –71.4; IR (film) 3398, 2923, 1719 cm^{-1}. MS (ESI) 552.2542 (552.2549 calcd for $C_{27}H_{38}F_3NO_6$, M + Na^+).

(+)-(1*S*,2*R*)-3-Benzylamino-3-(*p*-fluorophenyl)-2-hydroxypent-4-ene-1-ol (VII-42). The reaction of (–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-3'-benzylamino-3'-(*p*-fluorophenyl)-2'-hydroxypent-4-enoate (**VII-31**) (49 mg, 0.10 mmol) with lithium aluminum hydride (0.20 mL, 0.20 mmol, 1 M in THF) was conducted according to General Procedure C to afford 31 mg (97%) of the title compound as an oil. $[\alpha]^{23}_D$ +14.8 (*c* 0.10, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 4 H), 7.28–7.26 (m, 2 H),

7.23–7.13 (m, 1 H), 7.09–6.96 (m, 2 H), 5.70–5.65 (m, 1 H), 5.02–5.00 (m, 1 H), 4.92–4.89 (m, 1 H), 3.66–3.61 (m, 3 H), 3.56–3.55 (m, 1 H), 3.46–3.42 (m, 1 H), 2.08–1.94 (m, 2 H), 1.84–1.77 (m, 2 H), 1.60 (s, br, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 130.2, 128.7, 128.4, 127.9, 127.5, 118.9, 115.4 (d, *J*= 26.6 Hz), 74.3, 69.5, 67.7, 62.1, 50.9, 40.5, 25.7; IR (film) 3370, 2924 cm^{-1}. MS (ESI) 316.1705 (316.1713 calcd for $C_{19}H_{22}FNO_2$, M + Na^+).

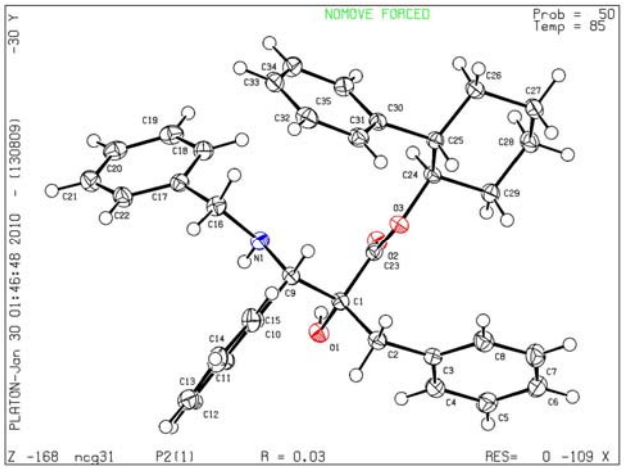
(+)-(1*S*,2*R*)-2-Allyl-2-hydroxymethyl-1-phenyloxazolidin-2-one (VII-43). The reaction of (–)-(1*R*,2*S*,2'*R*,3'*S*)-2-Phenylcyclohexyl-2'-allyl-2'-oxo-3'-phenyloxazolidine **VII-33** (34 mg, 0.08 mmol) with lithium aluminum hydride (0.17 mL, 0.17 mmol, 1 M in THF) was conducted according to General Procedure C to afford 13 mg (65%) of the title compound as an oil. $[\alpha]^{23}_D$ +45.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.34 (m, 3 H), 7.33–7.27 (m, 2 H), 5.60–5.49 (m, 1 H), 5.44, (s, br, 1 H), 5.16 (s, 1 H), 5.01–4.99 (m, 1 H), 4.91–4.87 (m, 1 H), 3.91 (d, *J*= 12.4 Hz, 1 H), 3.63 (d, *J*= 12.4 Hz, 1 H), 2.32 (s, br, 1 H), 2.21–2.04 (m, 1 H), 1.76–1.67 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 158.2, 136.3, 131.3, 128.9, 127.1, 119.5, 86.9, 64.9, 60.0, 37.7; IR (film) 3307, 2930, 1748 cm^{-1}. MS (ESI) 233.1059 (233.1052 calcd for $C_{13}H_{15}NO_3$, M + Na^+).

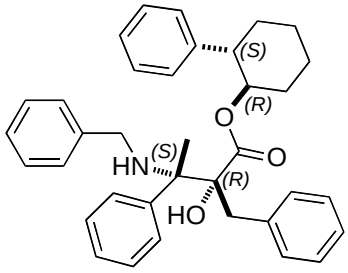
(+)-(1*R*,2*R*)-[(*tert*-Butoxycarbonyl)amino]-2-benzyl-1-phenylpropane-2,3-diol (VII-44). The reaction of (–)-(1*R*,2*S*,2'*R*,3'*R*)-2-Phenylcyclohexyl-2'-benzyl-3'-[(*tert*-butoxycarbonyl)amino]-2'-hydroxy-3'-phenylpropanoate (**VII-37**) (50 mg, 0.10 mmol)

with lithium aluminum hydride (0.38 mL, 0.38 mmol, 1 M in THF) was conducted according to General Procedure C to afford 26 mg (77%) of the title compound as an oil. $[\alpha]^{23}_{D}$ +16.4 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.45 (m, 2 H), 7.41–7.32 (m, 4 H), 7.29–7.27 (m, 1 H), 7.25–7.22 (m, 1 H), 7.14–7.13 (m, 2 H), 5.40–5.38 (m, 1 H), 4.85–4.83 (m, 1 H), 3.57–3.55 (m, 1 H), 3.40–3.36 (m, 1 H), 3.18–3.13 (m, 1 H), 2.97–2.94 (m, 1 H), 2.29–2.26 (m, 1 H), 1.63 (s, 1 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 138.4, 135.9, 130.6, 128.9, 128.6, 128.5, 127.9, 126.8, 80.5, 62.9, 58.4, 40.1, 28.3 (one carbon signal is absent due to incidental equivalence); IR (film) 3412, 2924, 1684 cm^{-1}. MS (ESI) 380.1842 (380.1838 calcd for $C_{21}H_{27}NO_4$, M + Na^+).

Assignment of Stereochemistry

Stereochemical Assignment of (VII-22). Stereochemical assignment of **VII-22** was accomplished by single-crystal x-ray analysis of product that had been recrystallized from dichloromethane/hexanes. The ORTEP of **VII-22** indicated this material had the ***1R,2S,2'R,3'S*** stereochemical configuration. The data for **VII-22** (CCDC 763869) can be obtained free of charge from The Cambridge Crystallographic Data Centre via the internet at www.ccdc.cam.ac.uk.





Stereochemical Analysis of Amino Alcohol (VII-40). Amino alcohol **VII-37** was converted to derivative (**VII-40**) via deprotection of the Boc group followed by conversion to the oxazolidin-2-one with CDI.

(–)-(1R,2S,2'S,3'S)-2-Phenylcyclohexyl-2'-benzyl-2'-oxo-3'-phenyloxazolidine-4'-carboxylate (VII-40). A flame-dried flask was charged with amino alcohol **VII-37** (32 mg, 0.06 mmol, 1.0 equiv) in dichloromethane (0.6 mL) and cooled to 0 °C. Trifluoroacetic acid (0.6 mL) was added dropwise, and the resulting solution was warmed to rt and stirred until the starting material had been completely consumed judged by TLC analysis (ca 1 h). Aqueous sodium carbonate (1.5 mL) and dichloromethane (8 mL) were added, and the resulting mixture was transferred to a separatory funnel. The layers were separated, and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product (24 mg, 0.06 mmol, 94%) was added as a solution in acetonitrile (0.6 mL) to a flame dried two-neck flask fitted with a reflux condenser. Carbonyldiimidazole (10 mg, 0.06 mmol, 1.1 equiv) was added and the

reaction mixture was heated to reflux until the starting material was completely consumed as judged by TLC analysis (ca 14 h). The reaction mixture was cooled to rt and concentrated *in vacuo*. The crude residue was diluted with H_2O (1 mL/mmol substrate), and extracted with dichloromethane (3 x 3 mL/mmol substrate). The phases were separated 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 affording 22 mg (84%) of the title compound as a white foam. $[\alpha]^{23}_{D}$ –36.2 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5 H), 7.24–7.21 (m, 5 H), 7.20–7.09 (m, 5 H), 4.97–4.93 (m, 1 H), 3.54 (s, 1 H), 3.40 (s, 1 H), 2.85–2.78 (m, 1 H), 2.68 (d, *J* = 14.0 Hz, 1 H), 2.28 (d, *J* = 13.6 Hz, 1 H), 2.03–1.91 (m, 2 H), 1.84–1.78 (m, 3 H), 1.63–1.52 (m, 2 H), 1.49–1.34 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 143.4, 141.4, 136.1, 130.1, 128.7, 128.3, 127.8, 127.6, 127.0, 126.6, 80.7, 79.0, 61.4, 50.2, 42.3, 34.1, 32.3, 25.7, 24.7, 24.4, 24.1, 21.0; IR (film) 3391, 2932, 1734 cm^{-1}. MS (ESI) 478.2017 (478.1994 calcd for $C_{29}H_{29}NO_4$, M + Na^+).

Table 1. Crystal data and structure refinement for ncg31.

Identification code	ncg31
Empirical formula	C35 H37 N O3
Formula weight	519.66
Temperature	85(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 12.2937(6) A alpha = 90 deg. b = 9.3548(4) A beta = 94.812(1) deg. c = 12.6676(6) A gamma = 90 deg.
Volume	1451.70(12) A^3
Z, Calculated density	2, 1.189 Mg/m^3
Absorption coefficient	0.075 mm^-1
F(000)	556
Crystal size	0.37 x 0.21 x 0.13 mm
Theta range for data collection	1.66 to 29.39 deg.
Limiting indices	-16<=h<=16, -12<=k<=12, -17<=l<=17
Reflections collected / unique	50503 / 4236 [R(int) = 0.0367]
Completeness to theta = 29.39	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9903 and 0.9729
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4236 / 1 / 360
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0338, wR2 = 0.0882
R indices (all data)	R1 = 0.0355, wR2 = 0.0898
Largest diff. peak and hole	0.304 and -0.151 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for ncg31. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3706(1)	299(1)	902(1)	20(1)
O(2)	3502(1)	134(1)	2980(1)	21(1)
O(3)	2324(1)	1993(1)	2930(1)	18(1)
N(1)	4674(1)	2738(1)	1842(1)	19(1)
C(1)	3054(1)	1379(2)	1323(1)	17(1)
C(2)	1915(1)	1343(2)	722(1)	19(1)
C(3)	1232(1)	51(2)	959(1)	20(1)
C(4)	1547(1)	-1342(2)	728(1)	24(1)
C(5)	894(1)	-2509(2)	946(1)	28(1)
C(6)	-79(1)	-2299(2)	1407(1)	28(1)
C(7)	-400(1)	-924(2)	1645(1)	30(1)
C(8)	245(1)	240(2)	1419(1)	25(1)
C(9)	3611(1)	2862(2)	1239(1)	17(1)
C(10)	3663(1)	3368(2)	101(1)	19(1)
C(11)	4269(1)	2627(2)	-606(1)	24(1)
C(12)	4314(2)	3109(2)	-1643(1)	30(1)
C(13)	3779(2)	4360(2)	-1976(1)	30(1)
C(14)	3198(1)	5124(2)	-1275(1)	29(1)
C(15)	3137(1)	4626(2)	-244(1)	24(1)
C(16)	5268(1)	4092(2)	2004(1)	21(1)
C(17)	6430(1)	3748(2)	2399(1)	19(1)
C(18)	6641(1)	2949(2)	3327(1)	23(1)
C(19)	7691(1)	2472(2)	3631(1)	26(1)
C(20)	8540(1)	2790(2)	3010(1)	26(1)

C(21)	8348(1)	3618(2)	2106(1)	27(1)
C(22)	7294(1)	4093(2)	1801(1)	24(1)
C(23)	2997(1)	1076(2)	2510(1)	17(1)
C(24)	2187(1)	1873(2)	4063(1)	17(1)
C(25)	1768(1)	3339(2)	4369(1)	17(1)
C(26)	1457(1)	3316(2)	5525(1)	23(1)
C(27)	631(1)	2137(2)	5693(1)	24(1)
C(28)	1091(1)	691(2)	5403(1)	24(1)
C(29)	1393(1)	668(2)	4252(1)	21(1)
C(30)	2564(1)	4533(2)	4192(1)	19(1)
C(31)	2260(1)	5663(2)	3513(1)	23(1)
C(32)	2963(2)	6812(2)	3391(1)	28(1)
C(33)	3978(2)	6839(2)	3948(1)	29(1)
C(34)	4311(1)	5704(2)	4611(1)	28(1)
C(35)	3605(1)	4559(2)	4731(1)	23(1)

Table 3. Bond lengths [A] and angles [deg] for ncg31.

O(1)-C(1)	1.4212(17)
O(2)-C(23)	1.2073(18)
O(3)-C(23)	1.3336(17)
O(3)-C(24)	1.4639(16)
N(1)-C(9)	1.4622(19)
N(1)-C(16)	1.4681(19)
C(1)-C(23)	1.5363(19)
C(1)-C(2)	1.537(2)
C(1)-C(9)	1.5546(19)
C(2)-C(3)	1.516(2)
C(3)-C(4)	1.398(2)

C(3)-C(8)	1.400(2)
C(4)-C(5)	1.396(2)
C(5)-C(6)	1.388(2)
C(6)-C(7)	1.386(3)
C(7)-C(8)	1.391(3)
C(9)-C(10)	1.5237(19)
C(10)-C(15)	1.395(2)
C(10)-C(11)	1.397(2)
C(11)-C(12)	1.394(2)
C(12)-C(13)	1.391(3)
C(13)-C(14)	1.385(3)
C(14)-C(15)	1.394(2)
C(16)-C(17)	1.508(2)
C(17)-C(22)	1.393(2)
C(17)-C(18)	1.399(2)
C(18)-C(19)	1.389(2)
C(19)-C(20)	1.391(2)
C(20)-C(21)	1.386(2)
C(21)-C(22)	1.395(2)
C(24)-C(29)	1.523(2)
C(24)-C(25)	1.5269(19)
C(25)-C(30)	1.514(2)
C(25)-C(26)	1.5445(19)
C(26)-C(27)	1.527(2)
C(27)-C(28)	1.523(2)
C(28)-C(29)	1.535(2)
C(30)-C(31)	1.394(2)
C(30)-C(35)	1.399(2)
C(31)-C(32)	1.396(2)
C(32)-C(33)	1.382(3)
C(33)-C(34)	1.393(3)

C(34)-C(35)	1.395(2)

C(23)-O(3)-C(24)	117.92(11)
C(9)-N(1)-C(16)	114.64(12)
O(1)-C(1)-C(23)	108.07(11)
O(1)-C(1)-C(2)	108.49(12)
C(23)-C(1)-C(2)	111.48(11)
O(1)-C(1)-C(9)	110.07(11)
C(23)-C(1)-C(9)	106.75(11)
C(2)-C(1)-C(9)	111.91(12)
C(3)-C(2)-C(1)	114.59(12)
C(4)-C(3)-C(8)	118.04(14)
C(4)-C(3)-C(2)	122.25(13)
C(8)-C(3)-C(2)	119.71(14)
C(5)-C(4)-C(3)	120.89(14)
C(6)-C(5)-C(4)	120.16(17)
C(7)-C(6)-C(5)	119.61(16)
C(6)-C(7)-C(8)	120.27(15)
C(7)-C(8)-C(3)	121.03(16)
N(1)-C(9)-C(10)	114.36(11)
N(1)-C(9)-C(1)	105.81(11)
C(10)-C(9)-C(1)	113.37(12)
C(15)-C(10)-C(11)	118.41(14)
C(15)-C(10)-C(9)	120.26(13)
C(11)-C(10)-C(9)	121.28(13)
C(12)-C(11)-C(10)	120.61(16)
C(13)-C(12)-C(11)	120.21(16)
C(14)-C(13)-C(12)	119.75(15)
C(13)-C(14)-C(15)	119.90(16)
C(14)-C(15)-C(10)	121.08(16)
N(1)-C(16)-C(17)	107.97(12)

C(22)-C(17)-C(18)	118.97(14)
C(22)-C(17)-C(16)	120.96(13)
C(18)-C(17)-C(16)	119.77(13)
C(19)-C(18)-C(17)	120.51(14)
C(18)-C(19)-C(20)	119.87(15)
C(21)-C(20)-C(19)	120.22(15)
C(20)-C(21)-C(22)	119.77(15)
C(17)-C(22)-C(21)	120.60(15)
O(2)-C(23)-O(3)	125.70(13)
O(2)-C(23)-C(1)	123.63(12)
O(3)-C(23)-C(1)	110.67(12)
O(3)-C(24)-C(29)	109.81(11)
O(3)-C(24)-C(25)	104.39(11)
C(29)-C(24)-C(25)	113.01(11)
C(30)-C(25)-C(24)	112.89(11)
C(30)-C(25)-C(26)	111.45(12)
C(24)-C(25)-C(26)	110.10(12)
C(27)-C(26)-C(25)	111.26(12)
C(28)-C(27)-C(26)	110.07(12)
C(27)-C(28)-C(29)	111.48(13)
C(24)-C(29)-C(28)	110.38(12)
C(31)-C(30)-C(35)	118.36(14)
C(31)-C(30)-C(25)	120.51(13)
C(35)-C(30)-C(25)	121.09(13)
C(30)-C(31)-C(32)	121.05(15)
C(33)-C(32)-C(31)	119.89(16)
C(32)-C(33)-C(34)	120.07(15)
C(33)-C(34)-C(35)	119.83(16)
C(34)-C(35)-C(30)	120.77(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for ncg31.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	23(1)	16(1)	22(1)	-1(1)	5(1)	4(1)
O(2)	25(1)	16(1)	23(1)	3(1)	4(1)	2(1)
O(3)	22(1)	17(1)	16(1)	0(1)	3(1)	2(1)
N(1)	22(1)	15(1)	21(1)	0(1)	2(1)	1(1)
C(1)	20(1)	14(1)	18(1)	0(1)	4(1)	1(1)
C(2)	21(1)	18(1)	19(1)	1(1)	2(1)	1(1)
C(3)	21(1)	22(1)	16(1)	0(1)	1(1)	-1(1)
C(4)	27(1)	24(1)	22(1)	-2(1)	6(1)	-3(1)
C(5)	33(1)	24(1)	25(1)	-1(1)	3(1)	-7(1)
C(6)	27(1)	34(1)	24(1)	3(1)	-1(1)	-11(1)
C(7)	21(1)	42(1)	28(1)	3(1)	3(1)	-2(1)
C(8)	21(1)	31(1)	24(1)	1(1)	2(1)	3(1)
C(9)	21(1)	13(1)	18(1)	1(1)	4(1)	1(1)
C(10)	21(1)	18(1)	19(1)	2(1)	3(1)	-2(1)
C(11)	34(1)	17(1)	23(1)	0(1)	8(1)	-2(1)
C(12)	46(1)	24(1)	22(1)	-4(1)	10(1)	-9(1)
C(13)	38(1)	31(1)	21(1)	5(1)	-1(1)	-15(1)
C(14)	25(1)	29(1)	32(1)	13(1)	-3(1)	-4(1)
C(15)	22(1)	23(1)	28(1)	7(1)	4(1)	2(1)
C(16)	24(1)	15(1)	23(1)	1(1)	1(1)	0(1)

C(17)	24(1)	15(1)	20(1)	-1(1)	2(1)	-2(1)
C(18)	28(1)	20(1)	20(1)	1(1)	2(1)	-3(1)
C(19)	33(1)	21(1)	22(1)	1(1)	-4(1)	1(1)
C(20)	26(1)	23(1)	28(1)	-7(1)	-2(1)	3(1)
C(21)	26(1)	28(1)	27(1)	-2(1)	6(1)	-1(1)
C(22)	28(1)	23(1)	21(1)	2(1)	5(1)	-2(1)
C(23)	18(1)	15(1)	19(1)	-1(1)	3(1)	-2(1)
C(24)	21(1)	16(1)	14(1)	1(1)	3(1)	0(1)
C(25)	20(1)	15(1)	16(1)	0(1)	3(1)	-1(1)
C(26)	28(1)	22(1)	19(1)	-1(1)	6(1)	-3(1)
C(27)	27(1)	25(1)	21(1)	0(1)	8(1)	-3(1)
C(28)	29(1)	22(1)	22(1)	4(1)	6(1)	-3(1)
C(29)	26(1)	17(1)	20(1)	1(1)	4(1)	-3(1)
C(30)	23(1)	15(1)	19(1)	-3(1)	6(1)	-2(1)
C(31)	30(1)	19(1)	20(1)	-1(1)	4(1)	-1(1)
C(32)	43(1)	18(1)	25(1)	1(1)	9(1)	-4(1)
C(33)	38(1)	24(1)	27(1)	-7(1)	14(1)	-12(1)
C(34)	25(1)	29(1)	29(1)	-8(1)	6(1)	-7(1)
C(35)	25(1)	22(1)	23(1)	-2(1)	3(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for ncg31.

	x	y	z	U(eq)
H(1A)	4064(18)	-120(30)	1408(18)	31(6)
H(1B)	5053(18)	2170(30)	1506(18)	33(6)
H(2A)	1515	2217	899	23
H(2B)	2001	1365	-48	23
H(4A)	2215	-1497	419	29

H(5A)	1116	-3449	779	33
H(6A)	-522	-3092	1557	34
H(7A)	-1063	-776	1964	36
H(8A)	13	1178	1579	30
H(9A)	3170	3574	1609	21
H(11A)	4655	1787	-378	29
H(12A)	4711	2580	-2123	36
H(13A)	3813	4689	-2682	36
H(14A)	2840	5987	-1496	35
H(15A)	2732	5151	230	29
H(16A)	4923	4688	2529	25
H(16B)	5252	4629	1329	25
H(18A)	6062	2732	3752	27
H(19A)	7828	1928	4262	31
H(20A)	9253	2439	3207	31
H(21A)	8934	3862	1697	32
H(22A)	7163	4657	1179	29
H(24A)	2909	1678	4462	20
H(25A)	1086	3534	3905	21
H(26A)	2122	3160	6009	27
H(26B)	1143	4253	5700	27
H(27A)	461	2127	6444	29
H(27B)	-55	2325	5248	29
H(28A)	542	-62	5501	29
H(28B)	1748	478	5883	29
H(29A)	1731	-262	4101	25
H(29B)	725	778	3766	25
H(31A)	1563	5651	3127	28
H(32A)	2744	7575	2925	34
H(33A)	4450	7631	3880	35
H(34A)	5016	5711	4980	33

H(35A)	3834	3787	5184	28

Table 6. Hydrogen bonds for ncg31 [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)...O(2)	0.84(2)	2.18(2)	2.6701(15)	117.4(19)

Symmetry transformations used to generate equivalent atoms:

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