Methodology Development for the Stereoselective Synthesis of Protected Pyrrolidines and α-Alkyl-α,β-Dihydroxy Esters

by

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À ma famille

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List of Acronyms and Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
Ar	generic aryl group
Binap	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1′-Bis(2-naphthol)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
Bz	benzoyl
Cbz	carbobenzyloxy
CDI	1,1'-Carbonyldiimidazole
Cp	cyclopentadienyl
DIP-Cl	B-chlorodiisopinocampheylborane
DIPEA	diisopropylethylamine
dba	trans, trans-Dibenzylideneacetone
Dpe-phos	Bis(2-diphenylphosphinophenyl)ether
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DMAP	4-dimethylaminopyridine
DME	1,2-Dimethoxyethane
IPC	isopinocampheyl
KHMDS	Potassium bis(trimethylsilyl)amide
L	generic neutral ligand
LDA	lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
MOM	methoxymethyl
Mes	2,4,6-trimethylphenyl
NaHMDS	Sodium bis(trimethylsilyl)amide
ND	Neodecanoate
Nixantphos	4,6-Bis(diphenylphosphino)phenoxazine
PMP	*para*-methoxyphenyl
Phane-phos	4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluorosulfonyl
TIPS	triisopropylsilyl

TMS	trimethylsilyl
o-tol	2-methylphenyl
p-tol	4-methylphenyl
Ts	4-methylbenzenesulfonyl
Xant-phos	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

Abstract

This thesis describes the development of methods for the stereoselective synthesis of protected pyrrolidines and α-alkyl-α,β-dihydroxy esters. The method for the synthesis of protected pyrrolidines is a palladium-catalyzed carboamination of protected γ-amino alkenes with aryl halides, and accomplishes the formation of both a carbon-nitrogen and carbon-carbon bond and up to two stereocenters in a single step with up to >20:1 diastereoselectivity. The scope of this transformation is described in detail, along with a refinement of reaction conditions which improve the functional group tolerance, and broaden the range of substrates that can be effectively transformed. A discussion of the diastereoselectivity obtained in the formation of disubstituted protected pyrrolidines is also presented. This methodology has been applied to the stereoselective synthesis of antifungal and antitumor agents preussin and 3-*epi*-preussin, along with new preussin analogs that differ in their aromatic ring substitution. Studies towards the synthesis of pyrrolidine alkaloid anisomycin are also described.

During the course of studies on Pd-catalyzed carboamination reactions that employ mild bases, we discovered a tandem directed carbopalladation/C–H bond functionalization that afforded cyclopentane-fused benzocyclobutene molecules. The scope of this new reaction is discussed along with a mechanistic hypothesis on the origin of these products.

The second part of this thesis describes a new method for the synthesis of α-alkyl-

α,β-dihydroxy esters. This transformation involves a tandem Wittig rearrangement-aldolreaction of methyl *O*-benzyl and methyl *O*-allyl glycolate esters, and was discovered during our work towards the synthesis of anisomycin. The reaction affords α-alkyl-α,β-dihydroxy esters in one step with >20:1 diastereoselectivity. The scope, limitations and mechanism of this new reaction are also discussed.

Part One

Palladium-Catalyzed Carboamination Reactions of Protected γ-Amino Alkenes with Aryl Halides

Chapter I

Introduction

The pyrrolidine moiety is displayed in many biologically active natural products and pharmaceutical agents (Figure 1).[1] For example, early studies on the natural product preussin (**I-1**) revealed its antifungal properties,[2] and more recent screens indicated that preussin (**I-1**) also has antitumor[3] and antiviral[4] activity (*vide infra*, Chapter V). The pyrrolidine alkaloid anisomycin (**I-2**) has also been shown to exhibit antifungal[5] and cytotoxic[6] activity (*vide infra*, Chapter VI), and broussonetine C (**I-3**), a member of the broussonetine family of alkaloids,[7] inhibits a variety of glycosidases.[7a] The drug Captopril (**I-4a**), marketed by Bristol-Myers Squibb under the trade name Capoten®, inhibits angiotensin converting enzyme (ACE) and is used in the treatment of hypertension.[8] Additionally, synthetic derivatives of Captopril with substituents at C2 and C3 such as **I-4b**, have shown even greater activity in ACE inhibition assays.[9] Finally, scientists at Schering-Plough identified pyrrolidine **I-5** as one of the most potent BACE-1 inhibitors discovered to date, and this compound constitutes a potential treatment for

Alzheimer's disease.[10]

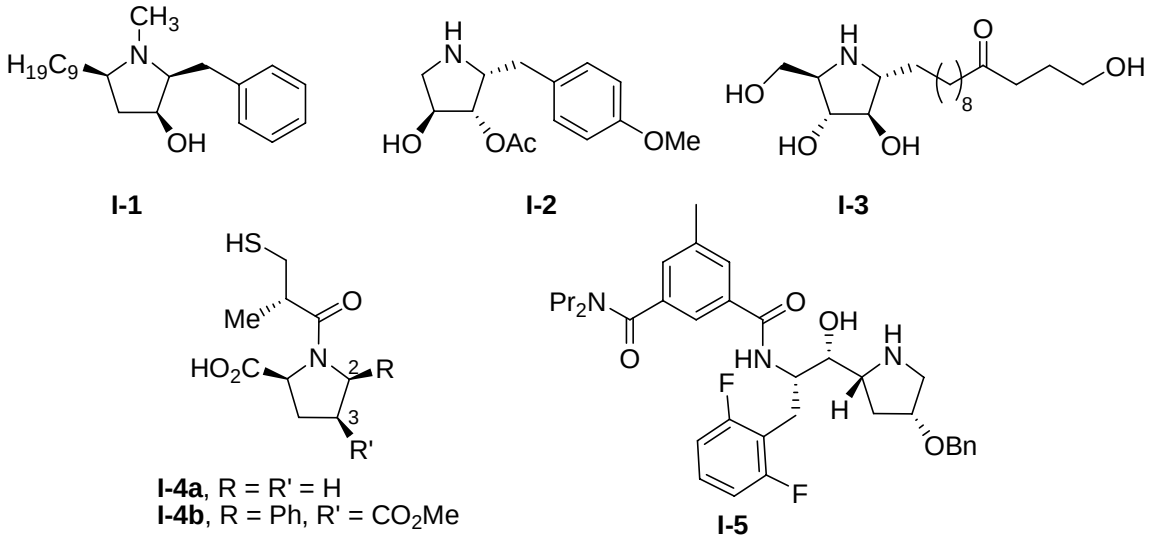
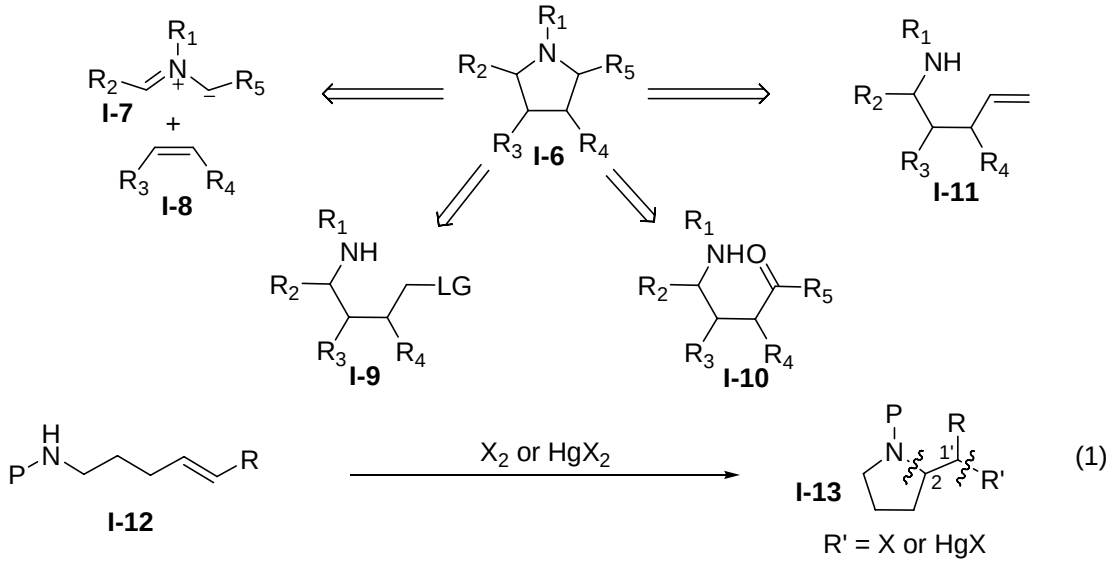


Figure 1. Biologically Active Pyrrolidines

Due to the interesting biological activity pyrrolidines exhibit, the synthesis of this nitrogen heterocycle has been the subject of extensive methodology development.[1,11] The methods developed can be divided in two general classes. The first class involves starting with the pyrrolidine ring from a common and inexpensive material (eg. proline) and functionalization of the heterocycle ring.[12] A more relevant class of reactions for the current report involves the formation of the pyrrolidine ring (**I-6**) from an acyclic precursor (Scheme 1). The [3+2] cycloaddition of azomethine ylides[13] (**I-7**) with substituted olefins (**I-8**) is a powerful method to rapidly obtain highly substituted pyrrolidine rings. Additionally, the pyrrolidine ring can be formed via intramolecular ring closure of **I-9** in a S_N2 reaction,[14] via reductive amination[15] of **I-10** or via radical cyclization of **I-11**.[16] Another traditional method to effect the pyrrolidine ring formation involves intramolecular cyclization of a nitrogen nucleophile onto a pendant olefin (**I-12**)

using activating reagents such as I_2 or $Hg(OAc)_2$ (eq 1).[1,17,18] This method allows formation of the pyrrolidine ring with concomitant formation of a C1' halogen bond or C1' mercury bond (eq 1, R' = X or HgX, **I-13**). In contrast, the carboamination chemistry discussed in this thesis allows for the formation of the pyrrolidine ring and a new C1'–C bond (eq 1, R' = alkenyl or aryl).[19]

Scheme 1. Traditional Methods for the Synthesis of Substituted Pyrrolidines

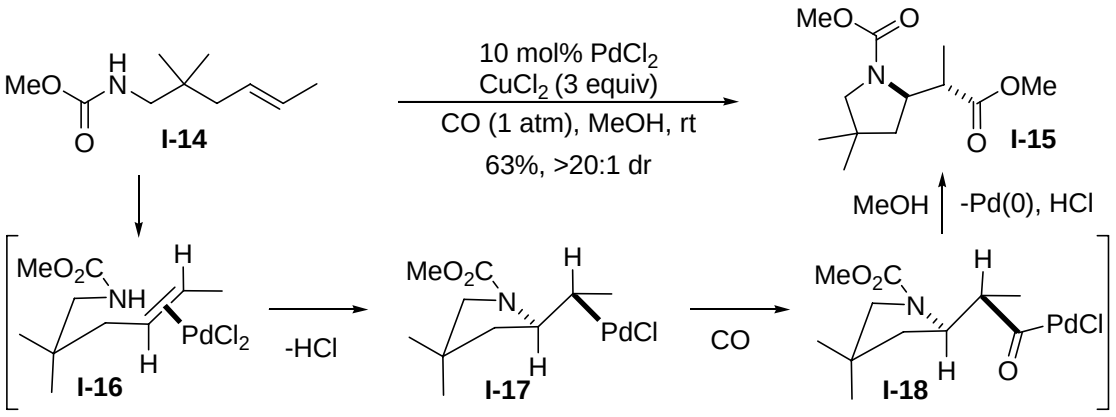


Palladium-Catalyzed Carboamination Reactions for the Synthesis of Pyrrolidines

The first examples of Pd-catalyzed alkene carboamination reactions were discovered by Tamaru and co-workers, and involved Pd(II)-catalyzed carbonylation of γ-aminoalkenes to afford pyrrolidines bearing C1' ester groups (Scheme 2).[20] For example, γ-aminoalkene **I-14** underwent *anti*-aminocarbonylation upon treatment with catalytic $PdCl_2$ and excess $CuCl_2$ in MeOH under an atmosphere of CO to afford **I-15** in moderate yield and as a single diastereomer.[21] This reaction is believed to occur via alkene (**I-16**)

coordination to Pd(II), followed by *anti*-aminopalladation to provide **I-17**, and CO insertion into the C1'–Pd bond to afford acylpalladium intermediate **I-18**. Methanolysis of intermediate **I-18** then affords pyrrolidine **I-15**. Other substrates bearing nitrogen nucleophiles such as sulfonamides[20] and ureas[20b–e] were also transformed into pyrrolidines in a similar fashion, and this methodology has been employed in the racemic synthesis of natural products ferruginine and anatoxin A.[22]

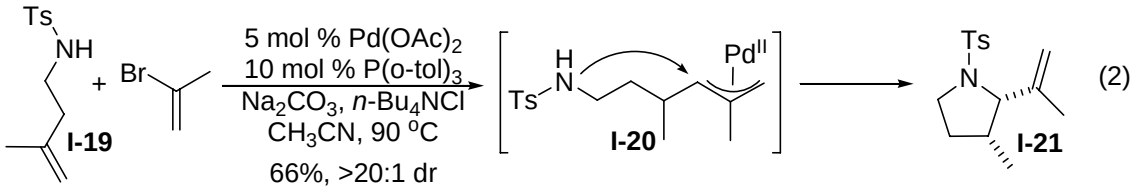
Scheme 2. Palladium-Catalyzed Aminocarbonylation Reaction



Although Pd(II)-catalyzed aminocarbonylation of γ-aminoalkenes has proven useful for the synthesis of pyrrolidine derivatives bearing C1' ester substituents, it is not without limitations. For example, synthetic manipulations would be required to convert **I-15** to alkyl, aryl, or vinyl substituted pyrrolidine derivatives. Additionally, the synthesis of pyrrolidines bearing multiple stereocenters around the ring has not been fully explored.

In later work, Larock and Weinreb reported the palladium-catalyzed 1,1-carboamination reaction of β-amino alkenes with vinyl bromides for the synthesis of 2-vinyl pyrrolidines.[23] In a representative example, a catalyst composed of $Pd(OAc)_2$/P(*o*-

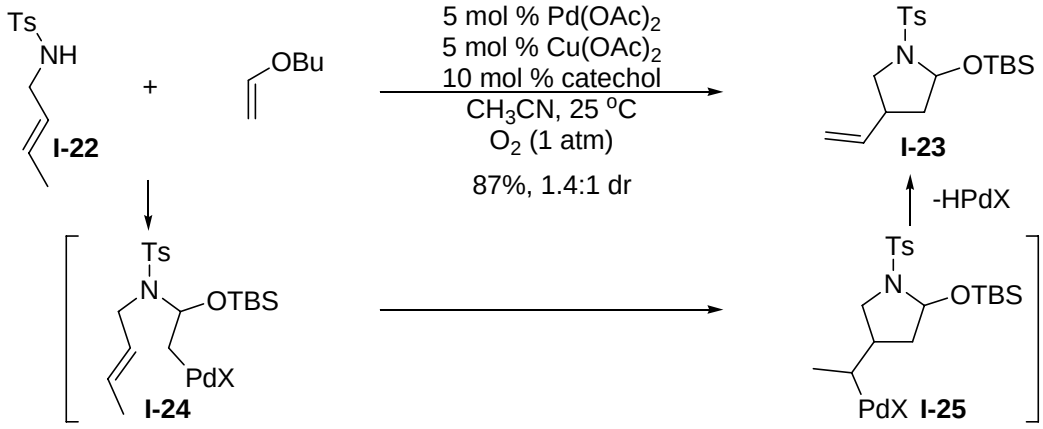
tol)$_3$ effects the coupling of **I-19** with 2-bromopropene to afford product **I-21** in moderate yield and high diastereoselectivity (eq 2). This reaction is believed to proceed via a Heck-type reaction between **I-19** and 2-bromopropene, which leads to π-allyl palladium intermediate **I-20**. Intramolecular trapping of π-allyl intermediate **I-20** by the amine moiety affords **I-21**. This method is effective for the preparation of various 2-vinyl pyrrolidines in moderate to good yield, however the stereochemical outcome of the reactions involving substituted amine substrates other than the example shown in eq 2 was not explored. Furthermore, generation of a stereocenter at C1' is not possible via this methodology.



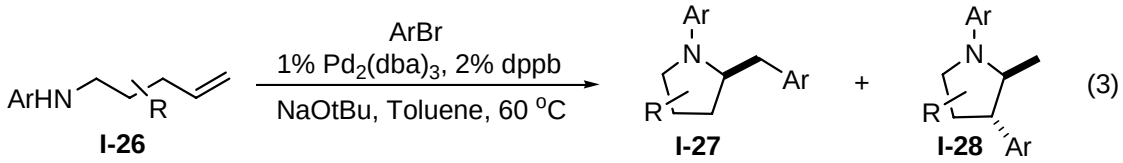
More recently, Stahl reported a palladium-catalyzed carboamination reaction between electron-rich alkenes or styrene derivatives with allylic sulfonamides that generates 2,4-disubstituted pyrrolidines.[24] For example, treatment of **I-22** with butyl vinyl ether in the presence of catalytic amounts of $Pd(OAc)_2$, $Cu(OAc)_2$ and catechol under an O_2 atmosphere affords product **I-23** (Scheme 3). The proposed mechanism for this reaction involves activation of the butyl vinyl ether by Pd(II) followed by aminopalladation to generate **I-24**. Migratory insertion followed by β-hydride elimination of **I-25** affords **I-23**. Although this reaction generates pyrrolidine products in good yields, the diastereoselectivity of the process is low, and a large excess (12 equiv) of coupling

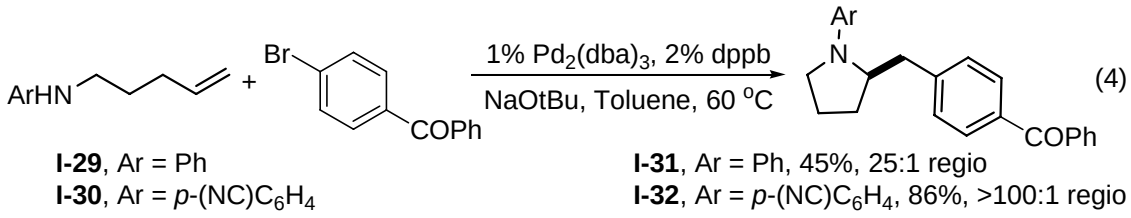
partner is required when styrene derivatives are used instead of butyl vinyl ether.

Scheme 3. Palladium-Catalyzed Carboamination Reaction of *N*-Tosyl Allylamines



In a seminal publication in 2004, Wolfe and Ney demonstrated the palladium(0)-catalyzed cyclization of γ-aryl amino alkene substrates **I-26** with aryl bromides to afford *N*-aryl pyrrolidines **I-27** (eq 3).[25,26] Regioisomeric products **I-28** were also formed in various ratios (8:1– >100:1), and competing *N*-arylation of the substrate was observed when electron-deficient aryl bromides were employed. Interestingly, as shown in equation 4, yields and regioselectivity increased dramatically when the phenyl *N*-substituent was replaced with an electron-withdrawing *p*-cyanophenyl group (**I-30** transformed to **I-32**).



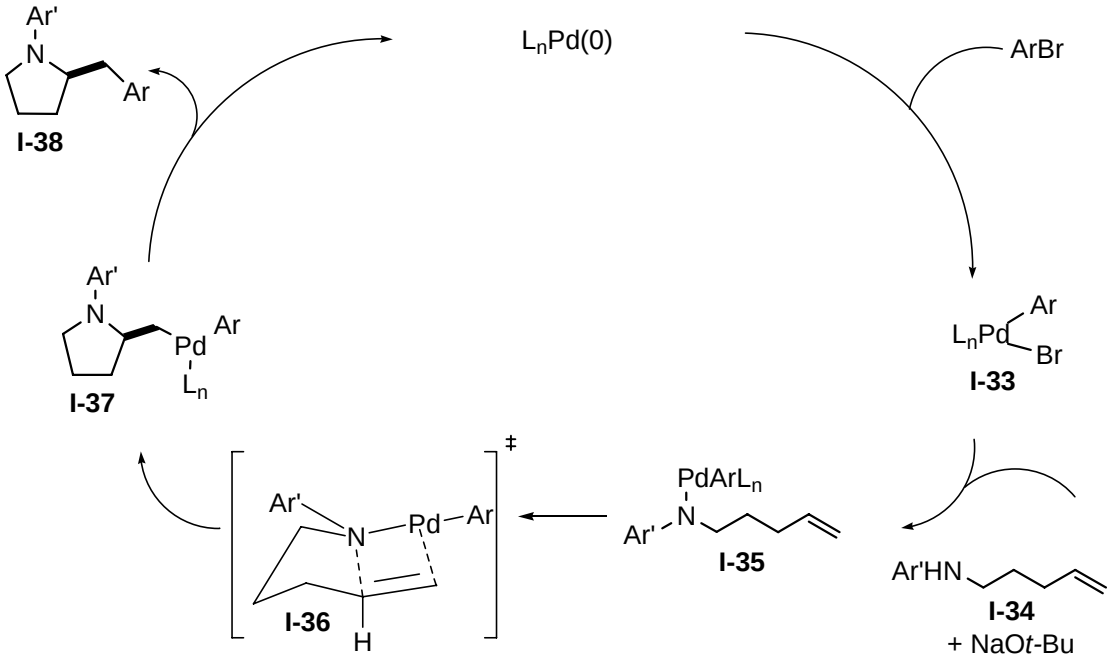


I-29, Ar = Ph
I-30, Ar = *p*-(NC)C_6H_4

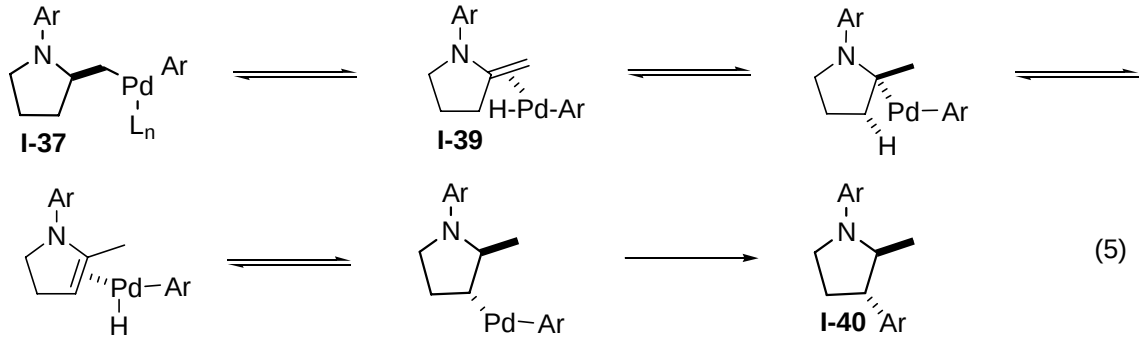
I-31, Ar = Ph, 45%, 25:1 regio
I-32, Ar = *p*-(NC)C_6H_4, 86%, >100:1 regio

The Pd-catalyzed carboamination reactions shown in eqs 3-4 are believed to proceed via the catalytic cycle illustrated below (Scheme 4). Oxidative addition of the ArBr to palladium(0) forms the palladium(II) complex **I-33**. Intermediate **I-33** is then converted to the Pd-amido complex **I-35** through reaction with the amine **I-34** and base.[27] Intermediate **I-35** then undergoes intramolecular syn-aminopalladation[28] via transition state **I-36** to produce intermediate **I-37**, and C–C bond forming reductive elimination from **I-37** affords product **I-38**.[29]

Scheme 4. Proposed Catalytic Cycle for the Palladium-Catalyzed Carboamination Reaction

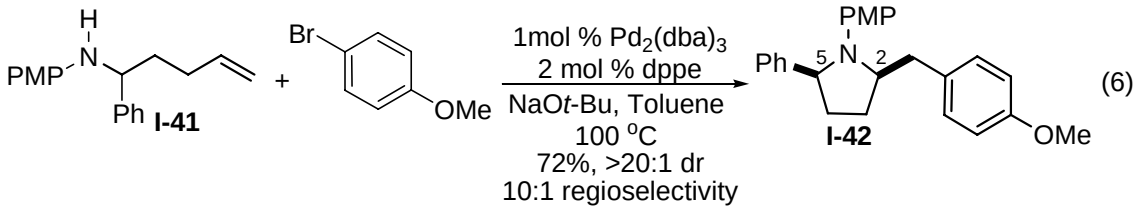


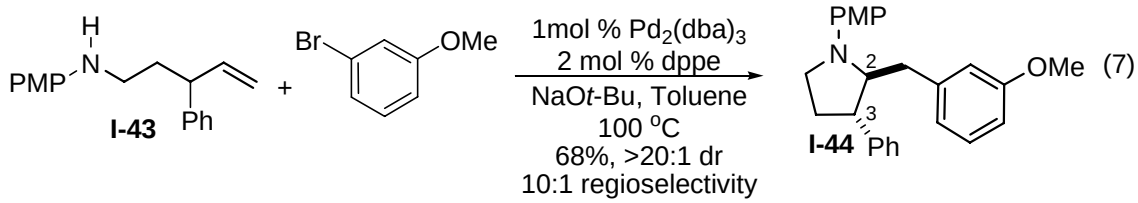
Regioisomer formation is believed to occur from competing β-hydride elimination of intermediate **I-37** to afford intermediate **I-39** (eq 5). Reinsertion of the Pd-H species with inverse regiochemistry followed by β-hydride elimination/reinsertion processes and C–C bond forming reductive elimination affords regioisomer **I-40**.

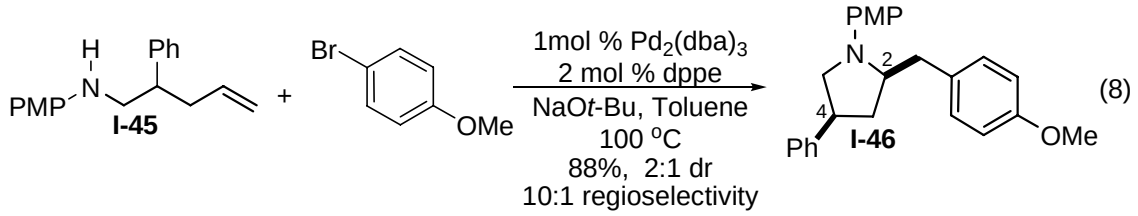


(5)

This new methodology allowed access to 2,5-*cis* (eq 6) and 2,3-*trans* (eq 7) disubstituted pyrrolidines in good yield and high diastereoselectivity (>20:1 dr). Formation of 2,4-*cis* disubstituted pyrrolidines was also achieved in high yield, albeit in low diastereoselectivity (eq 8).



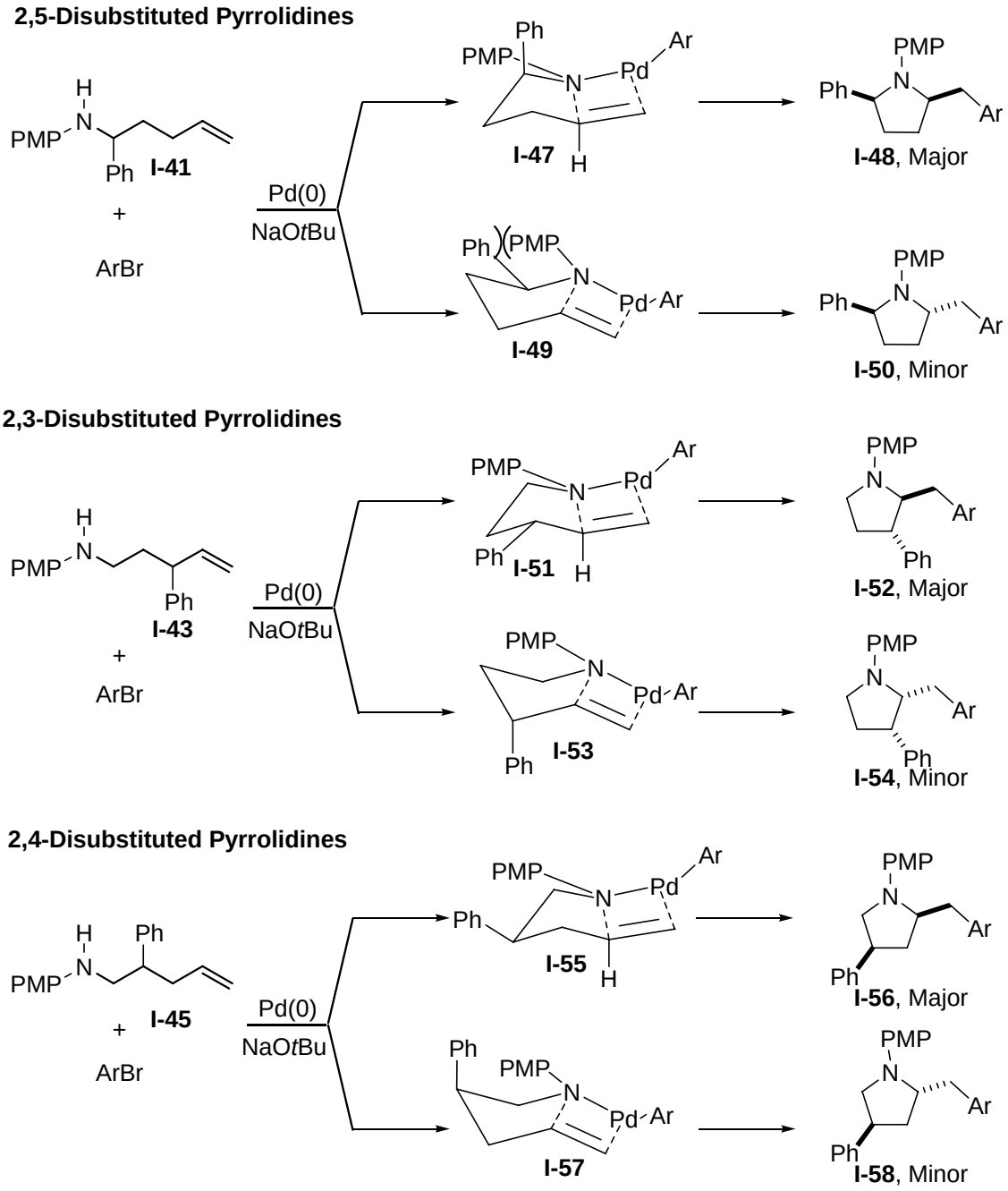




An hypothesis was developed to rationalize the observed product stereochemistry (Scheme 5). The formation of 2,5-*cis* pyrrolidines is believed to occur via transition state **I-47**, in which the α-phenyl group lies in a pseudoaxial position to avoid $A^{(1,3)}$-strain with the *N*-aryl substituent.[30] In the case of 2,3-*trans* pyrrolidines (**I-52**), cyclization occurs with the phenyl side-chain oriented in a pseudo-equatorial position. The low diastereoselectivity observed in the formation of 2,4-*cis* disubstituted pyrrolidines has been attributed to the remote position of the phenyl substituent relative to the reaction site

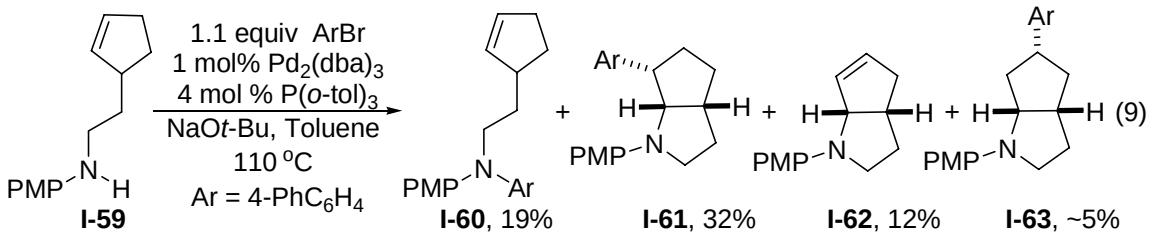
as seen in transition states **I-55** or **I-57**.

Scheme 5. Rationale for the Stereochemical Outcomes



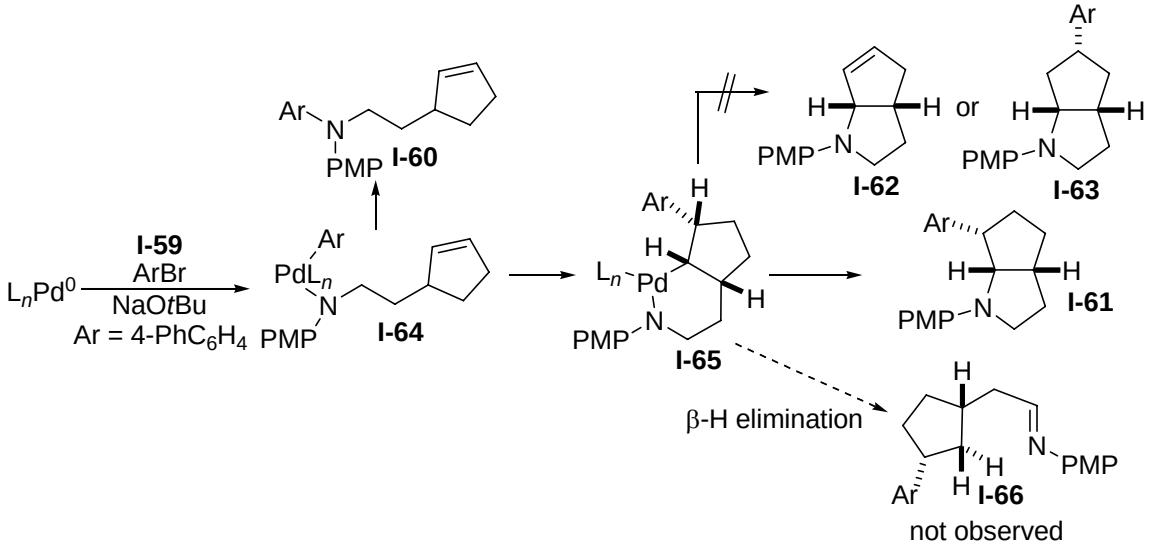
Evidence for the *syn*-aminopalladation mechanism was obtained in the reaction shown in eq 9. The cyclization of cyclopentene derivative **I-59** afforded a modest yield of

I-61. However, both the new C–N and C–C bonds were formed on the same side of the cyclopentane ring, indicating a *syn* insertion process. In addition, the side-products **I-60**, **I-62** and **I-63** were also isolated.



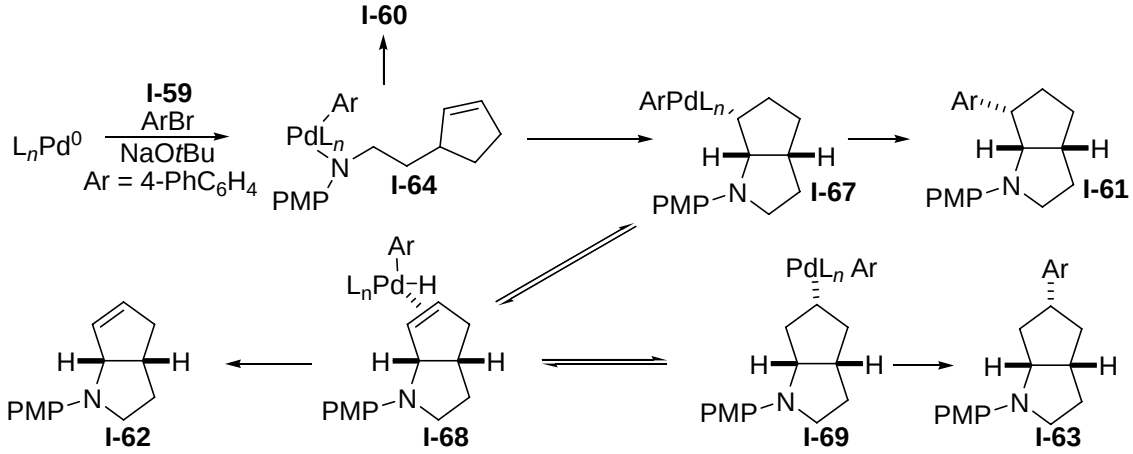
The authors considered two different mechanisms for the formation of product **I-61** from amido complex **I-64**: carbopalladation[31] (Scheme 6) and aminopalladation (Scheme 7). As shown in Scheme 6, intermediate **I-65** is accessed via olefin insertion in the Pd–Ar bond. From intermediate **I-65**, an unprecedented[32] palladium mediated sp^3 C–N bond forming reductive elimination could afford product **I-61**. However, this pathway cannot account for the formation of side products **I-62** and **I-63** (eq 9). In addition, imine **I-66**, a likely side-product resulting from β-hydride elimination of **I-65** was not observed in the crude reaction mixture.

Scheme 6. Proposed Carbopalladation Mechanism

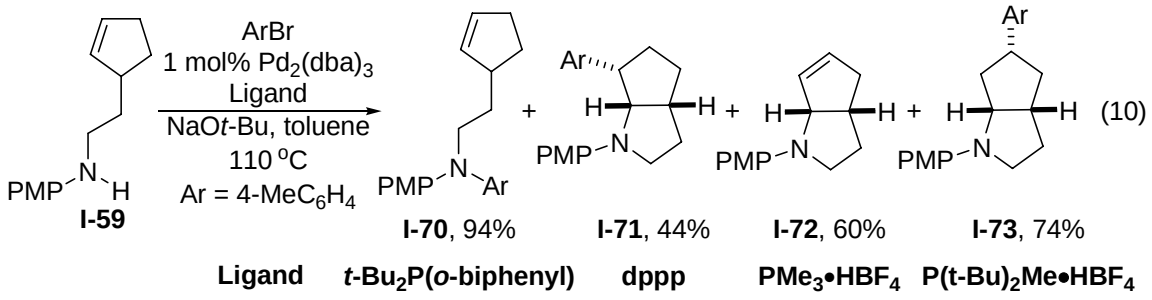


In the proposed aminopalladation mechanism shown in Scheme 7, intermediate **I-67** is produced by insertion into the Pd–N bond, and C–C bond forming reductive elimination[29] from **I-67** would afford product **I-61**. The observed side products **I-62** and **I-63** arise from intermediate **I-68**. Alkene displacement from **I-68** would afford **I-62**. Alternatively, alkene reinsertion into the Pd–H bond of **I-68** with inverse regioselectivity affords **I-69**, and C–C bond reductive elimination would afford product **I-63**.

Scheme 7. Proposed Aminopalladation Mechanism

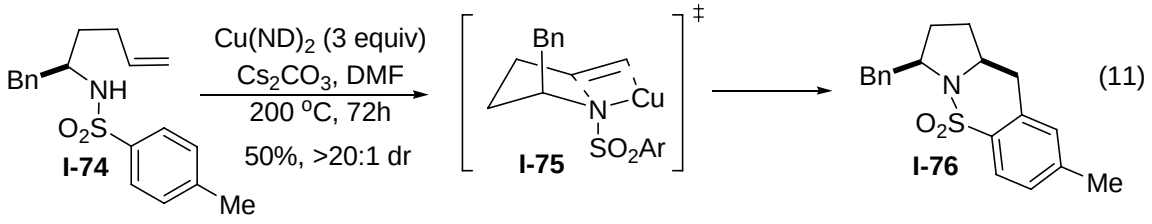


In 2005, Wolfe and Ney further investigated the reaction mechanism for the formation of products **I-61**, **I-62** and **I-63**.[33] Since the formation of each product is linked to the relative rate of a particular step in the aminopalladation pathway, they hypothesized that modifying the catalyst should have an effect on product distribution. Indeed, it was found that the phosphine ligand properties had a dramatic influence on the product outcome. They demonstrated that each product could be favored with choice of an appropriate ligand (eq 10). For example, *N*-arylation product **I-70** was selectively formed when bulky, electron rich phosphine ligand *t*-Bu_2P(*o*-biphenyl) was used.[27a,34] Use of a small and electron rich ligand PMe_3•HBF_4 permitted selective access to product **I-72**.[35] Product **I-73** was produced in good yield with the use of a medium-sized electron rich ligand that favored β-hydride elimination to **I-67** followed by C–C reductive elimination. Product **I-71** was more difficult to obtain because the necessary chelating ligand favoring C–C bond reductive elimination of **I-67** was also effecting C–N bond-forming reductive elimination of **I-64** (Scheme 7). Better results were obtained when an electron-deficient nitrogen substituent was used to reduce the amount of *N*-arylation side-product (Ar = C_6H_4*p*-CO_2*t*-Bu). Overall, the ligand effects observed are consistent with the proposed mechanism. This transformation is synthetically useful as four different products can be made from a common precursor.



(10)

Concurrent with the Wolfe group's studies on pyrrolidine synthesis, a copper mediated intramolecular carboamination of *N*-tosylsulfonyl γ-aminoalkene substrates **I-74** was developed by Chemler and co-workers (eq 11).[36] The proposed mechanism for this transformation involves *syn*-aminocupration (**I-75**) followed by C–C bond formation via an intramolecular cyclization of a primary alkyl radical onto the proximal aromatic ring.[37] The mechanistic proposal is based on the diastereoselectivity obtained in comparison with the Pd-catalyzed carboamination chemistry, and was confirmed through deuterium-labeling experiments. Although this method is useful for the preparation of compounds such as **I-76**, release of the pyrrolidine product requires an additional chemical step to cleave the N–S bond. Also, modification of the aromatic ring electronic or steric properties leads to reduced yields of the desired pyrrolidine products due to competing hydroamination and/or the formation of a mixture of regioisomers.

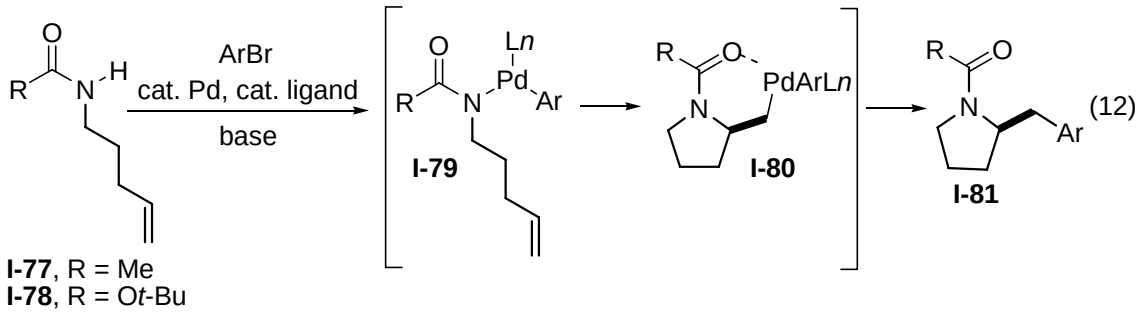


(11)

Proposed Palladium-Catalyzed Carboamination Reactions of Protected γ-Amino Alkenes

The palladium-catalyzed carboamination reactions of γ-(*N*-arylamino)alkenes are useful for the stereoselective preparation of various *N*-aryl pyrrolidines. However there are three main limitations that restricted the synthetic utility of this chemistry. First, deprotection of the *N*-aryl pyrrolidine would be necessary for further chemical modification of the nitrogen atom,[38] but *N*-aryl groups are difficult to cleave. Second, the scope of the aryl bromide coupling partner was limited to electron-rich and electron-neutral aryl bromides unless substrates bearing electron-poor *N*-aryl groups were employed. Finally, various amounts of pyrrolidine regioisomers were formed which were generally not separable by flash chromatography.

We hypothesized that one solution could potentially solve these three main limitations: use of carbamate or amide nitrogen protecting groups (eq 12). These protecting groups could be readily removed from the pyrrolidine products,[39] and the electron-withdrawing nature should help to minimize competing *N*-arylation and regioisomer formation.



With a carbonyl electron-withdrawing group, the nitrogen atom in **I-79** would be

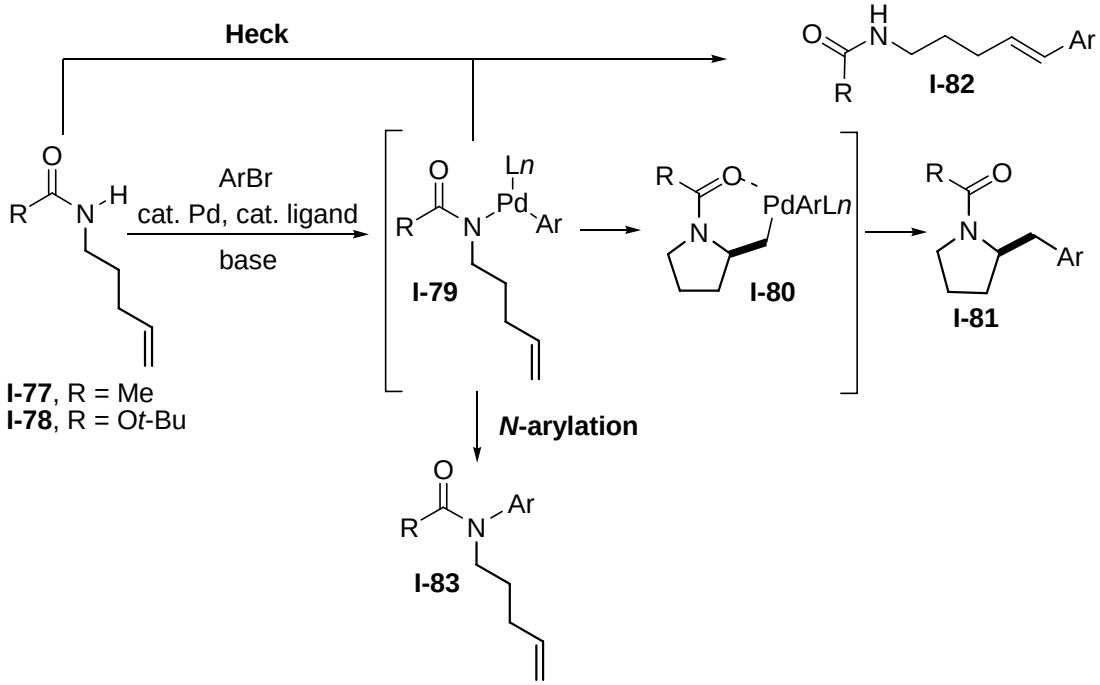
much less nucleophilic which should slow down C–N bond forming reductive elimination.[35b,40] This effect is well documented in Pd-catalyzed *N*-arylation chemistry,[34] and has been previously observed in the N-aryl pyrrolidine synthesis; a higher yield of **I-32** was obtained when a benzonitrile substituent was present on nitrogen (eq 4).

The electron-withdrawing group on nitrogen should also suppress the β-hydride elimination process that would take place from **I-80**, thus reducing the amount of regioisomer. This hypothesis was also demonstrated in the *N*-aryl pyrrolidine synthesis when a benzonitrile substituent on nitrogen significantly decreased the amount of regioisomer observed (eq 4). Moreover, since a partial positive charge develops at the reactive carbon during the β-hydride elimination process,[41] it is likely that this process would be disfavored by an electron-deficient nitrogen. Finally, it was believed that carbonyl chelation with the palladium catalyst (**I-80**) could also disfavor competing β-hydride elimination,[42] which requires an open coordination site on the metal and a co-planar relationship between the β-hydrogen atom and the metal.[43] In the event that carbonyl chelation occurred, a coordination site would be occupied and the chelation could prevent the required spacial arrangement for β-hydride elimination to occur.

When we set out to investigate the use of other nitrogen substituents, we were aware of the potential challenges of this proposal (Scheme 8). As a first step in the catalytic cycle, formation of Pd-amido complex **I-79** is required. In the event that this step is slow, a competing Heck arylation of the starting material (**I-77** or **I-78**) would afford **I-82**.[31] However, Pd-amido complex formation (**I-79**) should occur as the substrate's lower pKa should favor fast deprotonation and reaction with the Ar-Pd-Br

complex. Furthermore, *N*-arylation of amides and carbamates, presumably occurring via Pd-amido complexes similar to **I-79**, is precedented in similar systems.[34] A fast olefin insertion process would then be necessary to avoid *N*-arylation (**I-83**) and/or Heck-type (**I-82**) side-reactions from **I-79**. At the time of our study, the effects of nitrogen electronics on the olefin insertion in the Pd-N bond were unknown. Finally, carbonyl group chelation (**I-80**) would disfavor C-C reductive elimination; dissociation of a ligand would be required for the event to occur.[44] Despite these challenges, we were optimistic that the reaction proposed in equation 12 was feasible, and that suitable catalysts and conditions could be discovered that would facilitate the formation of **I-81**.

Scheme 8. Potential Side-Reactions in Pd-Catalyzed Carboaminations of Protected γ-Amino Alkenes



The chapters that follow describe our efforts to develop conditions appropriate for the carboamination reactions of protected γ-amino alkenes, the scope and limitations of the method, its application towards the synthesis of the natural product preussin and analogs, and our progress towards the synthesis of anisomycin.

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Chapter II

Carboamination of Protected γ-Amino Alkenes with Aryl Bromides[1]

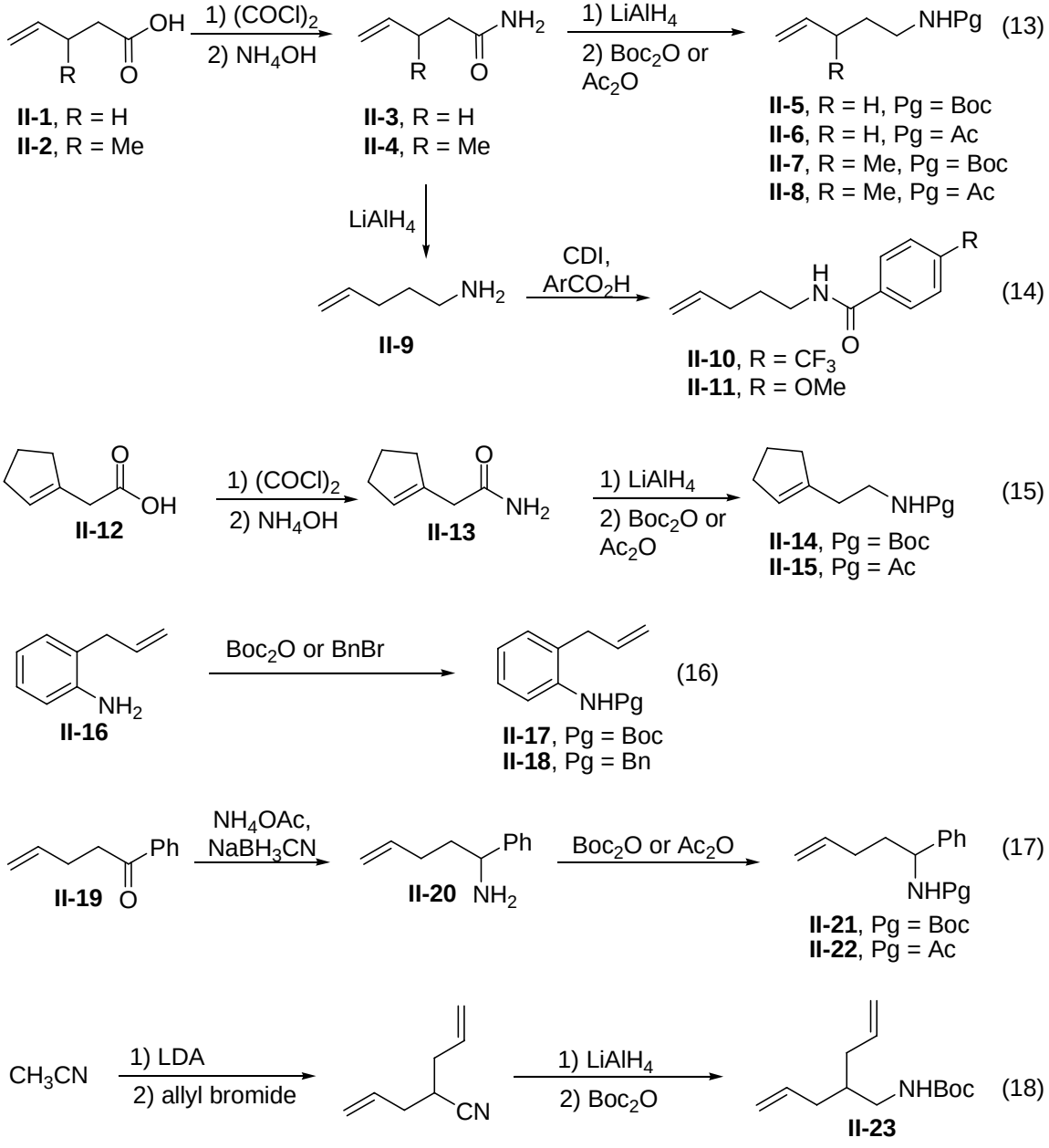
In our studies of alkene carboamination, we explored the reactions of various *N*-substituted γ-amino alkenes with aryl and vinyl bromides.[2] We chose to employ amides and carbamates as nitrogen protecting groups due to their ease of preparation, handling, and cleavage from the pyrrolidine products. Aryl and vinyl bromides were chosen as coupling partners due to their widespread availability from commercial sources. This chapter describes the synthesis of starting materials and development of reaction conditions for the carboamination. This chapter also outlines the scope, limitations, and diastereoselectivity of the method.

Substrate Synthesis

The protected γ-amino alkene substrates employed in the carboamination reactions described in this and the following chapters were prepared in 1–5 steps from commercial materials by one of several methods (Scheme 9). Substrates **II-5**–**II-8** were prepared starting from carboxylic acids **II-1** or **II-2**.[3] Treatment of the acids with $(COCl)_2$ followed by NH_4OH provided primary pent-4-enoyl amides **II-3**[4] and **II-4**. Reduction of the amides with lithium aluminum hydride followed by treatment of the primary amine with Boc_2O, Ac_2O, BzCl or CDI/$ArCO_2H$ afforded the protected substrates **II-5**–**II-8** and **II-10**–**II-11** (eqs 13 and 14). A similar four-step sequence of reactions was used to

convert cyclopent-2-enyl-acetic acid (**II-12**) to protected substrates **II-14** and **II-15** (eq 15). As shown in equation 16, the *N*-protected allylaniline substrates **II-17**[5] and **II-18**[6] were prepared via benzyl[7] or Boc protection of 2-allylaniline (**II-16**).[8] Substrates **II-21** and **II-22** bearing a phenyl substituent at the 1-position were obtained via a two-step reductive amination of known ketone **II-19**,[9] followed by protection of the resulting primary amine **II-20** (eq 17). Finally, substrate **II-23** bearing an allyl substituent at the 2-position was obtained via alkylation of acetonitrile with allyl bromide, reduction of the nitrile and protection of the primary amine (eq 18).

Scheme 9. Synthesis of Substituted Protected γ-Amino Alkenes Substrates

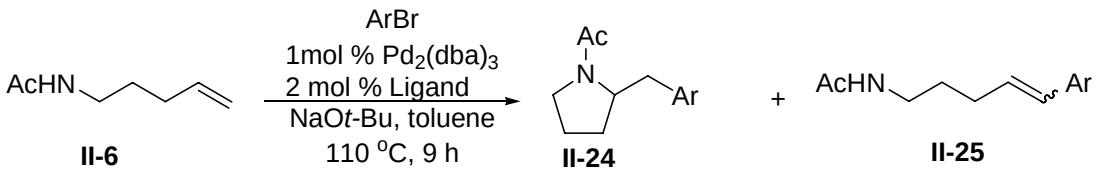


Optimization Studies

In order to investigate the formation of *N*-protected pyrrolidines via the Pd-catalyzed carboamination of *N*-protected γ-aminoalkenes, we initially examined the

palladium-catalyzed reaction of *N*-(4-pentenyl)acetamide **II-6** (Table 1). Since the nature of the ligand had an important effect in the reaction of γ-(*N*-arylamino)alkenes with aryl bromides,[10] we first performed a ligand screen. Substrate **II-6** was treated with 2-bromonaphthalene (1.2 equiv) and NaO*t*-Bu (2 equiv) in the presence of catalytic amount of $Pd_2(dba)_3$ (1 mol %) and various ligands (2–4 mol %). The reactions were heated to 110 ^oC for 9h, then quenched, and assayed by GC. Use of dppb as ligand, which had been employed in related carboamination reactions of γ-(*N*-arylamino)alkenes, resulted in only 61% conversion to 1-(2-naphthalen-2-ylmethylpyrrolidin-1-yl)ethanone (**II-24**) (Table 1, entry 1). A side-product[11] (**II-25**) resulting from a Heck arylation was observed in this reaction, and was the major side product generated in all reactions of **II-6** that were conducted. The best results were obtained with Dpe-phos as the ligand; a 96% conversion was observed with a 85:15 GC ratio of **II-24** to **II-25**. In general, the use of a rigid bidentate ligand provided higher yields than monodentate ligands. Additional studies described below have indicated that the optimal ligand for these transformations varies with substrate structure and aryl bromide electronics (Tables 3 and 4).

Table 1. Ligand Effects



			GC RATIOS		
Entry	**Ligand**	**% Conversion**	**II-24**	**II-25**	**Other[a]**
1	dppb	61	53	8	-
2	P(*o*-tol)$_3$[b,c]	35	9	23	3
3	PPh$_3$[c]	59	34	6	19
4	dppf	91	76	10	5
5	Xantphos	95	84	7	4
6	**Dpe-phos**	**96**	**85**	**5**	**6**

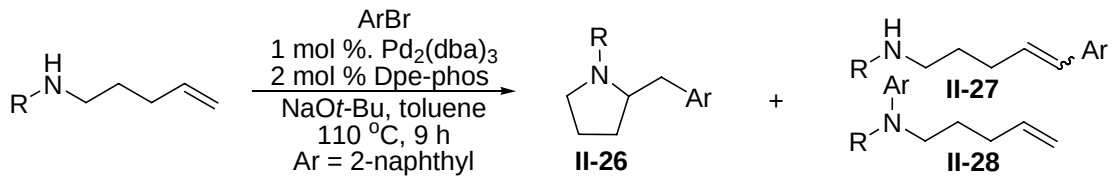
[a]Small amounts of other side-products including regioisomers of **II-25** and *N*-arylated compounds were also formed. [b]The reaction was conducted for 20 h. [c]The amount of monodentate ligand used was 4 mol %.

Next, we investigated the effect of *N*-protecting groups with the newly found optimized reaction conditions. Various *N*-protected γ-amino alkene derivatives were treated with 2-bromonaphthalene (1.2 equiv) in the presence of NaO*t*-Bu (2 equiv) and a catalytic amount of $Pd_2(dba)_3$/Dpe-phos (2 mol % Pd, 4 mol % ligand) (Table 2). These reactions afforded the desired pyrrolidine **II-26** along with Heck-type product **II-28** and *N*-arylation side-product **II-27**. It was found that the nitrogen electronics had a large impact on the product distribution. In most cases, as the electron-withdrawing ability of the protecting group increased, the amount of *N*-arylation decreased but the amount of Heck olefination increased. For example, the reaction of *N*-phenyl bearing substrate (**II-30**) afforded a 75:25 ratio of **II-26**:**II-28**, whereas the *N*-benzoyl substituted substrate **II-**

31 provided a 58:42 ratio of **II-26**:**II-27**; the formation of **II-28** was not observed. The best results were obtained with *N*-acyl and *N*-Boc substituted substrates **II-6** and **II-5**, which were converted to the desired pyrrolidines in good yield. In the reactions of benzyl (**II-29**) and *N*-(*p*-trifluoromethylbenzoyl) (**II-10**) substituted substrates, none of the desired pyrrolidines were observed.

The effect of other reaction parameters such as solvent and base was also investigated. In most cases, use of weak bases lead to formation of large amounts of Heck arylation side-products. However, this problem was eventually solved, and studies on the use of weak bases in these reactions are described in Chapter III. The solvent toluene was found to be optimal although ethereal solvents such as DME and dioxane proved satifactory in many instances. Use of THF as solvent in reactions of Boc-protected substrates led to diminished yields due to base-induced cleavage of the Boc-group from the substrate.[12,13]

Table 2. *N*-Substituent Effects



		GC ratio (isolated yield)		
Entry	***N*-Substituent**	**II-26**	**II-27**	**II-28**
1	R = Bn[a] (**II-29**)	-	40[b]	34
2	R = Ph (**II-30**)	75 (63%)[c-e]	-	25
3	R = Ac[a] (**II-6**)	88 (72%)	12	-
4	R = Boc[a] (**II-5**)	82 (77%)	4[b]	-
5	R = 4-MeO-Bz (**II-11**)	77 (63%)	23	-
6	R = Bz (**II-31**)	58 (48%)	42	-
7	R = 4-F_3C-Bz[a] (**II-10**)	-	89[b]	-

[a]Other minor, unidentified side-products were also observed. [b]Mixtures of alkene regioisomers were obtained. [c]GC yield. [d]This product was obtained as a 15:1 mixture of regioisomers. [e]Use of dppb as ligand provided a 94% isolated yield of **II-26** as a 25:1 mixture of regioisomers. See ref. [10].

Scope and Diastereoselectivity

As shown in Table 3, reactions of *N*-Boc and *N*-acyl protected substrates **II-5** and **II-6** with electron poor and electron-neutral aryl bromide coupling partners afforded good yields of the pyrrolidine products. Use of an electron-rich aryl bromide afforded a moderate yield of **II-38**, and partial oxidation of the *N*-acyl pyrrolidine product to the corresponding 2,3-dihydropyrrole occurred under the reaction conditions.[14] A single product regioisomer was observed in all cases examined. The major side-products observed in the reactions of **II-5** and **II-6** resulted from Heck arylation and/or *N*-arylation of the substrate. The competing Heck arylation was more problematic in the reactions of acetate protected substrate **II-6**.

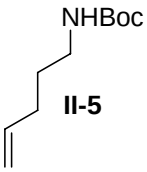
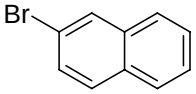
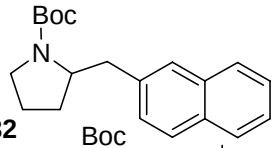
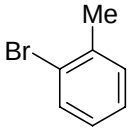
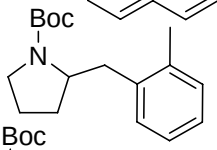
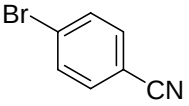
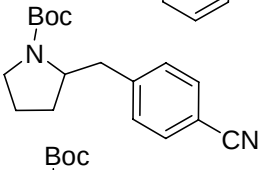
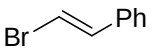
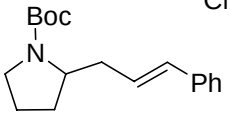
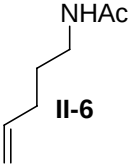
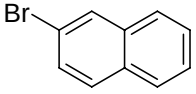
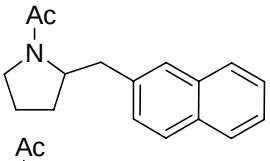
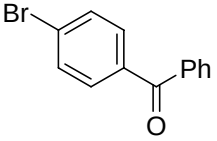
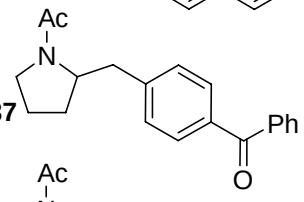
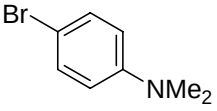
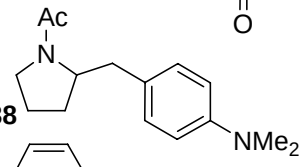
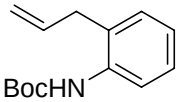
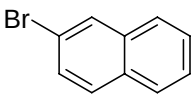
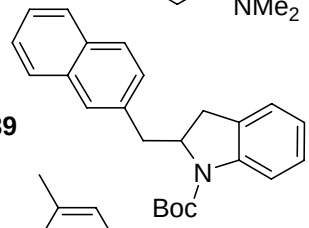
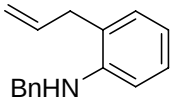
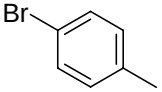
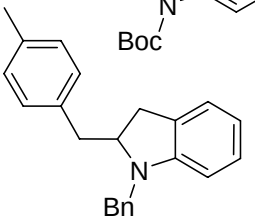
Most transformations are efficiently catalyzed by mixtures of $Pd_2(dba)_3$ and Dpe-phos. However, use of dppe as ligand provided higher yields for some substrate combinations by minimizing competing *N*-arylation or *N*-vinylation processes (Table 3, entries 4 and 6).[15] The reaction of the electron-rich *N*,*N*-dimethyl-4-bromoaniline was most efficiently catalyzed by a mixture of $Pd_2(dba)_3$ and Xantphos (entry 7).

The results obtained in the reactions of **II-5** and **II-6** described above contrast with related transformations of *N*-phenyl substituted substrate **II-30**. For example, the Pd-catalyzed reaction of **II-6** with 4-bromobenzophenone proceeded in 78% isolated yield (entry 6), whereas the analogous reaction of **II-30** provided only a modest 45% yield.[10] Additionally, the $Pd_2(dba)_3$/Dpe-phos catalyzed reaction of **II-5** with β–bromostyrene proceeded in low yield due to competing *N*-vinylation,[16,17] but the $Pd(OAc)_2$/dppe catalyzed reaction of **II-5** with this vinyl bromide afforded the desired product in 75% isolated yield (entry 4).

The synthesis of *N*-protected indolines from *N*-allylaniline derivatives was also briefly examined (Table 3, entries 8–9). Treatment of *N*-Boc-2-allylaniline (**II-17**) with 2-bromonaphthalene under the optimized reaction conditions afforded a 50% yield of the desired indoline product **II-39**. The moderate yield in this transformation was mainly due to competing base-induced cleavage of the Boc-group from the substrate[12] and/or base-induced olefin isomerization of the substrate.[18] In contrast to the reactions of *N*-benzyl protected aliphatic amine substrates, which did not generate significant amounts of the desired pyrrolidine products, *N*-benzyl-2-allylaniline (**II-18**) was converted to the *N*-benzyl-2-benzylindoline **II-40** in 48% yield. The major side product obtained in this reaction was *N*-benzyl-2-methylindole, which presumably derives from Pd-catalyzed

oxidative amination of the substrate (see Mechanistic Considerations Chapter III).[19] Attempts to transform *N*-acyl-2-allylaniline to the corresponding indoline were unsuccessful; competing Heck arylation was observed.

Table 3. Synthesis of *N*-Protected Pyrrolidines and Indolines[a]

Entry	Amine	Aryl bromide	Catalyst	Product	Yield
1	 **II-5**		$Pd(OAc)_2$ Dpe-phos	 **II-32**	77[b]
2			$Pd_2(dba)_3$ Dpe-phos	 **II-33**	81
3			$Pd_2(dba)_3$ dppb	 **II-34**	71
4			$Pd(OAc)_2$ dppe	 **II-35**	75[b]
5	 **II-6**		$Pd_2(dba)_3$ Dpe-phos	 **II-36**	72
6			$Pd_2(dba)_3$ dppe	 **II-37**	78
7			$Pd_2(dba)_3$ Xantphos	 **II-38**	67[c]
8	 **II-17**		$Pd_2(dba)_3$ Dpe-phos	 **II-39**	50
9	 **II-18**		$Pd_2(dba)_3$ Nixantphos	 **II-40**	48

[a]Conditions: 1.0 equiv substrate, 1.1–1.2 equiv ArBr, 1.2–2.0 equiv NaO*t*-Bu, 2 mol % Pd (1 mol % $Pd_2(dba)_3$ or 2 mol % $Pd(OAc)_2$), 2–4 mol % ligand, toluene (0.25 M), 105 °C. [b]The reaction was conducted at 65 °C. [c]This material contained ca 15% of the corresponding 2,3-dihydropyrrole (1-[5-(4-dimethylaminobenzyl)-2,3-dihydropyrrol-1-yl]ethanone).

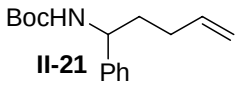
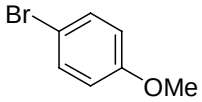
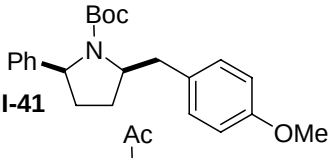
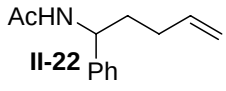
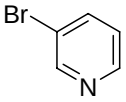
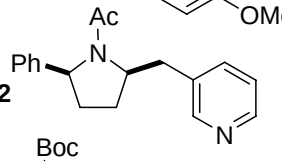
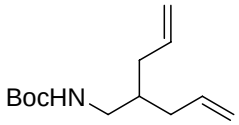
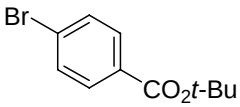
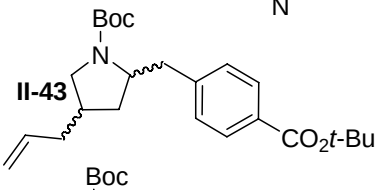
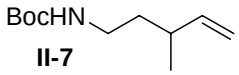
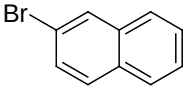
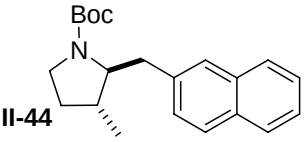
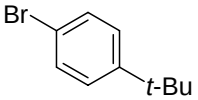
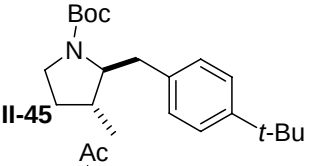
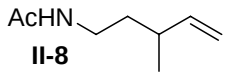
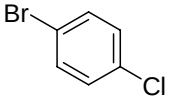
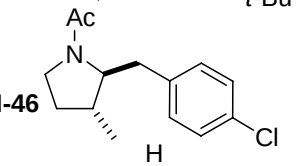
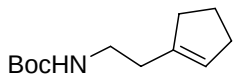
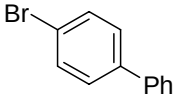
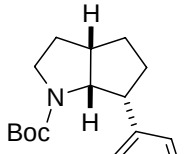
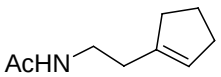
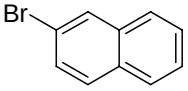
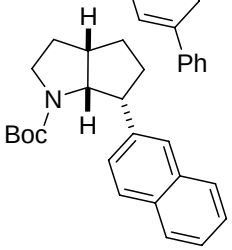
The stereoselective synthesis of disubstituted pyrrolidines bearing *N*-Boc or *N*-acyl groups was achieved via Pd-catalyzed carboamination of substrates **II-7**, **II-8**, **II-14**, **II-15**, **II-21**, **II-22** and **II-23** bearing substituents on the tether between the alkene and the nitrogen (Table 4). Comparable diastereoselectivities were obtained with both *N*-acyl and *N*-Boc protected substrates, and the nature of the aryl bromide did not have a large effect on diastereoselectivity in the transformations examined. The synthesis of *trans*-2,3-disubstituted pyrrolidines (entries 4–6) and *cis*-2,5-disubstituted pyrrolidines (entries 1–2) was effected in good yield with good levels of diastereoselectivity. Proton NMR analysis of the crude reaction mixtures revealed diastereomer ratios of 10–20:1; the minor diastereomer was usually readily separated by chromatography to provide isolated products with >20:1 dr.[20] In contrast, the reaction of **II-23** with *tert*-butyl-(4-bromo)benzoate afforded a 2,4-disubstituted pyrrolidine product in 72% yield, but with only modest (c.a. 3:1) diastereoselectivity (entry 3). The reactions of **II-7**, **II-8**, **II-14**, **II-15**, **II-21**, **II-22** and **II-23** proceed with similar diastereoselectivities and significantly higher regioselectivities than transformations of the analogous *N*-aryl substituted substrates discussed in Chapter I.[10]

The yields obtained in reactions of substrates bearing substituents at the 1- or 3-position were slightly lower than yields obtained in reactions of unsubstituted substrates. The diminished yields are due in part to competing base-induced cleavage of the Boc group from the more hindered substrates.[12] The rate of Boc cleavage is relatively rapid in THF at 65 °C and toluene at 110 °C, whereas little or no cleavage occurs in toluene at 65 °C. Competing Heck arylation also becomes more problematic as steric hindrance at C1

or C3 increases. The Heck-arylation side-products formed in reactions of *N*-acylated substrates were more difficult to separate from the desired product than the side-products obtained in analogous reactions of Boc-protected substrates, which also led to slightly diminished yields.

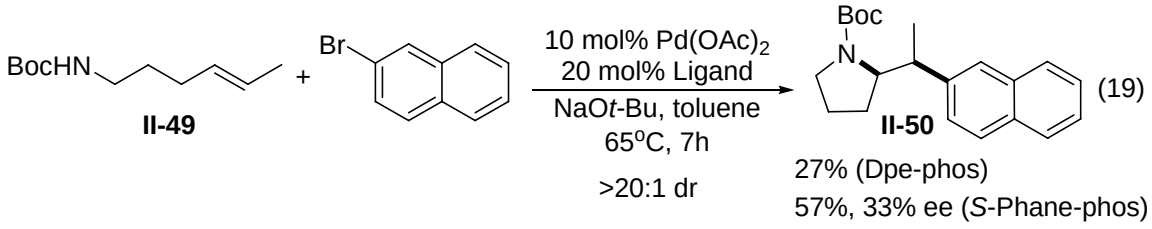
The transformations of substrates **II-14** and **II-15** bearing internal cyclic alkenes proceeded in moderate yield with excellent regioselectivity and diastereoselectivity (>20:1) to afford products **II-47** and **II-48** (entries 7–8). In both reactions the observed diastereomer derives from *syn* addition of the nitrogen and the aryl group across the double bond.[20] The yields and regioselectivities in these transformations sharply contrast with those obtained in the reaction of the analogous *N*-(4-methoxyphenyl)-substituted substrate discussed in Chapter I, which afforded a mixture of two regioisomeric products along with an *N*-arylated side product and a side product derived from oxidative amination of the substrate.[10,21]

Table 4. Stereoselective Synthesis of *N*-Protected Pyrrolidines[a]

Entry	Amine	Aryl bromide	Product	dr[b]	Yield
1	 **II-21**		 **II-41**	>20:1 (>20:1)	60[c]
2	 **II-22**		 **II-42**	>20:1 (>20:1)	82[c]
3	 **II-23**		 **II-43**	3:1 (3:1)	72[d]
4	 **II-7**		 **II-44**	>20:1 (10:1)	66[e,f]
5			 **II-45**	>20:1 (10:1)	59[e,f]
6	 **II-8**		 **II-46**	>20:1 (10:1)	61[d]
7	 **II-14**		 **II-47**	>20:1	53[f,g]
8	 **II-15**		 **II-48**	>20:1	61[h,i]

[a]Conditions: 1.0 equiv substrate, 1.1–1.2 equiv ArBr, 1.2–2.0 equiv NaO*t*-Bu, 2 mol % Pd(1 mol % $Pd_2(dba)_3$ or 2 mol % $Pd(OAc)_2$), 2–4 mol % ligand, toluene (0.25 M), 105 °C. [b]Diastereomeric ratios for the isolated product upon which the yield is based. Diastereomeric ratios observed in crude reaction mixture are shown in parentheses. [c]The $Pd_2(dba)_3$/dppb catalyst system was used for this example. [d]The $Pd_2(dba)_3$/Dpe-phos catalyst was used for this example. [e]The $Pd(OAc)_2$/Dpe-phos catalyst system was used for this example. [f]The reaction was conducted at 65 °C. [g]The $Pd(OAc)_2$/Nixant-phos catalyst system was used for this example. [h]The reaction was conducted using 2.5 mol % $Pd_2(dba)_3$ and 5 mol % Nixantphos. [i]The reaction was stopped at 77% conversion after two days at 110 °C.

Cyclization of *N*-protected internal alkene substrates would fully maximize the potential of the carboamination reaction since two new stereocenters would be formed in a single operation (eq 19). Preliminary studies indicated that higher catalyst loading was required to promote the conversion of substrate **II-49** to product **II-50**.[22,23] The desired pyrrolidine (**II-50**) was isolated in 27% yield as a single diastereoisomer; the main side-product observed resulted from *N*-arylation of the starting material. A ligand screen revealed (*S*)-Phane-phos to be a superior ligand for this reaction, and pyrrolidine **II-50** was isolated in 57% yield and 33% ee. Although the yield of the carboamination reaction was increased, the large amounts of palladium catalyst and expensive chiral ligand required limited the utility of this transformation.[24] A more practical solution to this problem is described in Chapter III of this thesis.



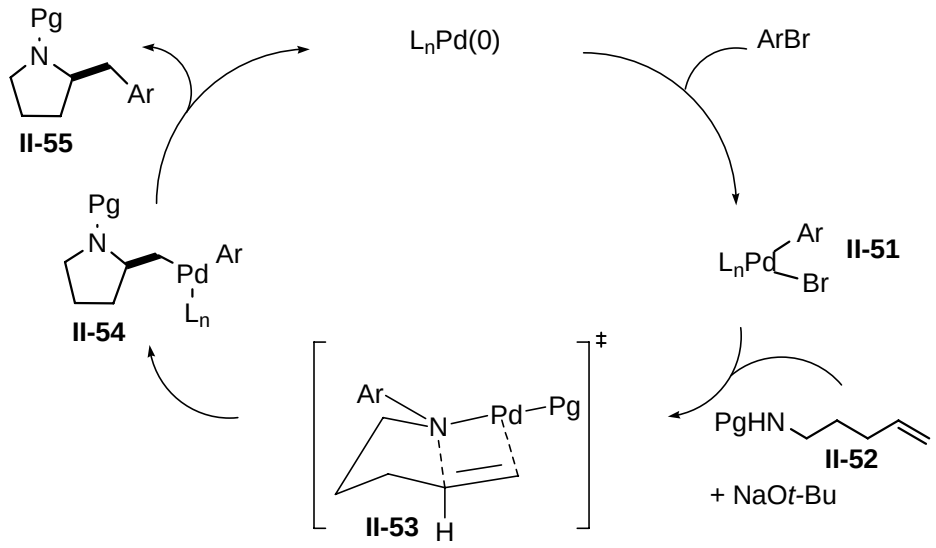
(19)

Mechanistic Considerations

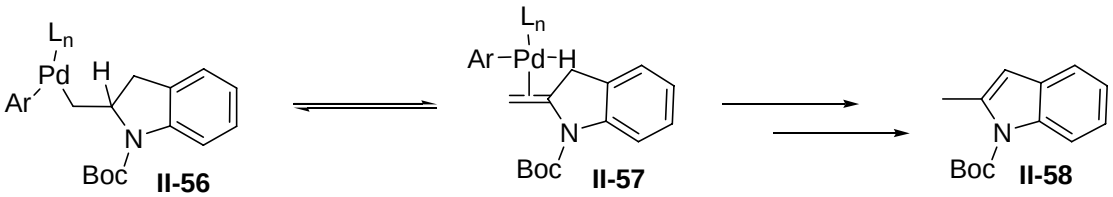
The proposed catalytic cycle for this transformation is analogous to that previously proposed for reactions of γ–(*N*-arylamino)alkene substrates (Scheme 4, Chapter I).[25] As shown below (Scheme 10), the catalytic cycle presumably commences with oxidative addition of the aryl bromide to the Pd(0) catalyst to afford Pd(Ar)(Br) complex **II-51**. Reaction of this complex with the γ–aminoalkene substrate (**II-52**) in the presence of NaO*t*-Bu likely results in the formation of palladium aryl(amido) complex **II-**

53,[15] which undergoes insertion of the alkene into the Pd–N bond[25,26] followed by C–C bond-forming reductive elimination[27] of the resulting intermediate **II-54** to afford the observed pyrrolidine **II-55**. The formation of products that result from *syn* addition of the aryl group and the nitrogen across the C–C double bond (Table 4, entries 7–8) is consistent with this mechanistic proposal. The increased yields obtained in reactions of *N*-Boc and *N*-acyl protected amines with electron-deficient aryl bromides and vinyl bromides compared to *N*-aryl amines is likely due to the fact that C–N bond-forming reductive elimination of intermediate **II-53** slows as the nucleophilicity of the amine, amide, or carbamate decreases.[28] This mechanism also accounts for the formation of *N*-benzyl-2-methylindole as a side product in the reaction of *N*-benzyl-2-allylaniline (Table 3, entry 9). As shown in Scheme 11, the *N*-benzyl-2-methylindole **II-58** likely derives from competing β–hydride elimination of intermediate **II-56** followed by double bond isomerization.[19a] Further discussions on the mechanism and diastereoselectivity of the carboamination reactions of *N*-protected γ-aminoalkenes are presented in Chapter III.

Scheme 10. Proposed Catalytic Cycle



Scheme 11. Formation of Side-Product **II-58**



Conclusion

In conclusion, the synthesis of *N*-Boc and *N*-acyl pyrrolidine derivatives via reactions of *N*-protected γ–aminoalkenes is achieved in good yield with excellent regioselectivity and diastereoselectivities of up to >20:1 dr. In contrast to related transformations of γ–(*N*-arylamino)alkenes, reactions of *N*-boc or *N*-acyl protected substrates with vinyl bromides or electron-deficient aryl bromides proceed in good yield with minimal competing *N*-arylation/vinylation. The *N*-boc and *N*-acyl substituents can

be readily cleaved from the products, which allows for potential access to a broad variety of pyrrolidine derivatives. Further efforts to expand the scope of these transformations along with a more detailed discussion of reaction mechanism are presented in the following chapters.

Experimental Section

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven or flame dried glassware. Palladium acetate, tris(dibenzylideneacetone)dipalladium (0), and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. Acetic anhydride, di-*tert*-butyldicarbonate, cyclopent-2-enyl-acetic acid, and all aryl bromides were obtained from commercial sources (Aldrich Chemical CO or Acros Chemical CO) and were used as without purification. Pent-4-enylphenylamine (**II-30**),[10] *N*-benzyl-4-pentenylamine (**II-29**),[29] *N*-(pent-4-enyl-benzamide) (**II-31**),[30] and 2-allylaniline[8] were prepared according to published procedures. Toluene and THF were purified using a GlassContour solvent purification system. Product regiochemistry was assigned on the basis of ^{1}H NMR 2-D COSY experiments; stereochemistry was assigned on the basis of ^{1}H NMR nOe experiments. Ratios of regioisomers and/or diastereomers were determined by either ^{1}H NMR or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, and either capillary GC (known compounds) or combustion analysis (new compounds). The yields reported in the experimental section describe the result of a single experiment, whereas the yields

reported in Tables 3–4 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 3–4.

Synthesis of *N*-Protected γ-Aminoalkenes

***N*-Pent-4-enyl-acetamide (II-6).**[31] A flame-dried flask was cooled under a stream of nitrogen and charged with 4-pentenoic acid (5.7 mL, 49.8 mmol). The flask was purged with nitrogen, benzene (100 mL) was added and the resulting solution was cooled to c.a. 10 °C using an ice water bath. Oxalyl chloride (8.7 mL, 100 mmol) was added dropwise via syringe to the solution and the resulting mixture was warmed to rt, stirred for 1h, and then concentrated *in vacuo*. The crude 4-pentenoyl chloride was dissolved in THF (100 mL), and slowly added to a separate flask containing aqueous ammonium hydroxide (100 mL) at 0 °C. The resulting mixture was stirred for 6 h and then concentrated *in vacuo.* The mixture was diluted with H_2O (50 mL) and ethyl acetate (100 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 3.86 g (77%) of 4-pentenamide[4] as a white solid, m.p. 104–106 °C (lit. m.p. 106 °C)[4] that was used without further purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with 4-pentenamide (3.30 g, 33.3 mmol). The flask was purged with nitrogen, THF (100 mL) was added via syringe and the resulting solution was cooled to 0 °C. A solution of $LiAlH_4$ in THF (100 mL, 100 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt and stirred for 36 h, then was cooled to 0 °C, quenched with H_2O (16 mL), and diluted with ether (200 mL). An aqueous solution of

NaOH (30 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered to afford a solution of 4-pentenylamine[32] in diethyl ether (c.a. 0.1 M), which was used without further purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of 4-pentenylamine in diethyl ether (165 mL, 16.5 mmol, 0.1 M). The solution was cooled to 0 °C and acetic anhydride (4.7 mL, 5.10 g, 50 mmol) was added via syringe. The resulting mixture was stirred for 5 h and then aqueous NaOH (100 mL, 1.0 M) was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo.* The crude product was then purified by flash chromatography on silica gel to afford 1.36 g (65%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.57 (m, 2 H), 5.07–4.93 (m, 2 H), 3.25 (q, J = 6.0 Hz, 2 H), 2.12–2.02 (m, J = 5.8 Hz, 2 H), 1.95 (s, 3 H), 1.59 (p, J = 7.7 Hz, 2 H).

Pent-4-enyl-carbamic acid *tert*-butyl ester (II-5).[33] A flame-dried round bottom flask was cooled under a stream of nitrogen and charged with a solution of 4-pentenylamine (165 mL, 16.5 mmol, 0.1 M). Di-*tert*-butyl dicarbonate (5.4 g, 25 mmol) was added to the solution and the resulting mixture was stirred for 4 h and then aqueous NaOH (100 mL,

1.0 M) was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo.* The crude product was then purified by flash chromatography on silica gel to afford 2.05 g (67%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.70 (m, 1 H), 5.01–4.90 (m, 2 H), 4.54 (s, br, 1 H), 3.13–2.98 (m, 2 H), 2.03 (q, *J* = 6.6 Hz, 2 H), 1.52 (p, *J* = 6.6 Hz, 2 H), 1.39 (s, 9 H).

***N*-(pent-4-enyl)-4-methoxybenzamide (II-11).**[30] An oven-dried round-bottom flask was charged with 1,1'-carbonyldiimidazole (486 mg, 3.0 mmol) and then purged with argon. THF (15 mL) and 4-methoxybenzoic acid (456 mg, 3.0 mmol) were added to the flask, and the resulting mixture was stirred at room temperature for 1 h. A solution of 4-pentenylamine in ether (30 mL, 3.0 mmol, 0.1 M) was then added via syringe and the mixture was stirred at room temperature for 4 h. The reaction mixture was then diluted with ethyl acetate (15 mL) and H_2O (15 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 438 mg (67%) of the title compound as a white solid, m.p. 42–44 °C (lit m.p not reported). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.10 (br s, 1 H), 5.85–5.75 (m, 1 H), 5.05–4.95 (m, 2 H), 3.80 (s, 3 H), 3.41 (q, *J* = 7.0 Hz, 2 H), 2.11 (q, *J* = 7.0 Hz, 2 H), 1.68 (p, *J*

= 7.7 Hz, 2 H).

***N*-Pent-4-enyl-4-trifluoromethyl benzamide (II-10).** Treatment of 570 mg (3.0 mmol) of 4-(trifluoromethyl)benzoic acid with a solution of 4-pentenylamine in ether (30 mL, 3.0 mmol) using a procedure analogous to that described above in the synthesis of **II-11** afforded 475 mg (63%) of the title compound as a white solid m.p. 69–71 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2 H), 7.60 (d, *J* = 8.1 Hz, 2 H), 6.60 (s, br, 1 H), 5.83–5.70 (m, 1 H), 5.05–4.90 (m, 2 H), 3.45–3.36 (m, 2 H), 2.15–2.05 (m, 2 H), 1.73–1.62 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 138.2, 137.8, 133.2 (q, *J* = 41 Hz), 127.5, 125.7, 123.8 (q, *J* = 340 Hz), 115.6, 40.0, 31.4, 28.8; IR (film) 3309, 2930, 1638, 1550 cm^{-1}. Anal calcd for $C_{13}H_{14}F_3NO_2$: C, 60.70; H, 5.49; N, 5.44. Found: C, 60.97; H, 5.46; N, 5.40.

(2-Allylphenyl)carbamic acid *tert*-butyl ester (II-17).[5] Treatment of 904 mg (6.8 mmol) of 2-allylaniline[8] with 2.2 g (10.2 mmol) of di-*tert*-butyldicarbonate using a procedure analogous to that described above in the synthesis of **II-5** (with THF used in place of diethyl ether as solvent) afforded 1.11 g (70 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1 H), 7.20 (t, *J* = 8.4 Hz, 1 H), 7.11 (d, *J* = 7.7 Hz, 1 H), 7.02 (t, *J* = 7.3 Hz, 1 H), 6.41 (s, br, 1 H), 5.97–5.88 (m, 1 H), 5.14–5.00 (m, 2 H), 3.33 (d, *J* = 6.2 Hz, 2 H), 1.47 (s, 9H).

(1-Phenylpent-4-enyl)carbamic acid *tert*-butyl ester (II-21). A flame-dried round bottom flask was cooled under a stream of argon and charged with 1-phenylpent-4-en-1-one[9] (11.0g, 69.0 mmol), activated 3 Å molecular sieves (10.0 g), and methanol (200 mL). The mixture was stirred at rt for 5 min and then ammonium acetate (53 g, 690 mmol) and sodium cyanoborohydride (4.3 g, 69 mmol) were added. The flask was purged with argon and then stirred at rt for 19 h. Ether (500 mL) was added, the mixture was decanted, and the organic phase was washed with 200 mL of aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with ether (1 x 100 mL), and the combined organic layers were extracted with 1 M HCl (3 x 100 mL). The organic phase was discarded and the combined acidic aqueous extracts were basicified to pH 10 with 10M NaOH and extracted with ether (3 x 100 mL). The combined organic extracts were diluted with hexanes (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 2.1 g (19%) of 1-phenyl-pent-4-enylamine[34] as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.36–7.29 (m, 4 H), 7.27–7.21 (m, 1 H), 5.87–5.76 (m, 1 H), 5.05–4.94 (m, 2 H), 3.92–3.87 (m, 1 H), 2.14–1.96 (m, 2 H), 1.84–1.70 (m, 2 H), 1.52 (s, 2 H).

Treatment of 1.51 g (9.4 mmol) of 1-phenylpent-4-enylamine with 2.62 g (12.0 mmol) of di-*tert*-butyl dicarbonate using a procedure analogous to that described above in the synthesis of **II-5** provided 2.26 g (92%) of the title compound as a white solid m.p. 76-78 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5 H), 5.83–5.70 (m, 1 H), 5.02–4.91 (m, 2 H), 4.88–4.74 (s, br, 1 H), 4.67–4.52 (s, br, 1 H), 2.10–1.92 (m, 2 H), 1.90–

1.71 (m, 2 H), 1.38 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 143.0, 137.8, 128.8, 127.4, 126.6, 115.4, 79.6, 54.7, 36.2, 30.6, 28.6; IR (film) 3370, 2978, 1687, 1519 cm^{-1}. Anal calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.41; H, 8.78; N, 5.32.

***N*-(1-Phenylpent-4-enyl)-acetamide (II-22).** Treatment of 517 mg (3.21 mmol) of 4-pentenylamine with 0.8 mL (8.03 mmol) of acetic anhydride using a procedure analogous to that described above in the synthesis of **II-6** provided 530 mg (81%) of the title compound as a white solid, m.p. 44–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5 H), 6.25 (d, *J* = 8.1 Hz, 1 H), 5.80–5.70 (m, 1 H), 4.97–4.90 (m, 3 H), 2.09–1.92 (m, 2 H), 1.90 (s, 3 H), 1.88–1.73 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 142.4, 137.8, 128.8, 127.5, 126.8, 115.4, 53.3, 35.5, 30.6, 23.5 IR (film) 3279, 2934, 1646, 1549 cm^{-1}. MS (ESI) 226.1206 (226.1208 calcd for $C_{13}H_{17}NO$, M + Na^+).

1-Allylbut-3-enyl-carbamic acid *tert*-butyl ester (II-23). A flame-dried round bottom flask was cooled under a stream of nitrogen and charged with diisopropylamine (8.4 mL, 60 mmol) and THF (100 mL). The flask was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (22 mL, 55 mmol, 2.5 M) was added dropwise. The mixture was stirred at –78 °C for 1 h and then acetonitrile (2.6 mL, 50 mmol) was added dropwise. The mixture was warmed to rt and stirred for 3 h, then allyl bromide (4.8 mL, 55 mmol) was added dropwise. The mixture was stirred for 1 h, then a solution of saturated aqueous ammonium chloride (50 mL) was added. The mixture was extracted

with ether (3 x 150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a mixture of 4-cyano-1-butene, 4-cyano-4-allyl-1-butene, and 4-cyano-4,4-diallyl-1-butene (c.a. 50 mmol) that was used without further purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a mixture of 4-cyano-1-butene, 4-cyano-4-allyl-1-butene, and 4-cyano-4,4-diallyl-1-butene (c.a. 50 mmol) The flask was purged with nitrogen, ether (200 mL) was added via syringe and the resulting solution was cooled to 0 °C. A solution of $LiAlH_4$ in ether (150 mL, 150 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt and stirred for 12 h, then was cooled to 0 °C, quenched with H_2O (30 mL), and diluted with ether (150 mL). An aqueous solution of NaOH (80 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the solution was dried over anhydrous sodium sulfate and filtered to afford a mixture of 4-pentenylamine, 3-allyl-4-pentenylamine, and 3,3-diallyl-4-pentenylamine as a solution in diethyl ether (550 mL, c.a. 0.1 M). This mixture was used without further purification.

A solution containing a mixture of 4-pentenylamine, 3-allyl-4-pentenylamine, and 3,3-diallyl-4-pentenylamine in ether (100 mL, 10 mmol, 0.1 M) was treated with 2.62 g (12 mmol) of di-*tert*-butyl dicarbonate using a procedure analogous to that described above in the synthesis of **II-5**. The three products were separated by flash chromatography on silica gel to afford 675 mg (30%) of **II-23** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.67 (m, 2H), 5.04–4.96 (m, 4 H), 4.52 (s, br, 1 H), 3.03 (t, J = 6.2 Hz, 2 H), 2.08–1.94 (m, 4 H), 1.72–1.57 (m, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 156.2, 136.5, 116.8, 79.9, 43.7, 38.3, 36.2, 28.6; IR (film) 3351; 2978, 1694, 1515 cm^{-1}. Anal calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.27; H, 10.26; N, 6.22.

(3-Methylpent-4-enyl)-carbamic acid *tert*-butyl ester (II-7). 3-Methyl-pent-4-enoic acid[3] (3.33 g, 29.2 mmol) was converted to 3.0 g (52 %) of the title compound using a four-step procedure analogous to that described above for the conversion of 4-pentenoic acid to **II-5**. The product was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62–5.53 (m, 1 H), 4.90–4.82 (m, 2 H), 4.59 (s, br, 1 H), 3.09–2.91 (m, 2 H), 2.15–2.02 (m, 1 H), 1.44–1.27 (m, 11 H), 0.91 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 143.9, 113.4, 79.0, 38.9, 36.7, 35.8, 28.5, 20.3 IR (film) 3351, 2977, 1694, 1526 cm^{-1}. Anal calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.04; H, 10.60; N, 6.97.

***N*-(3-Methylpent-4-enyl)acetamide (II-8).** Treatment of a solution of 3-methyl-4-pentenylamine in ether (100 mL, 10 mmol, 0.1 M) with 3 mL (30 mmol) of acetic anhydride using a procedure analogous to that described above in the synthesis of **II-6** provided 720 mg (51%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (s, br, 1 H), 5.61–5.52 (m, 1 H), 4.90–4.82 (m, 2 H), 3.15–3.07 (m, 2 H), 2.13–2.03 (m, 1 H), 1.85 (s, 3 H), 1.46–1.32 (m, 2 H); 0.90 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 143.8, 113.5, 38.0, 36.2, 35.9, 23.3, 20.4; IR (film)

3290, 2964, 1649, 1558 cm^{-1}. MS (ESI) 142.1228 (142.1232 calcd for $C_8H_{16}NO$, M + H^+).

(2-Cyclopent-2-enylethyl)carbamic acid *tert*-butyl ester (II-14). Cyclopent-2-enyl-acetic acid (3.0 g, 23.8 mmol) was converted to 2.41 g (48 %) of the title compound using a four-step procedure analogous to that described above the conversion of 4-pentenoic acid to **II-5**. ^1H NMR (400 MHz, $CDCl_3$) δ 5.69–5.65 (m, 1 H), 5.62–5.57 (m, 1 H), 4.52 (s, br, 1 H), 3.16–2.99 (m, 2 H), 2.67–2.56 (m, 1 H), 2.34–2.15 (m, 2 H), 2.06–1.94 (m, 1 H), 1.59–1.48 (m, 1 H), 1.45–1.31 (m, 11 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 134.5, 131.0, 79.2, 43.2, 39.5, 36.4, 32.1, 29.9, 28.6; IR (film) 3351, 2977, 1692, 1524 cm^{-1}. Anal calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.99 ; H, 10.06; N, 6.63.

***N*-(2-Cyclopent-2-enylethyl)acetamide (II-15).** Cyclopent-2-enyl-acetic acid (2.0 g, 15.9 mmol) was converted to 1.27 g (52 %) of the title compound using a four-step procedure analogous to that described above the conversion of 4-pentenoic acid to **II-6**. The product was obtained as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, br, 1 H), 5.68–5.63 (m, 1 H), 5.59–5.55 (m, 1 H), 3.18 (q, J = 7.3 Hz, 2 H), 2.65–2.55 (m, 1 H), 2.33–2.14 (m, 2 H), 2.03–1.93 (m, 1 H), 1.89 (s, 3 H), 1.59–1.49 (m, 1 H), 1.45–1.28 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 134.3, 131.1, 43.3, 38.5, 35.8, 32.1, 29.8, 23.4; IR (film) 3289, 2932, 1653, 1559 cm^{-1}. MS (ESI) 153.1154 (153.1153 calcd

for $C_9H_{15}NO$).

General procedures for the Pd-catalyzed synthesis of pyrrolidines

General procedure A: Palladium-catalyzed synthesis of pyrrolidines and indolines using $Pd(OAc)_2$. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol %) and a bidentate phosphine ligand (4 mol %). The tube was purged with nitrogen and toluene was added (2 mL/mmol amine). The mixture was stirred at rt for ~2 min then the aryl bromide (1.2 equiv) was added followed by a solution of the amine (1 equiv) in toluene (2 mL/mmol amine). The mixture was allowed to stir ~ 1 min before the addition of NaO*t*-Bu (2.0 equiv). The tube was purged with nitrogen and the sides of the flask were rinsed with toluene (2 mL/mmol amine; final concentration = 0.17 M). The mixture was heated to 65 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

General procedure B: Palladium-catalyzed synthesis of pyrrolidines and indolines using $Pd_2(dba)_3$. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), a bidentate

phosphine ligand (2 mol %), NaO*t*-Bu (1.2 equiv), and the aryl bromide (1.1 equiv). The tube was purged with nitrogen and a solution of the amine substrate (1.0 equiv) in toluene (4 mL/mmol amine) was added. The mixture was heated to 105 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was cooled to rt, quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

(4-Methoxyphenyl)-(2-naphthalen-2-ylmethylpyrrolidin-1-yl)methanone

(Table 2, Entry 5) Reaction of 52 mg (0.25 mmol) of **II-11** with 2-bromonaphthalene (57 mg, 0.28 mmol), Dpe-phos (2.7 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.30 mmol) following general procedure B afforded 54.3 mg (63%) of the title compound as a pale yellow oil that was contaminated with c.a. 5% of Heck-type side product **II-27**. The title compound was found to exist as a c.a. 9:1 mixture of rotamers as judged by ^{1}H NMR analysis. Data are for the major rotamer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.58 (m, 4 H), 7.57–7.30 (m, 5 H), 6.88 (d, J = 8.8 Hz, 2 H), 4.62–4.49 (m, 1 H), 3.80 (s, 3 H), 3.45–3.30 (m, 2 H), 3.26–3.14 (m, 1 H), 3.13–3.00 (m, 1 H), 2.01–1.83 (m, 1 H), 1.82–1.51 (m, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 161.2, 136.4, 133.7, 132.4, 129.6, 128.7, 128.4, 127.9, 127.8, 127.7, 126.1, 125.5, 113.7, 58.7, 55.5, 51.1, 39.0, 29.6, 25.3 (two aromatic signals are incidentally equivalent); IR (film) 2967, 1608, 1420 cm^{-1}. MS (ESI) 368.1625 (368.1626 calcd for $C_{23}H_{23}NO_2$, M + Na^+).

(2-Naphthalen-2-ylmethylpyrrolidin-1-yl)phenylmethanone (Table 2, Entry 6) Reaction of 48 mg (0.25 mmol) of **II-31** with 2-bromonaphthalene (57 mg, 0.28 mmol), Dpe-phos (2.7 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.30 mmol) following general procedure B afforded 38 mg (48%) of the title compound as a pale yellow oil. This compound was found to exist as a 4:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.78 (m, 3 H), 7.78–7.74 (m, 0.2 H), 7.72 (s, 0.8 H), 7.70–7.60 (m, 0.8 H), 7.56–7.42 (m, 1.4 H), 7.50–7.38 (m, 5.8 H), 7.19 (s, 0.2 H), 6.74–6.68 (m, 0.2 H), 4.62–4.52 (m, 1 H), 4.20–4.11 (m, 0.2 H), 3.78–3.67 (m, 0.4 H), 3.43–3.29 (m, 1.6 H), 3.22–3.13 (m, 0.8 H), 3.12–3.03 (m, 0.8 H), 2.77–2.18 (m, 0.2 H), 2.61–2.50 (m, 0.2 H), 2.04–1.88 (m, 1 H), 1.87–1.73 (m, 1 H), 1.72–1.54 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 137.6, 136.4, 135.8, 133.7, 132.4, 130.2, 129.6, 128.7, 128.5, 128.3, 128.0, 127.8, 127.7, 127.5, 127.3, 126.7, 126.2, 126.1, 125.7, 125.5, 60.9, 58.7, 50.9, 46.0, 41.2, 39.0, 29.9, 29.5, 25.1, 22.1 (three sets of carbons are incidentally equivalent); IR (film) 2968, 1625, 1412 cm^{-1}. MS (ESI) 338.1519 (338.1521 calcd for $C_{22}H_{21}NO$, $M + Na^+$).

2-Napthalen-2-ylmethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (Table 2, Entry 4, II-32). Reaction of 93 mg (0.50 mmol) of **II-5** with 2-bromonaphthalene (124 mg, 0.60 mmol), Dpe-phos (11 mg, 0.02 mmol 4 mol %) and NaO*t*-Bu (96 mg, 1.0 mmol) following general procedure A afforded 120 mg (77%) of the title compound as a

pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3 H), 7.78–7.58 (m, 1 H), 7.51–7.30 (m, 3 H), 4.21–4.02 (m, 1 H), 3.46–3.18 (m, 3 H), 2.78–2.63 (m, 1 H), 1.73 (m, 4 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 137.0, 133.8, 132.3, 128.5, 128.2, 128.0, 127.8, 127.7, 126.2, 126.1, 125.6 125.5, 79.5, 79.3, 59.0, 47.1, 46.5, 41.0, 39.9, 29.9, 29.1, 28.8, 23.7, 22.9 (nine sets of carbons are incidentally equivalent); IR (film) 3052, 2973, 1692, 1395 cm^{-1}. Anal calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.78; H, 8.24; N, 4.57.

2-(2-Methylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (II-33). Reaction of 93 mg (0.5 mmol) of **II-5** with 2-bromotoluene (66 μL, 94 mg, 0.55 mmol), Dpe-phos (5.4 mg, 0.01 mmol, 2 mol %) and NaO*t*-Bu (58 mg, 0.6 mmol) following general procedure B afforded 112 mg (81%) of the title compound as a pale yellow oil. This compound was found to exist as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.08 (m, 4 H), 4.02 (s, br, 1 H), 3.42–3.02 (m, 3 H), 2.50–2.29 (m, 4 H), 1.92–1.59 (m, 4 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8; 154.2, 137.9, 137.2, 130.7, 130.5, 126.9, 126.6, 126.1, 79.7, 79.6, 57.5, 46.9. 46.4, 38.5, 37.7, 37.0, 29.7, 29.2, 28.8, 28.7, 23.7, 22.8, 20.0, 19.9 (three sets of signals are incidentally equivalent); IR (film) 2973, 1693, 1394 cm^{-1}. Anal calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.84; H, 9.16; N, 5.10.

2-(4-Cyanobenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (I-34). Reaction of 185 mg (1.00 mmol) of **II-5** with 4-bromobenzonitrile (200 mg, 1.10 mmol), dppb (8.8 mg, 0.02 mmol, 2 mol %) and NaO*t*-Bu (116 mg, 1.20 mmol) following general procedure B afforded 203 mg (71%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2 H), 7.26–7.22 (m, 2 H), 3.80–3.97 (m, 1 H), 3.35–2.95 (m, 4 H), 2.62–2.55 (m, 1 H), 1.81–1.52 (m, 3 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 145.1, 132.6, 132.2, 130.4, 128.2, 119.0, 110.3, 79.5, 58.4, 46.81, 46.79, 41.0, 40.1, 30.1, 28.9, 28.7, 23.6, 22.9 (five sets of signals are incidentally equivalent); IR (film) 2974, 2228, 1690, 1395 cm^{-1}. Anal calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.15; H, 7.82; N, 9.69.

2-(3-Phenylallyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (II-35). Reaction of 93 mg (0.50 mmol) of **II-5** with β-bromostyrene (80 μL, 110 mg, 0.60 mmol), dppe (8 mg, 0.02 mmol, 4 mol %) and NaO*t*-Bu (96 mg, 1.00 mmol) following general procedure A afforded 108 mg (79%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.10 (m, 5 H), 6.38 (d, J = 16.0 Hz, 1 H), 6.20–6.05 (m, 1 H), 3.90–3.78 (m, 1 H), 3.42–3.32 (m, 2 H),

2.71–2.52 (m, 1 H), 2.32–2.23 (m, 1 H), 1.95–1.73 (m, 4 H); 1.44 (s, 9 H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 138.0, 137.7, 132.4, 128.7, 127.2, 126.2, 79.39, 79.36, 57.4, 46.9, 46.6, 38.4, 37.6, 30.5, 29.6, 28.8, 23.9, 23.2 (nine sets of signals are incidentally equivalent); IR (film) 2972, 1693, 1394 cm^{-1}. Anal calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.24; H, 8.59; N, 4.81.

1-(2-Naphthalen-2-ylmethylpyrrolidin-1-yl)ethanone (II-36). Reaction of 32 mg (0.25 mmol) of **II-6** with 2-bromonaphthalene (57 mg, 0.28 mmol), Dpe-phos (2.7 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.30 mmol) following general procedure B afforded 44 mg (70%) of the title compound as a pale yellow oil. This compound was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.78 (m, 3 H), 7.66 (s, 0.3 H), 7.60 (s, 0.3 H), 7.51–7.40 (m, 3 H), 4.45–4.38 (m, 0.7 H), 4.15–4.08 (m, 0.3 H), 3.63–3.48 (m, 0.7 H), 3.43–3.31 (m, 2 H), 3.07–3.00 (m, 0.3 H), 2.84–2.70 (m, 1 H), 2.14–2.03 (m, 3 H), 1.96–1.69 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 169.4, 137.0, 135.7, 135.7, 133.8, 132.5, 132.4, 128.7, 128.4, 128.15, 128.05, 128.03, 127.94, 127.87, 127.76, 127.72, 126.5, 126.2, 126.0, 125.6, 60.3, 58.6, 48.2, 45.8, 41.2, 39.1, 30.3, 28.7, 24.0, 23.4, 22.4, 22.1 (one set of carbons are incidentally equivalent); IR (film) 2968, 1637, 1417 cm^{-1}. MS (ESI) 276.1359 (276.1364 calcd for $C_{17}H_{19}NO$, M + Na^+).

1-[2-(4-Benzoylbenzyl)pyrrolidin-1-yl]ethanone (II-37). Reaction of 32 mg (0.25 mmol) of **II-6** with 4-bromobenzophenone (72 mg, 0.28 mmol), dppe (2.0 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.30 mmol) following the general procedure B afforded 61 mg (80%) of the title compound as a pale yellow oil. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.64 (m, 4 H), 7.58–7.51 (m, 1 H), 7.47–7.40 (m, 2 H), 7.32–7.22 (m, 2 H), 4.34–4.26 (m, 0.75 H), 4.08–4.00 (m, 0.25 H), 3.60–3.32 (m, 2 H), 3.24 (dd, *J* = 3.3, 12.8 Hz, 0.75 H), 2.92 (dd, *J* = 5.1, 13.6 Hz, 0.25 H), 2.72 (m, 0.25 H), 2.67–2.60 (m, 0.75 H), 2.20–2.05 (m, 0.75 H), 2.06–1.98 (m, 3 H), 1.90–1.74 (m, 3.25 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 196.6, 169.6, 169.5, 144.5, 143.0, 138.3, 138.0, 136.2, 135.8, 132.7, 132.5, 130.8, 130.5, 130.2, 129.6, 129.4, 128.5, 128.4, 60.0, 58.4, 48.2, 45.7, 41.1, 39.0, 30.3, 28.7, 24.0, 23.2, 22.3, 22.0 (one set of carbons are incidentally equivalent); IR (film) 2960, 1638, 1414 cm^{-1}. MS (ESI) 330.1466 (330.1470 calcd for $C_{20}H_{21}NO_2$, M + Na^+).

1-[2-(4-Dimethylaminobenzyl)pyrrolidin-1-yl]ethanone (II-38). Reaction of 32 mg (0.25 mmol) of **II-6** with *N*,*N*–dimethyl-4-bromoaniline (55 mg, 0.28 mmol), Xantphos (2.9 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.30 mmol) following general procedure B afforded 42 mg (67%) of the title compound as a pale yellow oil. This compound was found to exist as a 3:2 mixture of rotamers as judged by ^{1}H NMR analysis. This material contained c.a. 15% of the corresponding 2,3-dihydropyrrole (1-[5-(4-dimethylaminobenzyl)-2,3-dihydropyrrol-1-yl]ethanone), which could not be

separated by chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–6.95 (m, 2 H), 6.72–6.57 (m, 2 H), 4.32–4.20 (m, 0.6 H), 4.01–3.88 (m, 0.4 H), 3.57–3.39 (m, 0.8 H), 3.38–3.29 (m, 1.2 H), 3.06–2.98 (m, 0.6 H), 2.93–2.85 (m, 6 H), 2.77–2.70 (m, 0.4 H), 2.57–2.43 (m, 1 H), 2.07–1.95 (m, 3 H), 1.89–1.67 (m, 4 H); ^{13}C NMR (125 MHz, CD_3OH) δ 170.9, 170.6, 150.1, 149.8, 129.9, 129.8, 113.4 113.3, 112.6, 112.4, 60.9, 59.0, 45.3, 40.1, 40.0, 39.9, 39.8, 39.1, 38.9, 36.9, 23.1, 21.5, 21.33, 21.28, 20.6; IR (film) 2930, 1638, 1417 cm^{-1}. MS (ESI) 269.1361 (269.1630 calcd for $C_{15}H_{22}N_2O$, M + Na^+).

2-Naphthalen-2-ylmethyl-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (II-39). Reaction of 59 mg (0.25 mmol) of **II-17** with 2-bromonaphthalene (57 mg, 0.28 mmol), Dpe-phos (2.7 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.30 mmol) following general procedure B afforded 44 mg (50%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.76 (m, 3 H), 7.63 (s, 1 H), 7.48–7.34 (m, 4 H), 7.22–7.30 (m, 2 H), 6.94 (t, J = 7.3 Hz, 1 H), 4.71 (s, br, 1 H), 3.41 (s, br, 1 H) 3.21–3.00 (m, 1 H), 2.81–2.67 (m, 2 H), 1.59 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 142.2, 135.7, 133.8, 132.5, 130.2, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 126.2, 125.7, 125.3, 122.7, 115.6, 81.1, 60.8, 40.6, 31.7, 28.7; IR (film) 2974, 1702, 1483, 1392 cm^{-1}. MS (ESI) 382.1787 (382.1783 calcd for $C_{24}H_{25}NO_2$, M + Na^+).

1-Benzyl-2-(4-methylbenzyl)-2,3-dihydro-1*H*-indole (II-40). Reaction of 65 mg (0.29 mmol) of **II-18** with 4-bromotoluene (40 μL, 55 mg, 0.32 mmol), Nixantphos

(3.2 mg, 0.0058 mmol, 2 mol %) and NaO*t*-Bu (34 mg, 0.30 mmol) following general procedure B afforded 44 mg (48%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5 H), 7.07–6.94 (m, 6 H), 6.59 (t, *J* = 7.0 Hz, 1 H), 6.33 (d, *J* = 7.7 Hz, 1 H), 4.46 (d, *J* = 16.1 Hz, 1 H), 4.24 (d, *J* = 16.1 Hz, 1 H), 3.86–3.78 (m, 1 H), 3.12 (dd, *J* = 4.0, 13.2 Hz, 1 H), 2.96–2.89 (m, 1 H), 2.78–2.62 (m, 2 H), 2.29 (s, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 139.2, 136.0, 135.6, 129.33 129.29, 128.69, 128.67 127.56, 127.54, 127.2, 124.4, 117.7, 107.1, 66.7, 51.8, 40.1, 35.1, 21.2; IR (film) 2921, 2360, 1484 cm^{-1}; MS (ESI) 314.1901 (314.1909 calcd for $C_{23}H_{23}N$, M + H^+).

(±)–(2*S*,5*R*)-2-(4-Methoxybenzyl)-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (II-41). Reaction of 261 mg (1.00 mmol) of **II-21** with 4-bromoanisole (140 μL, 206 mg, 1.1 mmol), dppb (8.0 mg, 0.02 mmol, 2 mol %) and NaO*t*-Bu (116 mg, 1.20 mmol) following general procedure B afforded 219 mg (60%) of the title compound as a pale yellow oil. This compound was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.05 (m, 7 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 4.97–4.61 (m, 1 H), 4.22–3.98 (m, 1 H), 3.76 (s, 3 H), 3.56–3.29 (m, 1 H), 2.59 (t, *J* = 11.4 Hz, 1 H), 2.22 (sx, *J* = 6.6 Hz, 1 H), 1.97–1.81 (m, 1 H), 1.82–1.66 (m, 2 H), 1.62–1.04 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 155.1, 131.6, 130.5, 128.5, 128.3, 126.6, 125.8, 114.1, 79.5, 63.3, 61.3, 55.4, 40.6, 34.4, 28.5 (nine sets of carbons are incidentally equivalent); IR (film) 2974, 1686, 1454 cm^{-1}. MS (ESI) 390.2038

(390.2045 calcd for $C_{23}H_{29}NO_3$, M + Na^+).

(±)–(2*S*,5*R*)-1-(2-Phenyl-5-pyridin-3-ylmethylpyrrolidin-1-yl)ethanone (II-42). Reaction of 51 mg (0.25 mmol) of **II-22** with 3-bromopyridine (27 μL, 43.5 mg, 0.28 mmol), dppb (2.2 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.3 mmol) following general procedure B afforded 57.2 mg (82%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49–8.41 (m, 2 H), 7.67–7.62 (m, 1 H), 7.38–7.18 (m, 6 H), 4.85 (t, *J* = 7.3 Hz, 1 H), 4.41–4.34 (m, 1 H), 3.62 (dd, *J* = 7.3, 12.8 Hz, 1 H), 2.59 (dd, *J* = 10.6, 12.8 Hz, 1 H), 2.34 (sx, *J* = 7.6 Hz, 1 H), 2.03–1.94 (m, 1 H), 1.80–1.72 (m, 4 H), 1.66–1.58 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 150.6, 148.1, 143.2, 137.0, 134.8, 129.2, 127.6, 125.7, 123.7, 64.1, 60.6, 37.6, 35.5, 28.2, 23.4; IR (film) 2968, 1643, 1404 cm^{-1}. MS (ESI) 281.1653 (281.1654 calcd for $C_{18}H_{20}N_2O$, M + H^+).

4-Allyl-2-(4-*tert*-butoxycarbonyl-benzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (II-43). Reaction of 57 mg (0.25 mmol) of **II-23** with 4-bromo-*tert*-butyl benzoate (71 mg, 0.28 mmol), Dpe-phos (2.7 mg, 0.005 mmol, 2 mol %) and NaO*t*-Bu (29 mg, 0.3 mmol) following general procedure B afforded 80 mg (70%) of the title compound as a pale yellow oil. This product was isolated as a c.a. 3:1 mixture of diastereomers. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.79 (m, 2 H), 7.17 (s, br, 2 H), 5.72–5.57 (m, 1 H), 4.99–4.86 (m, 2 H), 4.06–2.83 (m, br, 3 H),

2.76–2.48 (m, 2 H), 2.07–1.88 (m, 4 H), 1.57–1.40 (m, 18 H), 1.27–1.11 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 157.5, 154.7, 149.5, 146.2, 143.8, 136.4, 130.2, 129.7, 116.3, 116.2, 81.0, 79.4, 77.6, 77.2, 76.9, 58.7, 52.7, 52.1, 51.7, 41.8, 41.0, 40.1, 37.9, 37.7, 37.3, 37.0, 36.3, 35.6, 34.9, 28.8, 28.4; IR (film) 2976, 1712, 1694, 1395 cm^{-1}. Anal calcd for $C_{24}H_{35}NO_4$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.60; H, 8.75; N, 3.45.

(±)–(2*R*,3*S*)-3-Methyl-2-naphthalen-2-ylmethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (II-44). The reaction of 100 mg (0.5 mmol) of **II-7** with 2-bromonaphthalene (124 mg, 0.60 mmol), Dpe-phos (10.8 mg, 0.02 mmol, 4 mol %) and NaO*t*-Bu (96 mg, 1.00 mmol) was conducted following general procedure A. ^{1}H NMR analysis of the crude product showed the formation of the desired product as a 10:1 mixture of diastereomers. The minor diastereomer was separated upon chromatographic purification to afford 106 mg (65%) of the title compound as a white solid with >20:1 dr, m.p. 107 °C. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.73 (m, 3 H), 7.62 (d, *J* = 16.3 Hz, 1 H), 7.50–7.28 (m, 3 H), 3.78–3.60 (m, 1 H), 3.61–3.38 (m, 1 H), 3.33–3.08 (m, 2 H), 2.96–2.73 (m, 1 H), 2.15–2.09 (m, 1 H), 1.98–1.80 (m, 1 H), 1.53 (s, 9 H), 1.49–1.34 (m, 1 H), 0.84 (s, br, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 136.8, 133.7, 132.3, 128.6, 128.2, 128.0, 127.8, 127.7, 126.2, 126.0, 125.5, 125.4, 79.6, 79.5, 66.0, 65.7, 45.7, 45.0, 40.6, 39.1, 37.0, 36.1, 31.3, 30.4, 28.8, 19.6, 19.4 (seven sets of carbons are incidentally equivalent); IR (film) 2964, 1692, 1396

cm^{-1}. MS (ESI) 348.1943 (348.1939 calcd for $C_{21}H_{27}NO_2$, M + Na^+).

(±)–(2*R*,3*S*)-2-(4-*tert*-Butylbenzyl)-3-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (II-45). The reaction of 100 mg (0.5 mmol) of **II-7** with 4-bromo-*tert*-butylbenzene (105 μL, 128 mg, 0.60 mmol), Dpe-phos (10.8 mg, 0.02 mmol, 4 mol %) and NaO*t*-Bu (96 mg, 1.00 mmol) was conducted following general procedure A. ^{1}H NMR analysis of the crude product showed the formation of the desired product as a 10:1 mixture of diastereomers. The minor diastereomer was separated upon chromatographic purification to afford 97.4 mg (59%) of the title compound as a pale yellow oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 3:2 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (m, 2 H), 7.16–7.06 (m, 2 H), 3.69–3.37 (m, 2 H), 3.31–2.92 (m, 2 H), 2.76–2.56 (m, 1 H), 2.05 (s, br, 1 H), 1.97–1.79 (m, 1 H), 1.51 (s, 9 H), 1.45–1.35 (m, 1 H), 1.32 (s, 9 H), 0.88 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 149.2, 149.0, 136.1, 129.5, 129.3, 125.5, 125.3, 79.4, 79.1, 66.1, 65.6, 45.6, 45.0, 39.9, 38.5, 37.1, 36.0, 34.6, 31.6, 31.2, 30.4, 28.8, 19.7, 19.5 (five sets of carbons are incidentally equivalent); IR (film) 2963, 1696, 1395 cm^{-1}. MS (ESI) 354.2402 (354.2409 calcd for $C_{21}H_{33}NO_2$, M + Na^+).

(±)–(2*R*,3*S*)-1-[2-(4-Chlorobenzyl)-3-methyl pyrrolidin-1-yl]ethanone (II-46). The reaction of 72 mg (0.5 mmol) of **II-8** with 4-bromochlorobenzene (106 mg, 0.55 mmol), Dpe-phos (10.8 mg, 0.02 mmol, 4 mol %) and NaO*t*-Bu (58 mg, 1.00 mmol) was

conducted following general procedure B. ^{1}H NMR analysis of the crude product showed the formation of the desired product as a 10:1 mixture of diastereomers. The minor diastereomer was separated upon chromatographic purification to afford 69.4 mg (61%) of the title compound as a pale yellow oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.16 (m, 2 H), 7.12–7.00 (m, 2 H), 3.86–3.78 (m, 0.7 H), 3.71–3.60 (m, 0.3 H), 3.55–3.48 (m, 0.3 H), 3.47–3.29 (m, 1 H), 3.26–3.16 (m, 0.7 H), 3.08–2.98 (m, 0.7 H), 2.81–2.73 (m, 0.3 H), 2.72–2.57 (m, 1 H), 2.14–2.08 (m, 0.3 H), 2.07–1.95 (m, 3.1 H), 1.92–1.84 (m, 1.6 H), 1.52–1.38 (m, 1 H), 0.89–0.80 (m, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.7, 137.5, 136.5, 132.8, 132.1, 131.1, 130.7, 129.1, 128.6, 67.4, 65.3, 46.9, 44.1, 40.6, 37.7, 37.2, 35.6, 31.4, 29.1, 23.2, 22.2, 19.8, 19.3; IR (film) 2961, 1641, 1417 cm^{-1}. MS (ESI) 274.0969 (274.0975 calcd for $C_{14}H_{18}ClNO$, M + Na^+).

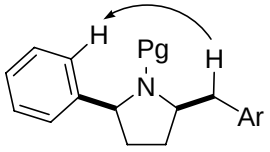
(±)–(3a*R*,6*S*,6a*S*)-6-Biphenyl-4-yl-hexahydrocyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (II-47) Reaction of 53 mg (0.25 mmol) of **II-14** with 4-bromobiphenyl (64 mg, 0.28 mmol), Xantphos (5.8 mg, 0.01 mmol, 4 mol %) and NaO*t*-Bu (36 mg, 0.38 mmol) following general procedure A afforded 42.8 mg (47%) of the title compound as a white solid, m.p. 128 °C. This compound was found to exist as a 3:2 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.34 (m, 6 H), 7.32–7.16 (m, 3 H), 4.54–4.30 (m, 1 H), 3.83–3.71 (m, 0.6 H), 3.55–3.17 (m, 1.4 H), 3.10–2.78 (m, 2 H), 2.12–1.98 (m, 1 H), 1.97–1.60 (m, 5 H), 1.21–0.89 (m, 9

H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 141.6, 141.2, 139.4, 129.6, 128.9, 127.2, 127.1, 127.0, 126.6, 94.6, 79.0, 65.4, 52.3, 51.2, 47.8, 43.5, 42.5, 34.2, 33.7, 32.4, 32.2, 31.8, 28.4, 27.9 (thirteen sets of carbons are incidentally equivalent); IR (film) 2952, 1689, 1392 cm^{-1}. MS (ESI) 386.2105 (386.2096 calcd for $C_{24}H_{29}NO_2$, M + Na^+).

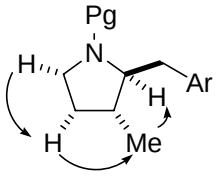
(±)–(3a*R*,6*S*,6a*S*)-1-(6-Naphthalen-2-yl-hexahydrocyclopenta[*b*]pyrrol-1-yl)ethanone (II-48) Reaction of 78 mg (0.25 mmol) of **II-15** with 2-bromonaphthalene (114 mg, 0.55 mmol), Nixantphos (13.8 mg, 0.025 mmol, 5 mol %), $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 2.5 mol %) and NaO*t*-Bu (58 mg, 0.60 mmol) following general procedure B afforded 85 mg (61%) of the title compound as a pale yellow oil. This compound was found to exist as a 7:3 mixture of rotamers as judged by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.69 (m, 3 H), 7.57 (s, 1 H), 7.48–7.34 (m, 2 H), 7.28–7.24 (m, 1 H), 4.90 (t, *J* = 8.6 Hz, 0.3 H), 4.43 (t, *J* = 7.0 Hz, 0.7 H), 4.14–4.06 (m, 0.70 H), 3.54 (q, *J* = 8.1 Hz, 0.3 H), 3.48–3.20 (m, 2 H), 3.13–3.04 (m, 0.7 H), 2.92–2.82 (m, 0.3 H), 2.17–1.92 (m, 4 H), 1.85–1.72 (m, 2 H), 1.64 (s, 0.6 H), 1.11 (s, 2.4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 168.8, 139.2, 138.2, 133.6, 133.5, 132.7, 132.4, 128.31, 128.29, 128.1, 127.91, 127.90, 129.86, 127.81, 127.2, 127.0, 126.6, 126.4, 125.9, 125.8, 125.3, 67.0, 65.2, 53.4, 49.9, 49.1, 47.4, 44.0, 42.3, 33.7, 32.6, 32.4, 32.3, 32.2, 31.4, 22.5, 21.8; IR (film) 2950, 1638, 1413 cm^{-1}. MS (ESI) 302.1523 (302.1521 calcd for $C_{19}H_{21}NO$, M + Na^+).

Assignment of Stereochemistry

2,5-Disubstituted Pyrrolidines (II-41 and II-42). The *cis* stereochemistry of the 2,5-disubstituted pyrrolidine products (±)–(2*S*,5*R*)-2-(4-Methoxybenzyl)-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (**II-41**) and (±)–(2*S*,5*R*)-1-(2-Phenyl-5-pyridin-3-ylmethylpyrrolidin-1-yl)ethanone (**II-42**) was assigned on the basis of nOe signals between the *ortho* protons of the C5 phenyl group and one of the benzylic hydrogens on C1' as shown below.

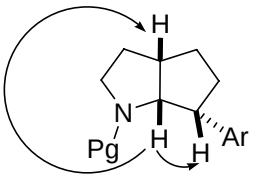


2,3-Disubstituted Pyrrolidine (II-44, II-45, II-46). The *trans* stereochemistry of the 2,3-disubstituted pyrrolidine products (±)–(2*R*,3*S*)-3-Methyl-2-naphthalen-2-ylmethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**II-44**), (±)–(2*R*,3*S*)-2-(4-*tert*-Butylbenzyl)-3-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**II-45**) and (±)–(2*R*,3*S*)-1-[2-(4-Chlorobenzyl)-3-methyl pyrrolidin-1-yl]ethanone (**II-46**) was assigned on the basis of nOe signals as shown below.



1,5-aryloctahydrocyclopenta[b]pyrroles (II-47, II-48). The relative stereochemistry of (±)–(3a*R*,6*S*,6a*S*)-6-Biphenyl-4-yl-hexahydrocyclopenta[*b*]pyrrole-1-

carboxylic acid *tert*-butyl ester (**II-47**) and (±)–(3a*R*,6*S*,6a*S*)-1-(6-Naphthalen-2-yl-hexahydrocyclopenta[*b*]pyrrol-1-yl)ethanone (**II-48**) was assigned on the basis of nOe signals as shown below.



References

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[14] The product isolated from this reaction contained ca 15% of the corresponding dihydropyrrole. Similar side reactions have been previously observed in reactions of 2-allylaniline or γ-*N*-arylaminoalkenes with electron-rich aryl bromides. See ref 10.

[15] For reviews of Pd-catalyzed N-arylation of amines, which involve $Pd(Ar)(NR_2)$ intermediates, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. (b) Hartwig, J. F. In *Modern Arene Chemistry*; Astruc, D.; Ed.; Wiley-VCH: Weinhem, Germany, 2002; pp 107–168.

[16] Recent studies indicated that the use of ligand $P(2\text{-furyl})_3$ in palladium-catalyzed carboamination reaction of **II-30** with β-bromostyrene afforded good yield of 2-

cinnamyl-1-phenylpyrrolidine. See: Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614–1620.

[17] For recent studies on Pd-catalyzed *N*-vinylation of amines, see: Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2004**, *10*, 494–507.

[18] The base induced substrate olefin isomerization was only observed in reactions of 2-allylaniline derivatives.

[19] For Pd-catalyzed oxidative amination reactions that afford indole products, see: (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807. (b) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585.

[20] The relative stereochemistry of the pyrrolidine products was assigned on the basis of ^{1}H NMR nOe experiments. Diastereomeric ratios were determined by GC and/or ^{1}H NMR analysis.

[21] Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651.

[22] Increasing the reaction temperature to >100 ^{o}C led to starting material decomposition via Boc deprotection. See ref. [12].

[23] See Chapter III for the synthesis of substrate **II-49**, and characterization data/stereochemical determination of product **II-50**.

[24] Development of new mild reaction conditions permitted access to pyrrolidine product **II-50** in 50% yield and high selectivity (>20:1 dr). See Chapter III.

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

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Chapter III

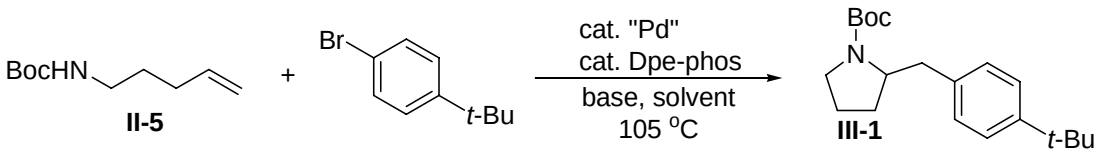
Development of Milder Reaction Conditions for the Carboamination Reaction[1]

A significant improvement of the carboamination methodology described in Chapter II would involve the development of milder reaction conditions. Indeed, the reactions are typically conducted in the presence of the strong base NaO*t*-Bu, which limits the scope of the methodology in terms of substrates and coupling partners. For example, Cbz nitrogen protecting groups, which are frequently employed in the synthesis of complex alkaloids, are incompatible with the strongly basic conditions. Additionally, aryl triflates, desirable coupling partners since they are readily available synthetic intermediates from the corresponding phenol,[2] decompose in the presence of strong base. Their use has not been reported in the carboamination chemistry. Finally, many common functional groups, such as enolizable ketones and unhindered esters, are not tolerated under the strongly basic conditions. This chapter describes the development of new conditions that replace NaO*t*-Bu with weaker bases (Cs_2CO_3 or K_3PO_4), which significantly expands the scope of the carboamination method. This chapter also presents studies on the mechanism of the carboamination reactions of γ-(*N*-Boc-amino)alkenes.

Optimization Studies

In our preliminary studies on palladium-catalyzed carboamination reactions of γ-(*N*-Boc-amino) or γ-(*N*-acylamino)alkenes, our attempts to conduct the transformations using bases other than NaO*t*-Bu were met with limited success. For example, the $Pd_2(dba)_3$/Dpe-phos catalyzed carboamination of **II-5** with 4-bromo-*tert*-butylbenzene afforded **III-1** in 81% yield when the reaction was conducted in toluene solvent with NaO*t*-Bu as base (Table 5, entry 1). However, use of Cs_2CO_3 in place of NaO*t*-Bu provided only a 38% isolated yield of **III-1**, and led to the formation of large amounts of side-products resulting from Heck arylation (entry 2).[3] Other weak bases such as K_2CO_3 and Et_3N also provided unsatisfactory yields of pyrrolidine products. To improve the yields obtained in Pd-catalyzed carboamination reactions that employ mild bases, the effect of palladium source and solvent were systematically examined; the key results of these studies are summarized in Table 5. After some experimentation, it was discovered that use of $Pd(OAc)_2$ in place of $Pd_2(dba)_3$ leads to significantly improved yields of **III-1** (63%, entry 3), and replacement of toluene with dioxane as solvent provides optimal results (82%, entry 4).[4]

Table 5. Optimization Summary[a]



Entry	Base	"Pd"	Solvent	Yield (%)
1	NaO*t*-Bu	$Pd_2(dba)_3$	Toluene	81
2	Cs_2CO_3	$Pd_2(dba)_3$	Toluene	38
3	Cs_2CO_3	$Pd(OAc)_2$	Toluene	63
4	Cs_2CO_3	$Pd(OAc)_2$	Dioxane	82[b]

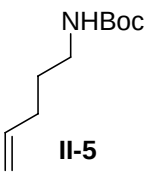
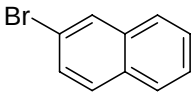
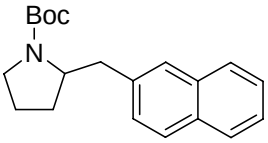
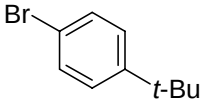
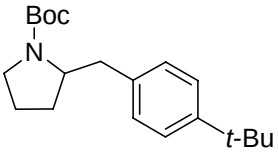
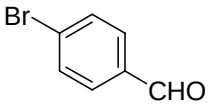
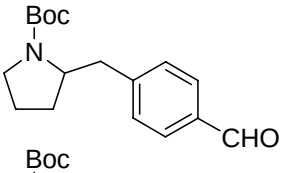
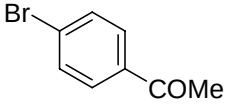
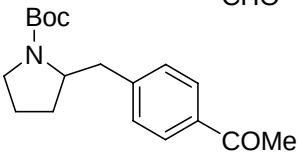
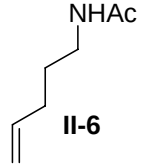
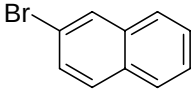
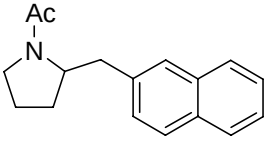
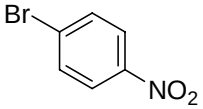
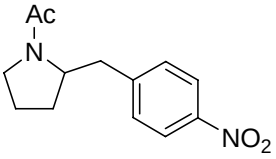
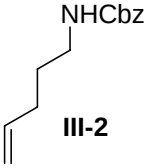
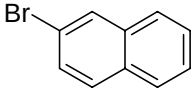
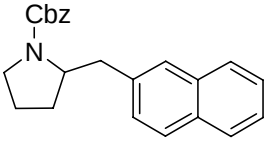
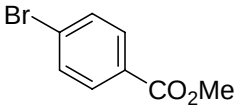
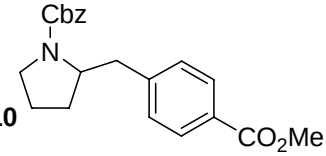
[a]Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 2.3 equiv base, 1 mol % $Pd_2(dba)_3$ (2 mol % Pd) or 2 mol % $Pd(OAc)_2$, 2 mol % Dpe-phos (with $Pd_2(dba)_3$) or 4 mol % Dpe-phos (with $Pd(OAc)_2$), solvent (0.25 M), 105 °C. [b]The reaction was conducted at 100 °C.

Scope and Diastereoselectivity

As shown in Tables 6 and 7, the new reaction conditions described above are effective for the transformation of a number of different substrate combinations. A variety of functional groups are tolerated under these mild conditions, including aldehydes (entry 3, Table 6), enolizable ketones (entry 4, Table 6), nitro groups (entry 6, Table 6 and entry 3, Table 7), methyl esters (entry 8, Table 6), and alkyl acetates (entry 1, Table 7). In addition, the carboamination reactions of electron-rich (entry 2, Table 7), electron-neutral (entries 1, 2, 5, and 7, Table 6), and heterocyclic (entry 4, Table 7) aryl bromides proceed with good chemical yields. In addition to providing increased tolerance of base-sensitive functional groups, the new reaction conditions also allow the efficient carboamination of substrates bearing Cbz-protecting groups. For example, the Pd-catalyzed coupling of **III-2** with 2-bromonaphthalene using Cs_2CO_3 as base provided the desired product **III-9** in 88% isolated yield (entry 7, Table 6). In contrast, cleavage of the

Cbz-group from the substrate was problematic when reactions were conducted with NaO*t*-Bu as base; these conditions provided only a 17% yield of **III-9**.

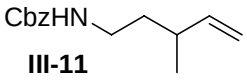
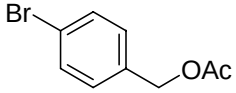
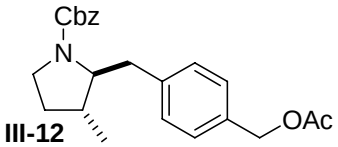
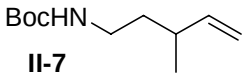
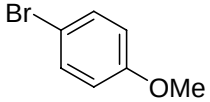
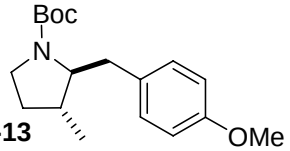
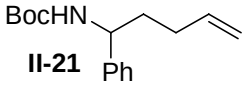
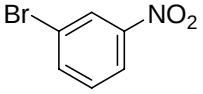
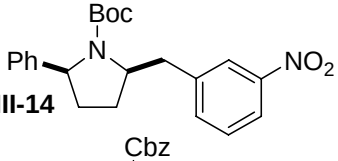
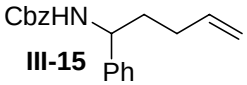
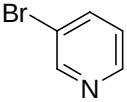
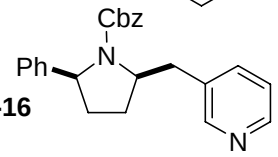
Table 6. Palladium-Catalyzed Carboamination of *N*-Protected γ–Aminoalkenes with Functionalized Aryl Bromides[a]

Entry	Amine	Aryl bromide	Product	Yield (%)[b]
1	 **II-5**		 **III-3**	75
2			 **III-4**	82
3			 **III-5**	78[e]
4			 **III-6**	76[e]
5	 **II-6**		 **III-7**	79
6			 **III-8**	76[c,e]
7	 **III-2**		 **III-9**	88 17[d]
8			 **III-10**	88[e]

[a]Conditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.3 equiv Cs_2CO_3, 2 mol % $Pd(OAc)_2$, 4 mol % Dpe-phos, dioxane (0.2–0.25 M), 100 °C. [b]Yield refers to average isolated yield obtained in two or more experiments. [c]Dppe used in place of Dpe-phos. [d]NaO*t*-Bu used in place of Cs_2CO_3. [e]The reaction was conducted at 85 °C in DME solvent.

The mild conditions are also effective for stereoselective reactions, and provide selectivities that are comparable to those observed in reactions that use NaO*t*-Bu as base (Chapter II). For example, transformation of starting material substrates **III-11** and **II-7**, which are substituted at the allylic position, are transformed to *trans*-2,3-disubstituted products **III-12** and **III-13** with good stereocontrol (Table 7, entries 1–2). Similarly, substrates **II-21** and **III-15** bearing a substituent adjacent to the nitrogen atom, provide *cis*-2,5-disubstituted products **III-14** and **III-16** with excellent (>20:1) diastereoselectivity (entries 3–4).

Table 7. Palladium-Catalyzed Carboamination of Substituted *N*-Protected γ–Aminoalkenes with Functionalized Aryl Bromides[a]

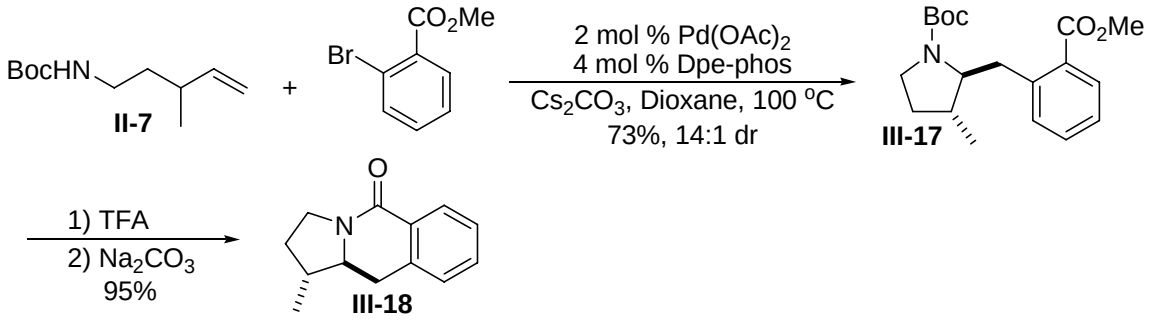
Entry	Amine	Aryl bromide	Product	dr	Yield(%)[b]
1	 **III-11**		 **III-12**	12:1	80
2	 **II-7**		 **III-13**	15:1	76
3	 **II-21**		 **III-14**	>20:1	75
4	 **III-15**		 **III-16**	>20:1	74

[a]Conditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.3 equiv Cs_2CO_3, 2 mol % $Pd(OAc)_2$, 4 mol % Dpe-phos, dioxane (0.2–0.25 M), 100 °C. [b]Yield refers to average isolated yield obtained in two or more experiments.

The high degree of functional group tolerance of this method also allows

straightforward access to 1-substituted tetrahydropyrroloisoquinolin-5-ones. As shown in Scheme 12, the Pd-catalyzed reaction of **II-7** with methyl-2-bromobenzoate afforded pyrrolidine **III-17** in 73% yield with 14:1 dr. Treatment of this product with trifluoroacetic acid followed by an alkaline workup gave **III-18** in 95% yield.

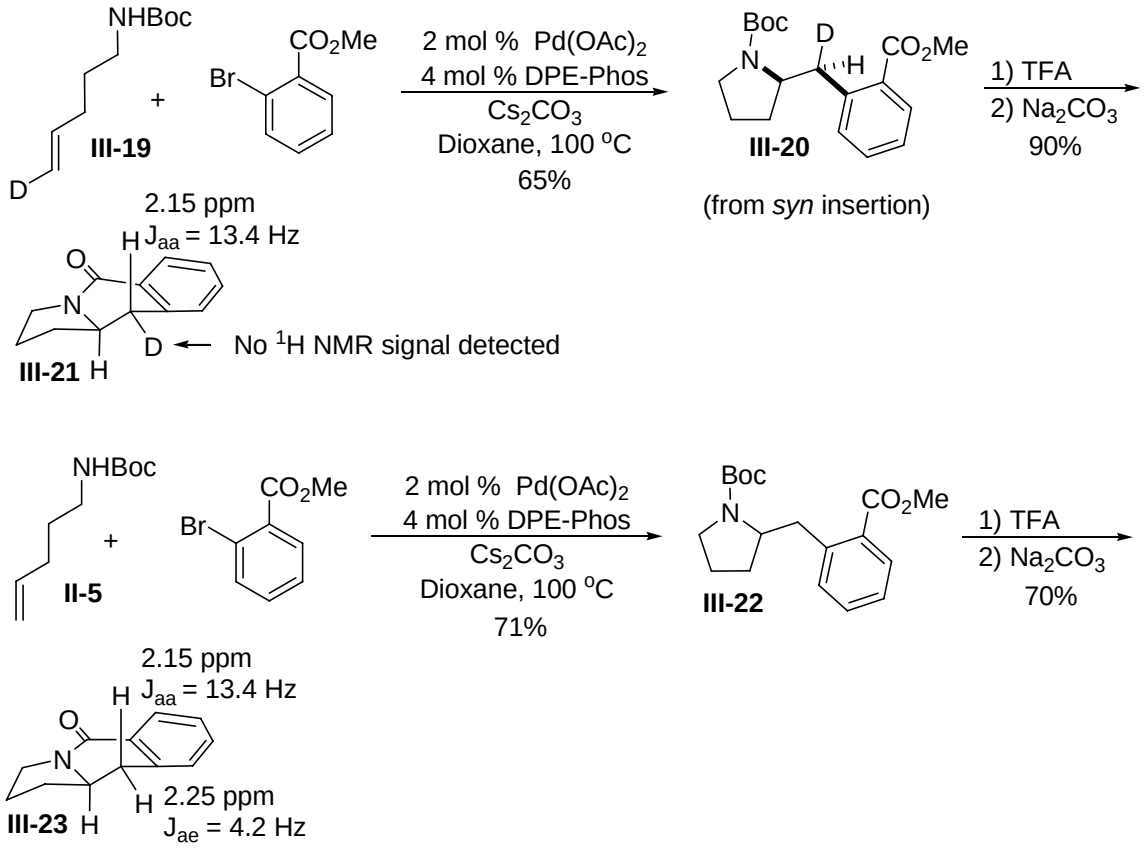
Scheme 12. Stereoselective Synthesis of **III-18**



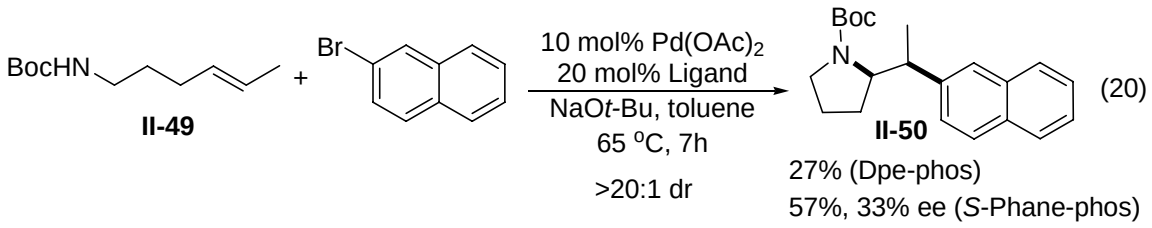
Finally, we investigated the stereochemistry of olefin insertion in the reactions of terminal alkenes using these new, mild reaction conditions. We conducted a deuterium labeling experiment to accomplish this task (Scheme 13). The strategy involved the coupling of a substrate (**III-19**) containing a deuterium atom at the terminal carbon with methyl 2-bromobenzoate under the optimized carboamination reaction conditions. Product **III-20** was obtained in moderate yield and was subjected to our newly developed protocol for tetrahydropyrroloisoquinolin-5-one synthesis to afford derivative **III-21**. The same two-step sequence was performed with the all-proteo substrate **II-5**. ^{1}H NMR analysis of both cyclic derivatives permitted assignment of the stereochemistry at the deuterium-bearing carbon center in **III-20**, which indicated that the olefin insertion

process occurred in a *syn* fashion under the mild reaction conditions.

Scheme 13. Deuterium-Labeling Experiment



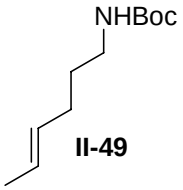
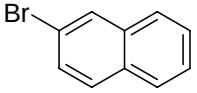
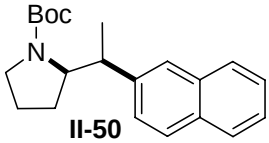
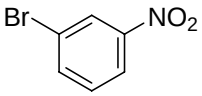
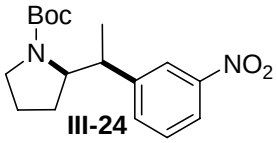
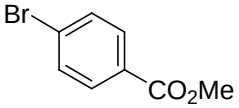
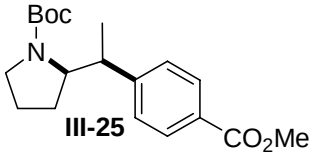
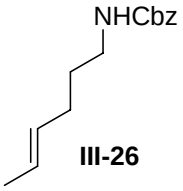
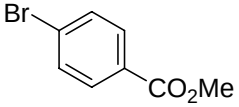
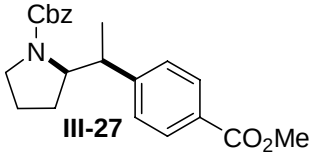
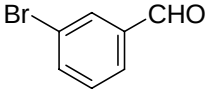
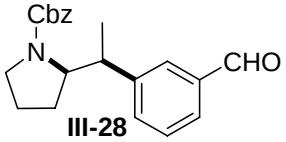
Important substrates in the carboamination chemistry are *N*-protected internal alkenes, since their cyclization would create two new stereocenters in one step. Previous studies[5] with the strong base NaO*t*-Bu indicated that high catalyst loading (10 mol %) was required to promote the conversion of **II-49** to pyrrolidine **II-50** in moderate yield (eq 20).



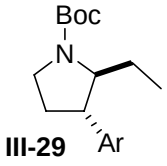
(20)

We investigated the cyclization of substrate **II-49** under the mild reaction conditions and, following an extensive ligand screen, we found that the ligands Nixantphos and (±)-BINAP were optimal (Table 8). Catalyst loadings of 5 mol % were needed to effect complete conversion of the starting materials, along with reaction times of 24–72 h. The substrate scope was limited to electron-neutral and electron-poor aryl bromides; use of electron-rich aryl bromides led to low conversions (<50%) and formation of large amounts of side-products resulting from competing Heck arylation of the alkene. Moderate yields of the desired pyrrolidine products were obtained in high diastereoselectivity (>20:1 dr). Regioisomeric product **III-29** (Figure 2) was also observed in the reactions of *N*-Boc substrate **II-49** used in combination with electron-poor aryl bromides (Table 8, entries 2 and 3).

Table 8. Palladium-Catalyzed Carboamination of *N*-Protected γ–Aminoalkenes **II-49** and **III-26** with Functionalized Aryl Bromides[a]

Entry	Amine	Aryl bromide	Product	Regio	Yield (%)[b]
1	 **II-49**		 **II-50**	—	59
2			 **III-24**	11:1	50[c]
3			 **III-25**	5:1	44[c,d]
4	 **III-26**		 **III-27**	—	43[d,e]
5			 **III-28**	—	43[d,e,f]

[a]Conditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.3 equiv Cs_2CO_3, 5 mol % $Pd(OAc)_2$, 7.5 mol % Nixantphos, dioxane (0.25 M), 100 °C, 24 h. [b]Yield refers to average isolated yield obtained in two or more experiments. [c]This reaction was conducted at 100 °C for 48 h. [d](±)-BINAP used in place of Nixantphos. [e]This reaction was conducted at 100 °C for 72 h. [f]This reaction was conducted with 2.0 equiv ArBr, 10 mol % $Pd(OAc)_2$ and 15 mol % (±)-BINAP.

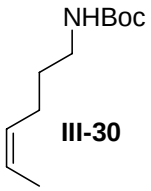
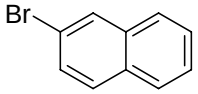
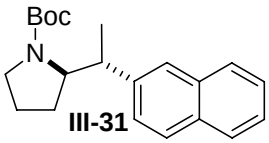
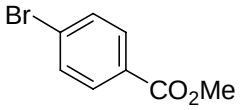
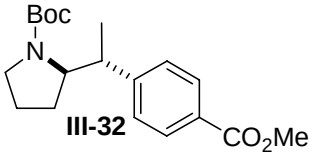
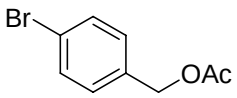
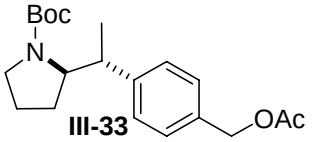
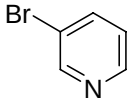
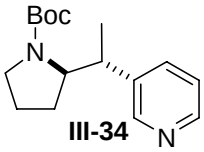
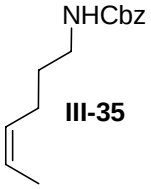
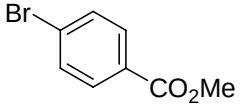
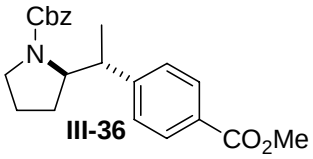
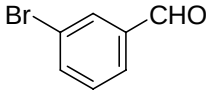
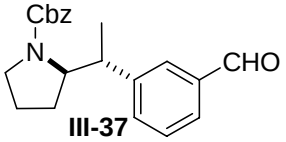


III-29

Figure 2. Regioisomeric Product **III-29**.

A change in phosphine ligand from Nixantphos to (±)-BINAP was required for the optimal cyclization of *N*-protected (*Z*)-aminoalkene substrates **III-30** and **III-35** (Table 9). Moderate yields of the pyrrolidine products were obtained with electron-neutral and electron-poor aryl bromides. However, use of electron-rich aryl bromides lead to low conversions (<50%) and formation of large amounts of side-products resulting from Heck arylation. In most cases, high diastereoselectivity (dr >20:1) and regioselectivity was observed. In general, the reaction of *N*-protected (*Z*)-aminoalkene substrates **III-30** and **III-35** were faster than *N*-protected (*E*)-aminoalkene substrates **II-49** and **III-26**. For example, reaction of **II-49** with methyl 4-bromobenzoate required 48 h to proceed to completion compared to 24 h for substrate **III-30**.

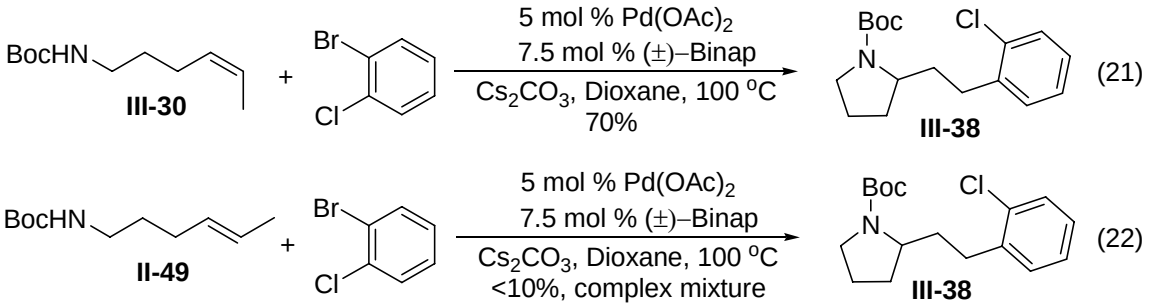
Table 9. Palladium-Catalyzed Carboamination of *N*-Protected γ–Aminoalkenes **III-30** and **III-35** with Functionalized Aryl Bromides[a]

Entry	Amine	Aryl bromide	Product	Yield (%)[b]
1	 **III-30**		 **III-31**	59
2			 **III-32**	55
3			 **III-33**	60[c]
4			 **III-34**	62[d]
5	 **III-35**		 **III-36**	49
6			 **III-37**	44[d,e]

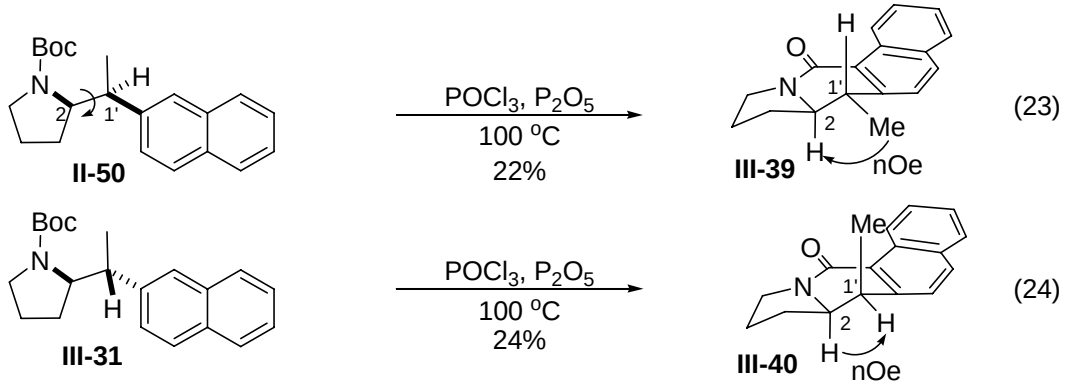
[a]Conditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.3 equiv Cs_2CO_3, 5 mol % $Pd(OAc)_2$, 7.5 mol % (±)-BINAP, dioxane (0.25 M), 100 °C, 24 h [b]Yield refers to average isolated yield obtained in two or more experiments. [c]This reaction proceeded to 94% conversion. [d]This reaction was conducted at 100 °C for 48 h. [e]This reaction was conducted with 2.0 equiv ArBr, 10 mol % $Pd(OAc)_2$ and 15 mol % (±)-BINAP for 72 h.

Interestingly, regioisomeric product **III-38** was isolated in 70% yield when 2-bromochlorobenzene was used as an aryl bromide (eq 21). However, the analogous reaction of *N*-protected (*E*)-aminoalkene substrate **II-49** with 2-bromochlorobenzene

under the same reaction conditions resulted in a complex mixture of products containing less than 10% of regioisomer **III-38** (eq 22).

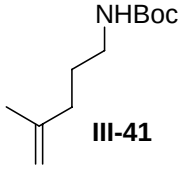
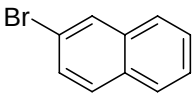
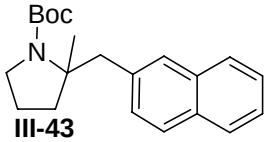
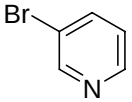
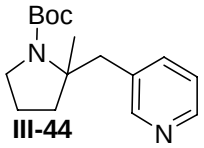
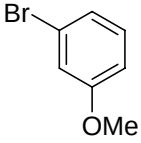
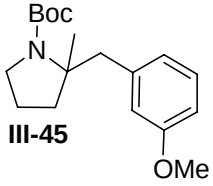
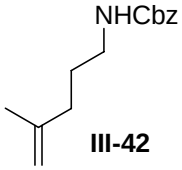
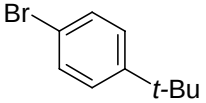
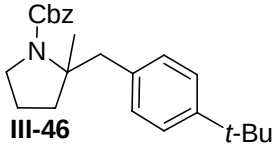
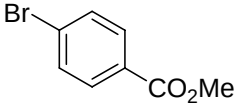
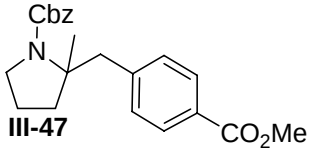


The C2/C1'relative stereochemistry in products **II-50** and **III-31** was determined by nOe experiments on cyclic lactam derivatives **III-39** and **III-40**, respectively, prepared via intramolecular Bischler-Napieralski cyclization (eqs 23 and 24).[6] A crystal structure of derivative **III-39** was obtained to confirm the stereochemical assignment. This experiment also provided the information that the olefin insertion process occurred in a *syn* fashion during the key step of the carboamination reaction.



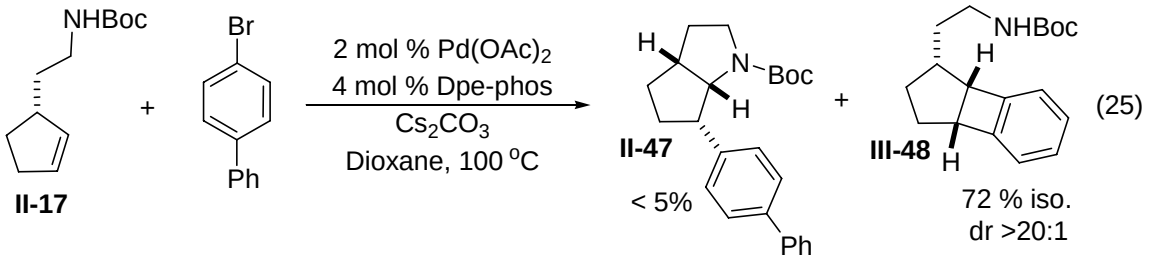
The cyclization of substituted olefin substrates **III-41** and **III-42** was achieved using the ligand Nixantphos (Table 10). The 1,1-disubstituted alkenes were more reactive than the 1,2-disubstituted alkenes, and cyclization of **III-41** and **III-42** could be effectively achieved using only 2 mol % Pd. As shown in Table 10, various aryl bromides were effectively coupled, including electron-poor, electron-rich and heteroatom substituted aryl bromides. These reactions afforded moderate to good yields of the corresponding pyrrolidine products containing a quaternary carbon at C2.

Table 10. Palladium-Catalyzed Carboamination of Substrates **III-41** and **III-42**.[a]

Entry	Amine	Aryl bromide	Product	Yield (%)[b]
1	 **III-41**		 **III-43**	73
2			 **III-44**	75
3			 **III-45**	66
4	 **III-42**		 **III-46**	71
5			 **III-47**	61

[a]Conditions: 1.0 equiv amine, 1.2 equiv ArBr, 2.3 equiv Cs_2CO_3, 2 mol % $Pd(OAc)_2$, 4 mol % Nixantphos, dioxane (0.25 M), 100 °C. [b]Yield refers to average isolated yield obtained in two or more experiments. [c]This reaction was conducted with 4 mol % $Pd(OAc)_2$ and 8 mol % Nixantphos.

Interestingly, attempts to couple cyclic 1,2-disubstituted olefin substrate **II-14** with 4-bromobiphenyl under the optimized mild reaction conditions afforded less than 5% of **II-47** (eq 25). Instead, the majority of the material was converted to benzocyclobutene **III-48**, which was isolated in 72% yield and >20:1 dr. Details on the investigation of this new transformation are described in Chapter IV.



II-17

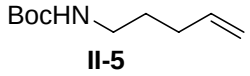
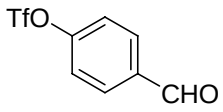
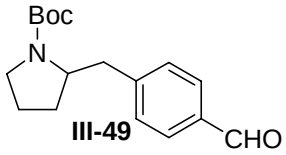
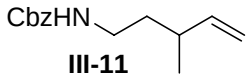
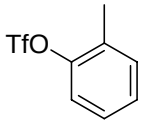
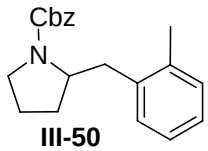
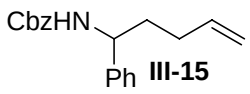
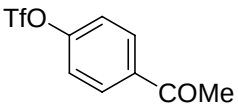
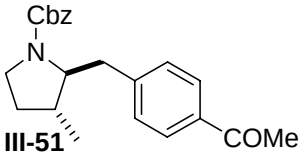
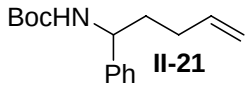
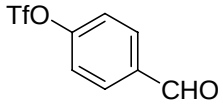
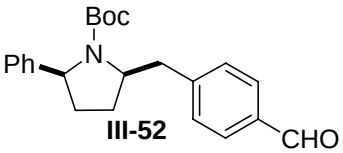
II-47 < 5%

III-48 72 % iso. dr >20:1

In addition to greatly expanding the scope of Pd-catalyzed carboamination reactions involving aryl bromide substrates, the use of mildly basic reaction conditions also allowed the first Pd-catalyzed carboamination reaction with aryl triflates. Our preliminary efforts to conduct these transformations with the strong base NaO*t*-Bu were unsuccessful due to competing cleavage of the trifluoromethanesulfonate ester, which resulted in conversion of the aryl triflate to the corresponding phenol. For example, treatment of **II-5** with 4-formylphenyl triflate in the presence of catalytic $Pd(OAc)_2$/Dpe-phos and stoichiometric NaO*t*-Bu failed to generate the desired pyrrolidine product **III-49** (Table 11). However, subsequent experiments demonstrated that use of K_3PO_4 as base provided the desired pyrrolidine **III-49** in 67% yield (Table 11, entry 1). These conditions are effective with both Boc- and Cbz-protected substrates, and

diastereoselectivities are similar to those obtained in related reactions with aryl bromide electrophiles (entries 3-4).

Table 11. Palladium-Catalyzed Carboamination of Aryl Triflates[a]

Entry	Amine	Aryl triflate	Product	dr	Yield(%)[b]
1	 **II-5**		 **III-49**	—	67 0[c]
2	 **III-11**		 **III-50**	—	74
3	 **III-15**		 **III-51**	12:1	70
4	 **II-21**		 **III-52**	>20:1	64

[a]Conditions: 1.0 equiv amine, 1.2 equiv ArOTf, 2.3 equiv K_3PO_4, 4 mol % $Pd(OAc)_2$, 8 mol % Dpe-phos, dioxane (0.25 M), 100 °C. [b]Yield refers to average isolated yield obtained in two or more experiments. *c*. NaO*t*-Bu used in place of K_3PO_4.

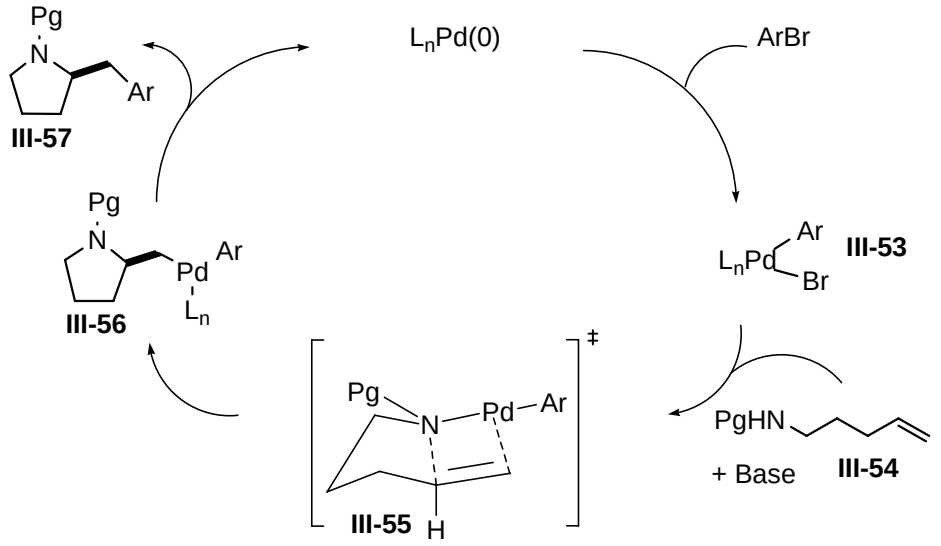
Mechanistic Considerations

The proposed catalytic cycle for the Pd-catalyzed carboamination reaction described in Chapters II and III is likely analogous to that previously proposed for reactions of γ–(*N*-arylamino)alkene substrates.[7] As shown below (Scheme 14), the catalytic cycle presumably commences with oxidative addition of the aryl bromide to the

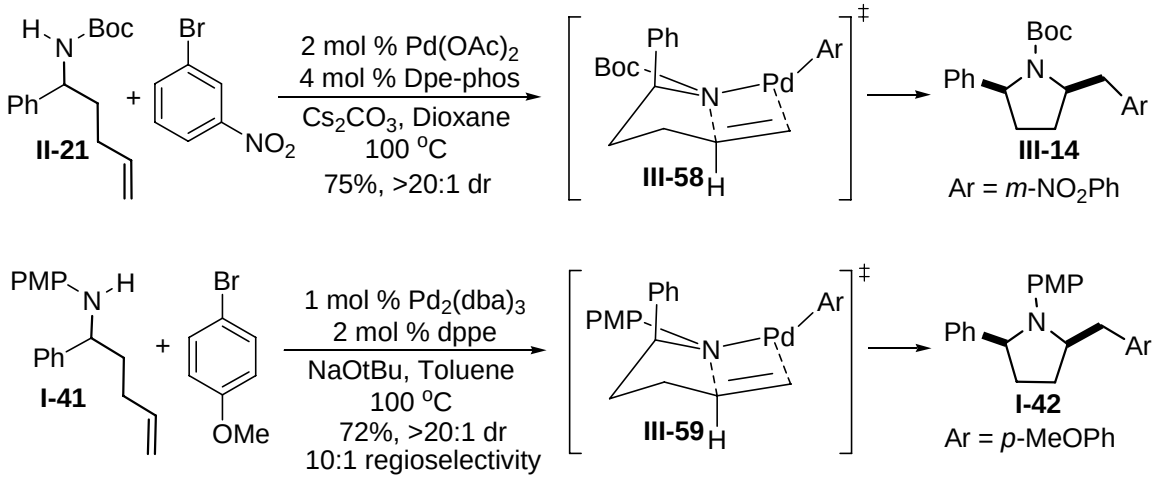
Pd(0) catalyst to afford Pd(Ar)(Br) complex **III-53**. Reaction of this complex with the γ–aminoalkene substrate in the presence of base likely results in the formation of palladium aryl(amido) complex **III-55**,[3] which undergoes insertion of the alkene into the Pd–N bond[25,8] followed by C–C bond-forming reductive elimination[9] of the resulting intermediate **III-56** to afford the observed pyrrolidine with concomitant regeneration of the Pd(0) catalyst. The formation of products that result from *syn* addition of the aryl group and the nitrogen across the C–C double bond is consistent with this mechanistic proposal.

The observed stereochemical outcomes of reactions of chiral γ-(*N*-Boc-amino) and γ-(*N*-acyl-amino) alkenes are similar to the stereoselectivity observed in related reactions of γ-(*N*-arylamino) substrates. For example, cyclization of substrates **II-21** and **I-41** both afforded 2,5-*cis*-pyrrolidine products (**III-14** and **I-42**) with high diastereoselectivity (Scheme 15). The results can be rationalized on the basis of the same cyclic, chair-like transition state models **III-58** and **III-59** describing the amidopalladation step of the catalytic cycle. Pseudoaxial orientation of the phenyl group is favored to minimize $A^{(1,3)}$-strain interactions with the *N*-substituent.

Scheme 14. Proposed Catalytic Cycle



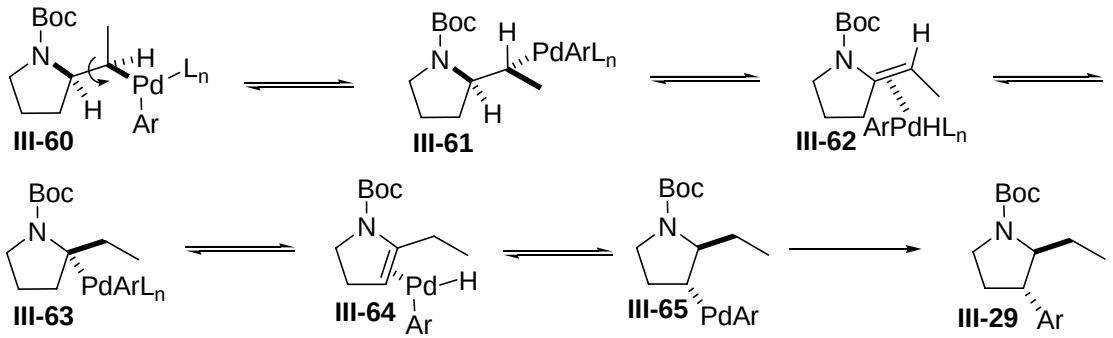
Scheme 15. Formation of 2,5-*cis*-Pyrrolidines: Stereochemical Analysis



The mechanism shown in Scheme 14 also accounts for the formation of several observed side-products. The formation of regioisomer **III-29** from *N*-protected (*E*)-aminoalkene **II-49** likely derives from β-hydride elimination of arylpalladium alkyl

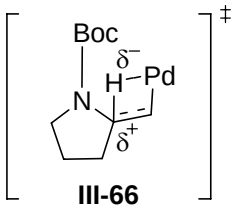
intermediate **III-61** to afford π-olefin complex **III-62** (Scheme 16).[10] Reinsertion of the olefin into the Pd–H bond with reversal of regiochemistry would provide **III-63**,[11] which could undergo a second β-hydride elimination/reinsertion process to afford **III-65**. Carbon–carbon bond-forming reductive elimination would generate regioisomer **III-29** with concomitant regeneration of the palladium(0) catalyst.[9,12]

Scheme 16. Origin of Regioisomer **III-29**.



Formation of 3-aryl pyrrolidines side-products is observed in most carboamination reactions of γ-(*N*-arylamino) alkenes. However, this has only been observed in analogous reactions of γ-*N*-Boc-aminoalkenes when substrates bearing (*Z*)-1,2-disubstituted alkenes are employed. The absence of these side-products in reactions of *N*-Boc and *N*-acyl protected substrates may result from a decrease in the rate of β–hydride elimination of intermediate **III-56** relative to the analogous *N*-arylamino derivative (Scheme 14). This may be due to stabilization of **III-56** through chelation of the metal to the carbonyl of the amide or carbamate,[13] or due to electronic effects induced by the less electron-donating nature of the protected nitrogen. Electron-donating groups

are known to facilitate β–hydride elimination by stabilizing the developing positive charge on the β–carbon in the transition state (Figure 3).[14] The small size of the *N*-acyl and *N*-Boc substituents relative to *N*-aryl groups may also alter the rate of β–hydride elimination in some systems.

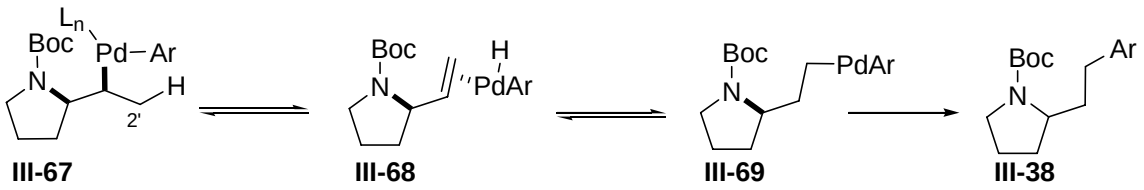


III-66

Figure 3. Beta-Hydride Elimination Transition State **III-66**.

The formation of regioisomeric product **III-38** (eq 21) likely involves β-hydride elimination from the C2' terminal carbon of intermediate **III-67** (Scheme 17). The formation of a 2(1-phenylethyl)pyrolidine side-product has only been observed with 2-bromochlorobenzene as coupling partner. The steric bulk at the metal center in **III-67** may slow reductive elimination and/or facilitate β-hydride elimination and migration towards C2' to release steric strain. It appears that a considerable energy difference exists between diastereomeric intermediates **III-67** and **III-60** and/or the respective transition states for reductive elimination or β-hydride elimination from these intermediate (Scheme 16) since the use of 2-bromochlorobenzene with *N*-protected (*E*)-aminoalkene substrate **II-49** under the same conditions lead to a complex mixture of products with less than 10% of **III-38** observed (eq 22).

Scheme 17. Origin of Product **III-38**.



The large energy difference between diastereomeric intermediates **III-67** and **III-60** could also be responsible for the different regioselectivities observed in the reaction of electron-poor aryl bromide with *N*-protected (*E*)-aminoalkene substrate **II-49** and *N*-protected (*Z*)-aminoalkene substrate **III-30**. In the former case, a regioisomer was observed indicating that **III-60** and/or the transition state leading to **III-60** is higher in energy. In addition, formation of regioisomer **III-29** was only observed in the cases of N-Boc protected substrates. This is possibly due to steric reasons, the Boc *t*-butyl group being more bulky and less flexible that the Cbz benzyl group, thus disfavoring reductive elimination from **III-60**. Finally, a regioisomer was observed only in cases where an electron-poor aryl bromide was used (Table 8, entries 2-3). It is possible that an electron deficient aryl substituent on the palladium(II) species shown in **III-60** would facilitate β-hydride elimination due to the increased electrophilicity of the metal. The difference in reactivity between *N*-protected (*E*)-aminoalkene substrate **II-49** and *N*-protected (*Z*)-aminoalkene substrate **III-30** presumably originates from a different rate of olefin insertion (Figure 4). This hypothesis implies an important energy difference between the transition states **III-70** and **III-71**, although the exact nature of this effect is unclear.

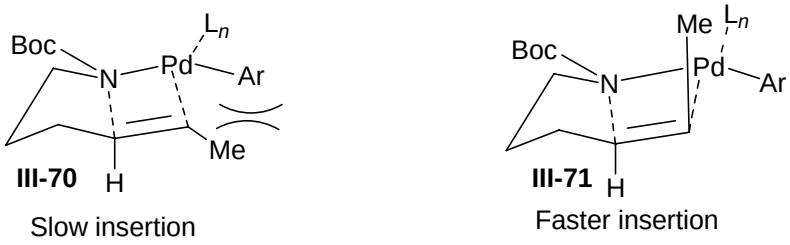


Figure 4. Transition State Analysis for (*Z*)- and (*E*)-Olefin Insertions

Conclusion

In conclusion, we have developed new conditions for palladium-catalyzed carboamination reactions of *N*-protected γ–aminoalkenes with aryl bromides and triflates. These conditions, which use Cs_2CO_3 or K_3PO_4 in place of the strong base NaO*t*-Bu, tolerate the presence of a broad array of functional groups, and significantly expand the scope of the carboamination methodology. In addition, the mild conditions also allow the cyclization of substrates containing 1,1- and 1,2-disubstituted alkenes, forming two stereocenters in one step in high diastereoselectivity. The mechanism of these reactions is likely analogous to that previously demonstrated for related reaction of γ-*N*-arylamino alkenes. Results from deuterium labeling studies indicate that the olefin insertion occurs in a *syn* fashion for both terminal and internal alkene substrates. Application of these new mild reaction conditions towards the synthesis of interesting benzocyclobutene derivatives and pyrrolidine natural products preussin and anisomycin is described in Chapters IV–VI.

Experimental Section

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts, reagents, anhydrous dioxane, and anhydrous DME were obtained from commercial sources and were used without further purification. Pent-4-enyl-carbamic acid *tert*-butyl ester (**II-5**),[15] *N*-pent-4-enylacetamide (**II-6**),[15] (3-methylpent-4-enyl)carbamic acid *tert*-butyl ester (**II-7**),[15] (1-phenylpent-4-enyl)carbamic acid *tert*-butyl ester (**II-21**),[15] 4-pentenylamine,[15] 4-formylphenyl trifluromethanesulfonate,[16] and 2-methylphenyltrifluoromethanesulfonate[16] were prepared according to published procedures. Ratios of regioisomers and/or diastereomers were determined by ^{1}H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas the yields reported in Tables 6–11, Scheme 2 and equation 21 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 6–11, Scheme 2 and equation 21.

Synthesis of Substrates

4-Bromobenzyl acetate.[2b] A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 4-bromobenzyl alcohol (4.0 g, 21.4 mmol), acetic anhydride (20 mL), pyridine (20 mL), and DMAP (268 mg, 2.14

mmol, 10 mol %). The tube was purged with nitrogen, and the mixture was stirred at rt for 22 h until the starting material had been consumed as determined by TLC analysis. Water (10 mL) and ethyl acetate (10 mL) were added, and the layers were separated. The organic layer was washed with 1 M aqueous HCl (10 mL) and brine (10 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluent to afford 4.4 g (90%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) □7.45 (d, J = 8.4 Hz, 2 H), 7.21 (d, J = 8.2 Hz, 2 H), 5.03 (s, 2 H), 2.08 (s, 3 H).

Pent-4-enylcarbamic acid benzyl ester (III-2).[17] A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of 4-pentenylamine (175 mL, 17.5 mmol, 0.1 M in diethyl ether). Triethylamine (7.4 mL, 52.5 mmol) and benzyl chloroformate (3.8 mL, 26.3 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 2 h). A solution of aqueous HCl (100 mL, 1.0 M) was added, the mixture was transferred to a separatory funnel, and was extracted with diethyl ether (100 mL). The layers were separated and the organic layer was washed with a solution of saturated aqueous Na_2CO_3 (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 10% → 15% ethyl acetate/hexanes as the eluent to afford 1.9 g (50%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) □7.42–7.27 (m, 5 H), 5.86–5.70 (m, 1 H), 5.19–4.93 (m, 4 H), 4.92–4.62 (m, 1 H), 3.26–3.08 (m, 2

H), 2.16–2.00 (m, 2 H), 1.67–1.52 (m, 2 H).

3-Methylpent-4-enylcarbamic acid benzyl ester (III-11). A flame-dried flask was cooled under a stream of nitrogen and charged with 3-methylpent-4-enoic acid[18] (6.85 g, 60 mmol). The flask was purged with nitrogen, benzene (100 mL) was added and the resulting solution was cooled to ca. 10 °C using an ice water bath. Oxalyl chloride (14 mL, 160 mmol) was added dropwise via syringe to the solution and the resulting mixture was warmed to rt, stirred for 1 h, and then concentrated *in vacuo*. The crude 3-methylpentenoyl chloride product of this reaction was dissolved in THF (100 mL), and slowly added to a separate flask containing aqueous ammonium hydroxide (100 mL) at 0 °C. The resulting mixture was stirred for 6 h and then concentrated *in vacuo.* The mixture was diluted with H_2O (50 mL) and ethyl acetate (100 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude 3-methylpent-4-enylcarboxamide was dissolved in THF (100 mL) and cooled to 0 °C. A solution of $LiAlH_4$ in THF (200 mL, 200 mmol, 1.0 M) was added dropwise. The reaction mixture was warmed to rt and stirred for 36 h, then was cooled to 0 °C, quenched with H_2O (16 mL), and diluted with ether (200 mL). An aqueous solution of NaOH (30 mL, 10 M) was added and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered to afford a solution of 3-methylpentenylamine in diethyl ether (ca. 0.1 M). The solution of 3-methylpentenylamine (300 mL, 30 mmol, 0.1 M) was

cooled to 0 °C, triethylamine (11.5 mL, 90 mmol) and benzyl chloroformate (6.6 mL, 45 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 16 h). A solution of 1.0 M aqueous HCl (200 mL) was added, the mixture was transferred to a separatory funnel, and was extracted with diethyl ether (100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 5% → 10% ethyl acetate/hexanes as the eluent to afford 1.2 g (17% over the five steps) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5 H), 5.73–5.60 (m, 1 H), 5.16–5.05 (m, 2 H), 5.02–4.90 (m, 2 H), 4.87–4.58 (m, 1 H), 3.27–3.08 (m, 2 H), 2.25–2.11 (m, 1 H), 1.58–1.40 (m, 2 H), 1.00 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 143.6, 136.6, 128.4, 128.1, 128.0, 113.4, 66.5, 39.2, 36.4, 35.6, 20.2; IR (film) 1706 cm^{-1}. Anal calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.28; H, 8.29; N, 6.08.

1-Phenylpent-4-enylcarbamic acid benzyl ester (III-15). Treatment of a solution of 1-phenylpent-4-enyl-amine[1] in diethyl ether (250 mL, 25 mmol, 0.1 M) with triethylamine (9.6 mL, 75 mmol) and benzyl chloroformate (5.5 mL, 37.5 mmol) using a procedure analogous to that described above for the synthesis of **6** afford 3.86 g (52%) of the title compound as a waxy white solid, m.p. 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–6.97 (m, 10 H), 5.86–5.65 (m, 1 H), 5.43–5.21 (m, 1 H), 5.14–4.90 (m, 4 H), 4.79–4.47 (m, 1 H), 2.12–1.94 (m, 2 H), 1.92–1.64 (m, 2 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 155.6, 142.3, 137.4, 136.4, 128.5, 128.4, 128.0, 127.2, 126.3, 115.2, 66.6, 54.9, 35.6, 30.2 (two aromatic carbons are incidentally equivalent); IR (film) 1710 cm^{-1}. Anal calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.06; H, 7.19; N, 4.69.

(*E*)-*tert*-Butyl hex-4-enylcarbamate (II-49). A flame-dried flask equipped with a distillation apparatus and magnetic stirbar was cooled under a stream of nitrogen and charged with 3-buten-2-ol (6.4 g, 100 mmol), triethyl orthoacetate (37 mL) and acetic acid (0.4 mL, 0.006 mmol). The mixture was heated until all the ethanol generated in the reaction had distilled over (80 → 120 °C). The mixture was then heated to 140 °C with stirring for 12 h. The solution was cooled to rt, tetrahydrofuran (50 mL) and 1 M HCl (100 mL) were added and the mixture was stirred at rt for 1 h. Ethyl acetate (50 mL) was added and the layers were separated. The organic layer was washed with water (50 mL) and brine (30 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluent to afford 7.5 g (53%) of (*E*)-ethyl hex-4-enoate[19] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54–5.38 (m, 2 H), 4.13 (p, *J* = 7.1 Hz, 2 H), 2.37–2.33 (m, 2 H), 2.32–2.27 (m, 2 H), 1.66–1.63 (m, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

A flame-dried flask was cooled under a stream of nitrogen and charged with ammonium chloride (4.3 g, 80.1 mmol), and toluene (100 mL), and was cooled to 0 °C. A solution of trimethylaluminum in toluene (40 mL, 80 mmol, 2.0 M) was then added slowly. The mixture was allowed to warm to rt and was stirred for 30 min (bubbling was

observed). To another flame-dried flask cooled under a stream of nitrogen was added (*E*)-ethyl hex-4-enoate (4.6 g, 32.0 mmol), and toluene (30 mL) and the solution was cooled to 0 ^{o}C. The first solution was then added dropwise to this mixture slowly. The resulting mixture was heated to 50 ^{o}C with stirring until the starting material was consumed as judged by TLC analysis (ca. 18h). The mixture was cooled to 0 ^{o}C and a 1 M solution of HCl was added slowly dropwise (60 mL). Ethyl acetate was added and the layers were separated. The organic layer was washed with a solution of saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 2.39 g (66%) of (*E*)-hex-4-enamide[20] as a white solid; m.p. 97-98 ^{o}C (lit. m.p. 98-100 ^{o}C)[20] that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, br, 1 H), 5.61 (s, br, 1 H), 5.56–5.48 (m, 1 H), 5.47–5.40 (m, 1 H), 2.35–2.25 (m, 4 H), 1.67–1.64 (m, 3 H).

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (*E*)-hex-4-enamide (2.83 g, 25 mmol). The flask was purged with nitrogen, THF (100 mL) was added, and the resulting solution was cooled to 0 ^{o}C. A solution of $LiAlH_4$ in THF (75 mL, 75 mmol, 1.0 M) was added dropwise. The reaction mixture was warmed to rt and stirred for 21 h, then was cooled to 0 ^{o}C, quenched with H_2O (10 mL), and diluted with ether (50 mL). An aqueous solution of NaOH (20 mL, 10 M) was added followed by H_2O (4 mL), and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (150 mL). The combined extracts were dried over anhydrous sodium sulfate and filtered to afford a solution of (*E*)-hex-4-en-1-yl-amine in diethyl ether (ca 0.1 M),

which was used without purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of (*E*)-hex-4-en-1-yl-amine (250 mL, 25 mmol, 0.1M). Di-*tert*-butyl dicarbonate (8.2 g, 37.5 mmol) was added to the solution and the resulting mixture was stirred for 3 h and then aqueous NaOH (200 mL, 1.0 M) was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography using 5%→ 10% ethyl acetate/hexanes as the eluent to afford 3.56 g (71%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49–5.36 (m, 2 H), 4.65 (s br, 1 H), 3.16–3.04 (m, 2 H), 2.03–1.97 (m, 2 H), 1.64 (d, *J* = 5.4 Hz, 3 H), 1.53 (p, *J* = 7.1 Hz, 2 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 130.2, 125.4, 78.8, 40.0, 29.7, 28.3, 17.8 (two aliphatic carbons are incidentally equivalent). IR (film) 1694 cm^{-1}. MS (ESI): 222.1463 (222.1470 calculated for $C_{11}H_{21}NO_2$, M + Na^+).

(*E*)-Benzyl hex-4-enylcarbamate (III-26). Treatment of a solution of (*E*)-hex-4-en-1-yl-amine (prepared as described above) in diethyl ether (210 mL, 21 mmol, 0.1 M) with triethylamine (8.5 mL, 63 mmol) and benzyl chloroformate (6.0 mL, 42 mmol) using a procedure analogous to that described above for the synthesis of (**II-49**) afforded 3.4 g (69%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5 H), 5.49–5.32 (m, 2 H), 5.17–5.05 (m, 2 H), 4.82 (s, br, 1 H), 3.18 (p, *J* = 6.8

Hz, 2 H), 2.08–1.95 (m, 2 H), 1.63 (d, J = 4.9 Hz, 3 H), 1.54 (p, J = 7.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 136.6, 130.1, 128.4, 128.1, 128.0, 125.7, 66.5, 40.5, 29.7, 29.6, 17.8; IR (film) 1706 cm^{-1}. MS (ESI): 256.1319 (256.1313 calculated for $C_{14}H_{19}NO_2$, M + Na^+).

(*Z*)-*tert*-Butyl hex-4-enylcarbamate (III-30). A flame-dried flask was cooled under a stream of nitrogen and charged with phthalimide (6 g, 40.8 mmol), triphenylphosphine (7.85 g, 30 mmol), THF (120 mL), and cis-4-hexenol (2.5 g, 25 mmol). The resulting mixture was cooled to 0 ^oC, and diethylazodicarboxylate (4.72 mL, 30 mmol) was added slowly over 15 min. The mixture was allowed to warm to rt and was stirred until the starting material was consumed as judged by TLC analysis (ca. 3h). Hexanes (500 mL) was added to the mixture and an insoluble white material precipitated. The solution was filtered through a fritted funnel and the residue was rinsed with a solution of 5% EtOAc/Hexanes (3 x 100 mL). The filtrate was concentrated *in vacuo* and the crude material was purified by flash chromatography using 10%→ 20% ethyl acetate/hexanes as the eluent to afford 4.75 g (83%) of (*Z*)-2-(hex-4-enyl)isoindoline-1,3-dione[21] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.79 (m, 2 H), 7.73–7.69 (m, 2 H), 5.51–5.43 (m, 1 H), 5.42–5.35 (m, 1 H), 3.69 (t, J = 6.3 Hz, 2 H), 2.11 (q, J = 7.3 Hz, 2 H), 1.75 (p, J = 7.6 Hz, 2 H), 1.61–1.57 (m, 3 H).

A flame-dried flask was cooled under a stream of nitrogen and charged with (*Z*)-2-(hex-4-enyl)isoindoline-1,3-dione (4.75 g, 20.7 mmol), ethanol (80 mL), and hydrazine monohydrate (1.26 g, 24.9 mmol). The mixture was heated to reflux with stirring until the

starting material was consumed as judged by TLC analysis (ca. 16h). The reaction mixture was cooled to rt and di-*tert*-butyl dicarbonate (10.4 g, 37.5 mmol) was added. The resulting mixture was stirred at rt for 4 h and then aqueous 1 M NaOH (200 mL) was added. The biphasic mixture was vigorously stirred for 12 h and the mixture was concentrated in vacuo. The aqueous layer was extracted with diethyl ether (3 x 100 mL), and the combined organic layers were then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 4.03 g (98%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53–5.42 (m, 1 H), 5.41–5.32 (m, 1 H), 4.56 (s, br, 1 H), 3.18–3.06 (m, 2 H), 2.07 (q, J = 7.2 Hz, 2 H), 1.62–1.58 (m, 3 H), 1.57–1.50 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 129.5, 124.6, 77.3, 40.2, 29.8, 28.4, 24.1, 12.7; IR (film) 1694 cm^{-1}. MS (ESI): 222.1471 (222.1470 calculated for $C_{11}H_{21}NO_2$, M + Na^+).

(*Z*)-Benzyl hex-4-enylcarbamate (III-35). A solution of (*Z*)-hex-4-en-1-yl-amine in ethanol (200 mL, 13.7 mmol, 0.07 M) obtained via the procedure described above for the synthesis of **30** was treated with triethylamine (8.5 mL, 63 mmol) and benzyl chloroformate (6.0 mL, 42 mmol) at rt. The mixture was stirred for 12 h and was then concentrated *in vacuo*. The aqueous layer was extracted with diethyl ether (3 x100 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 3.15 g (99%) of the title

compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5 H), 5.54–5.42 (m, 1 H), 5.41–5.30 (m, 1 H), 5.19–5.05 (m, 2 H), 4.83 (s, br, 1 H), 3.26–3.11 (m, 2 H), 2.14–2.01 (m, 2 H), 1.66–1.48 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 136.6, 129.3, 128.4, 128.1, 128.0, 124.7, 66.5, 40.7, 29.6, 24.0, 12.7; IR (film) 1704 cm^{-1}. MS (ESI): 256.1314 (256.1313 calculated for $C_{14}H_{19}NO_2$, M + Na^+).

***tert*-Butyl 5-methylhex-5-enoate (III-41).** A flame-dried flask equipped with a distillation apparatus and magnetic stirbar was cooled under a stream of nitrogen and charged with 2-methyl-propen-1-ol (3.6 g, 50.0 mmol), triethyl orthoacetate (22 mL) and acetic acid (0.2 mL, 0.003 mmol). The mixture was heated until all the ethanol generated in the reaction had distilled over (80 → 120 °C). The mixture was then heated to 140 °C with stirring for 15 h. The solution was cooled to rt, tetrahydrofuran (25 mL) and 1 M HCl were added and the mixture was stirred at rt for 1 h. Ethyl acetate (50 mL) was added and the layers were separated. The organic layer was washed with water (50 mL) and brine (30 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluent to afford 4.5 g (64%) of ethyl 4-methylpent-4-enoate[22] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (s, 1 H), 4.69 (s, 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 2.47–2.42 (m, 2 H), 2.37–2.31 (m, 2 H), 1.74 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

A flame-dried flask was cooled under a stream of nitrogen and charged with ammonium chloride (2.83 g, 52.8 mmol), and toluene (90 mL), and was cooled to 0 °C. A

solution of trimethylaluminum in toluene (35 mL, 70 mmol, 2.0 M) was then added slowly. The mixture was allowed to warm up to rt and was stirred for 30 min (bubbling was observed). To another flame-dried flask cooled under a stream of nitrogen was added ethyl 4-methylpent-4-enoate (3.0 g, 21.1 mmol), and toluene (20 mL), and the solution was cooled to 0 ^{o}C. The first solution was then added dropwise to this mixture slowly. The resulting mixture was heated to 50 ^{o}C with stirring until the starting material was consumed as judged by TLC analysis (ca. 22h). The mixture was cooled to 0 ^{o}C and a 1 M solution of HCl was added slowly dropwise (60 mL). Ethyl acetate was added and the layers were separated. The organic layer was washed with a solution of saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 965 mg (40%) of 4-methylpent-4-enamide[23] as a white solid; m.p. 80-81 ^{o}C (lit. m.p. 79-80 ^{o}C)[23] that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, br, 1 H), 5.62 (s, br, 1 H), 4.81–4.71 (m, 2 H), 2.43–2.32 (m, 4 H), 1.76 (s, 3 H).

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with of 4-methylpent-4-enylamide (965 mg, 8.5 mmol). The flask was purged with nitrogen, THF (20 mL) was added via syringe and the resulting solution was cooled to 0 ^{o}C. A solution of $LiAlH_4$ in THF (35 mL, 35 mmol, 1.0 M) was added dropwise via syringe. The reaction mixture was warmed to rt, and stirred for 20 h, then was cooled to 0 ^{o}C, quenched with H_2O (5 mL), and diluted with ether (20 mL). An aqueous solution of NaOH (10 mL, 10 M) was added followed by H_2O (2 mL), and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask

and the precipitate was washed with ether (60 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered to afford a solution of 4-methylpent-4-en-1-yl-amine[24] in diethyl ether (ca 0.1 M), which was used without purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of 4-methylpent-4-en-1-yl-amine (85 mL, 8.5 mmol, 0.1M). Di-*tert*-butyl dicarbonate (2.8 g, 12.8 mmol) was added to the solution, the resulting mixture was stirred for 4 h, and then aqueous 1M NaOH (100 mL) was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography using 5%→ 10% ethyl acetate/hexanes as the eluent to afford 1.1 g (62%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (s br, 1 H), 4.75–4.67 (m, 2 H), 3.16–3.04 (m, 2 H), 2.03 (t, *J* = 7.6 Hz, 2 H), 1.72 (s, 3 H), 1.63 (p, *J* = 7.6 Hz, 2 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 144.7, 110.1, 78.6, 40.1, 34.8, 28.2, 27.8, 22.1; IR (film) 1692 cm^{-1}. MS (ESI): 222.1465 (222.1470 calculated for $C_{11}H_{21}NO_2$, M + Na^+).

Benzyl 4-methylpent-4-enylcarbamate (III-42). A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of 4-methylpent-4-en-1-yl-amine (87 mL, 8.7 mmol, 0.1 M) obtained via the procedure above, and was cooled to 0 °C. Triethylamine (3.5 mL, 26.2 mmol) and benzyl chloroformate (2.5 mL, 17.5 mmol) were added, and the resulting mixture was stirred at rt until the starting

material was consumed as judged by TLC analysis (ca. 24 h). A solution of 1 M aqueous HCl (100 mL) was added, the mixture was transferred to a separatory funnel, and was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 1.3 g (64%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 5.17–5.06 (m, 2 H), 4.85 (s, br, 1 H), 4.75–4.64 (m, 2 H), 3.24–3.09 (m, 2 H), 2.03 (t, J = 7.6 Hz, 2 H), 1.71 (s, 3 H), 1.64 (p, J = 7.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 144.7, 110.1, 78.6, 40.1, 34.8, 28.2, 27.8, 22.1; IR (film) 1699 cm^{-1}. MS (ESI): 256.1307 (256.1313 calculated for $C_{14}H_{19}NO_2$, M + Na^+).

Synthesis of Functionalized Pyrrolidines via Coupling with Aryl Bromides (Tables 6–7 and Scheme 12)

General Procedure A for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (2 mol %), Dpe-phos (4 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (5 mL/mmol substrate) was then added via syringe. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL)

and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

2-(4-*tert*-Butylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (III-1). General procedure A was employed for the reaction of 4-*tert*-butyl bromobenzene (52 μL, 0.30 mmol) with pent-4-enyl-carbamic acid *tert*-butyl ester (47 mg, 0.25 mmol). This procedure afforded 66 mg (83%) of the title compound as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (m, 2 H), 7.22–7.07 (m, 2 H), 4.12–3.84 (m, 1 H), 3.49–3.23 (m, 2 H), 3.23–2.96 (m, 1 H), 2.60–2.42 (m, 1 H), 1.92–1.67 (m, 4 H), 1.55–1.48 (s, 9 H), 1.36–1.28 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 148.9, 136.1, 129.1, 125.2, 79.0, 58.8, 46.4, 40.0, 34.3, 31.4, 29.7, 28.6, 22.7; IR (film) 1695 cm^{-1}. Anal calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.46; H, 9.88; N, 4.38.

2-Napthalen-2-ylmethylpyrrolidine-1-carboxylic acid tert-butyl ester (III-3).15 General procedure A was employed for the reaction of 2-bromonapthalene (62 mg, 0.30 mmol) with pent-4-enyl-carbamic acid tert-butyl ester (47 mg, 0.25 mmol). This procedure afforded 58 mg (75%) of the title compound as a colorless oil. 1H NMR (300 MHz, CDCl3) □7.85–7.74 (m, 3 H), 7.66–7.60 (m, 1 H), 7.51–7.40 (m, 2 H), 7.40–7.33 (m, 1 H), 4.16– 4.02 (m, 1 H), 3.43–3.21 (m, 3 H), 2.77–2.65 (m, 1 H), 1.83–1.70 (m, 4

H), 1.56–1.50 (s, 9 H).

2-(4-Formylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (III-5). General procedure A was employed for the reaction of 4-bromobenzaldehyde (89 mg, 0.48 mmol) with pent-4-enyl-carbamic acid *tert*-butyl ester (74 mg, 0.40 mmol) except DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 94 mg (81%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{13}C NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1 H), 7.80 (d, J = 8.0 Hz, 2 H), 7.41–7.29 (m, 2 H), 4.13–3.92 (m, 1 H), 3.46–3.01 (m, 3 H), 2.74–2.58 (m, 1 H), 1.85-1.60 (m, 4 H), 1.52–1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 154.4, 146.6, 134.7, 130.1, 129.8, 79.3, 58.4, 46.3, 40.8, 39.9, 29.6, 28.5, 28.3, 23.4, 22.6; IR (film) 1693, 1606 cm^{-1}. Anal calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.45; H, 8.14; N, 4.72.

2-(4-Acetylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (III-6). General procedure A was employed for the reaction of 4-bromoacetophenone (120 mg, 0.60 mmol) with pent-4-enyl-carbamic acid *tert*-butyl ester (93 mg, 0.50 mmol) except DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 118 mg (78%) of the title compound as a white solid, m.p. 63–65 °C. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.85 (m, 2 H),

7.35–7.22 (m, 2 H), 4.11–3.94 (m, 1 H), 3.46–3.04 (m, 3 H), 2.74–2.55 (m, 4 H), 1.85–1.60 (m, 4 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 197.7, 154.5, 154.4, 145.0, 144.9, 135.3, 135.2, 129.7, 129.5, 128.5, 128.3, 79.4, 79.1, 58.5, 58.3, 46.7, 46.2, 40.6, 39.6, 29.7, 28.9, 28.5, 26.5, 23.4, 22.6; IR (film) 1686, 1607 cm^{-1}. Anal calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.18; H, 8.30; N, 4.60.

1-[2-(Naphthalen-2-ylmethyl)pyrrolidin-1-yl]ethanone (III-7).[1] General procedure A was employed for the reaction of 2-bromonapthalene (125 mg, 0.60 mmol) with *N*-pent-4-enyl-acetamide (64 mg, 0.50 mmol). This procedure afforded 101 mg (80%) of the title compound as a pale yellow oil. This compound was found to exist as a ~ 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3 H), 7.66–7.58 (m, 1 H), 7.51–7.37 (m, 2.3 H), 7.32–7.27 (m, 0.7 H), 4.45–4.37 (m, 0.7 H), 4.17–4.09 (m, 0.3 H), 3.63–3.49 (m, 0.7 H), 3.45–3.32 (m, 2 H), 3.09–3.02 (m, 0.3 H), 2.86–2.69 (m, 1 H), 2.11 (s, 2 H), 2.06 (s, 1 H), 1.96–1.72 (m, 4 H).

1-[2-(4-Nitrobenzyl)pyrrolidin-1-yl]ethanone (III-8). General procedure A was employed for the reaction of 1-bromo-4-nitrobenzene (97 mg, 0.48 mmol) with *N*-pent-4-enyl-acetamide (51 mg, 0.4 mmol) except dppe was used in place of Dpe-phos as ligand, DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 77 mg (77%) of the title compound as a white solid, m.p. 139–140 °C. This compound was found to exist as a ~ 7:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8

Hz, 0.3 H), 8.12 (d, *J* = 8.8 Hz, 1.7 H), 7.38 (d, *J* = 8.8 Hz, 1.7 H), 7.32 (d, *J* = 8.8 Hz, 0.3 H), 4.34–4.24 (m, 0.85 H), 4.11–4.03 (m, 0.15 H), 3.64–3.51 (m, 0.3 H), 3.50–3.35 (m, 1.7 H), 3.28 (dd, *J* = 3.4, 13.2 Hz, 0.85 H), 2.97 (dd, *J* = 5.2, 13.2 Hz, 0.15 H), 2.80 (dd, *J* = 8.8, 13.6 Hz, 0.15 H), 2.68 (dd, *J* = 9.2, 13.2 Hz, 0.85 H), 2.07 (s, 2.55 H), 1.99 (s, 0.45 H), 1.94–1.73 (m, 3.15 H), 1.71–1.60 (m, 0.85 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 147.0, 146.5, 145.5, 130.2, 130.0, 123.8, 123.5, 59.4, 57.9, 47.8, 45.4, 40.6, 38.8, 30.1, 28.5, 23.7, 22.9 22.0, 21.7; IR (film) 1640, 1516 cm^{-1}. Anal calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.85; H, 6.44; N, 11.08.

2-(Naphthalen-2-ylmethyl)pyrrolidine-1-carboxylic acid benzyl ester (III-9). General procedure A was employed for the reaction of 2-bromonaphthalene (125 mg, 0.6 mmol) with pent-4-enylcarbamic acid benzyl ester (110 mg, 0.5 mmol). This procedure afforded 151 mg (88%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.63 (m, 3.5 H), 7.56–7.32 (m, 7.5 H), 7.25–7.19 (m, 1 H), 5.27–5.16 (m, 2 H), 4.28–4.12 (m, 1 H), 3.54–3.35 (m, 2.5 H), 3.25–3.16 (m, 0.5 H), 2.82–2.69 (m, 1 H), 1.87–1.72 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 154.8, 137.1, 136.8, 136.5, 136.4, 133.4, 132.1, 128.4, 128.1, 128.0, 127.9, 127.85, 127.79, 127.74, 127.65, 127.6, 127.4, 125.93, 125.86, 125.34, 125.26, 67.0, 66.5, 59.3, 58.8, 46.8, 46.6, 40.8, 39.6, 29.7, 28.9, 23.5, 22.7; IR (film) 1698 cm^{-1}. Anal calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 80.01; H, 6.78; N, 4.11.

2-(4-(Methoxycarbonyl)benzyl)pyrrolidine-1-carboxylic acid benzyl ester

(III-10). General procedure A was employed for the reaction of methyl 4-bromobenzoate (129 mg, 0.6 mmol) with pent-4-enylcarbamic acid benzyl ester (110 mg, 0.5 mmol) except DME was used in place of dioxane and the reaction was conducted at 85 °C. This procedure afforded 152 mg (86%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.86 (m, 2 H), 7.44–7.23 (m, 6 H), 7.16–7.08 (m, 1 H), 5.22–5.11 (m, 2 H), 4.18–4.02 (m, 1 H), 3.90 (s, 3 H), 3.51–3.31 (m, 2 H), 3.28–3.17 (m, 0.5 H), 3.11–3.00 (m, 0.5 H), 2.76–2.58 (m, 1 H), 1.88–1.61 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 167.0, 154.8, 144.4, 144.3, 137.0, 136.7, 129.64, 129.56, 129.3, 128.5, 128.2, 128.1, 127.9, 127.8, 67.0, 66.5, 58.9, 58.5, 52.0, 46.8, 46.6, 40.7, 39.5, 29.8, 28.9, 23.5, 22.7; IR (film) 1721, 1700 cm^{-1}. Anal calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.15; H, 6.62; N, 4.03.

(±)–(2*R*,3*S*)-2-[4-(Acetoxymethyl)benzyl]-3-methylpyrrolidine-1-carboxylic acid benzyl ester (III-12). General procedure A was employed for the reaction of 4-bromobenzyl acetate (138 mg, 0.6 mmol) with 3-methylpent-4-enylcarbamic acid benzyl ester (117 mg, 0.5 mmol). The diastereoselectivity of the transformation was assessed by LAH reduction of the crude product obtained in a duplicate reaction, and was found to be 12:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 143 mg (82%) of the title compound as a colorless oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR

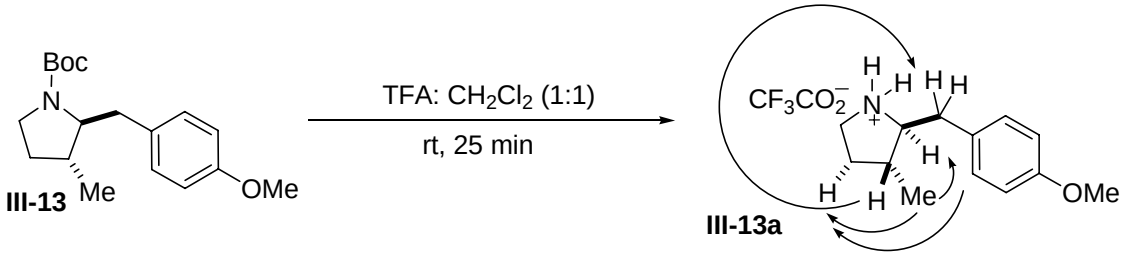
(500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5 H), 7.28–7.13 (m, 3 H), 7.09–7.02 (m, 1 H), 5.23–5.10 (m, 2 H), 5.09–5.02 (m, 2 H), 3.73–3.48 (m, 2 H), 3.34–3.18 (m, 1 H), 3.15–3.07 (m, 0.5 H), 3.01–2.92 (m, 0.5 H), 2.82–2.73 (m, 0.5 H), 2.70–2.61 (m, 0.5 H), 2.12–1.99 (m, 4 H), 1.94–1.80 (m, 1 H), 1.50–1.37 (m, 1 H), 0.87 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.1, 154.9, 138.8, 137.1, 136.8, 133.9, 133.7, 129.8, 129.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 67.0, 66.5, 66.15, 66.09, 65.9, 65.7, 45.4, 45.2, 39.9, 38.3, 36.8, 35.8, 31.1, 30.2, 21.0, 19.3, 19.1. IR (film) 1740, 1698 cm^{-1}. MS (ESI): 404.1839 (404.1838 calculated for $C_{20}H_{27}NO_4$, $M + Na^+$).

The stereochemistry of the above compound was assigned based on comparison of ^1H and ^{13}C NMR spectra to those obtained for the related product **III-51**, the stereochemistry of which was elucidated through ^1H NMR nOe experiments as described below.

(±)–(2*R*,3*S*)-2-(4-Methoxybenzyl)-3-methylpyrrolidine-1-carboxylic acid *tert*-butyl ester (III-13). General procedure A was employed for the reaction of 4-bromoanisole (38 μL, 0.3 mmol) with 3-methylpent-4-enylcarbamic acid benzyl ester (50 mg, 0.25 mmol). The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be 15:1 dr as judged by ^1H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 58 mg (78%) of the title compound as a pale yellow oil with >20:1 dr. Data are for the major diastereomer, which was found to exist as a 1:1 mixture of rotamers as judged by ^1H NMR analysis; data are

for the mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.03 (m, 2 H), 6.86–6.78 (m, 2 H), 3.79 (s, 3 H), 3.63–3.34 (m, 2 H), 3.26–3.06 (m, 1 H), 3.05–2.89 (m, 1 H), 2.75–2.52 (m, 1 H), 2.09–1.95 (m, 1 H), 1.91–1.75 (m, 1 H), 1.51 (s, 9 H), 1.45–1.30 (m, 1 H), 0.85 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 154.7, 131.0, 130.6, 130.3, 113.8, 113.6, 79.2, 78.9, 65.9, 65.5, 55.2, 45.5, 44.9, 39.1, 37.7, 36.7, 35.8, 31.1, 30.3, 28.6, 19.4, 19.2; IR (film) 1692 cm^{-1}. Anal calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.56; H, 8.87; N, 4.60.

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **III-13** with TFA to afford **III-13a** as shown below.



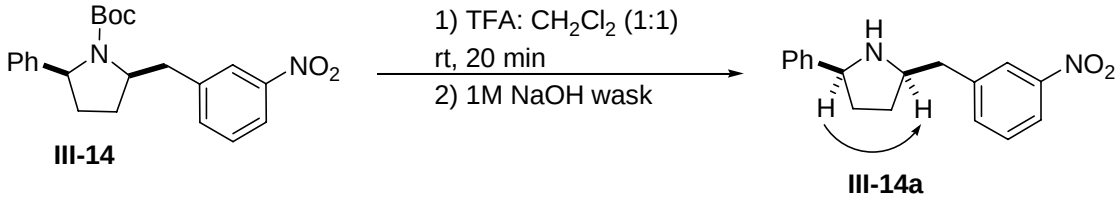
(±)–(2*R*,3*S*)-2-(4-Methoxybenzyl)-3-methylpyrrolidinium-2,2,2-trifluoroacetate (III-13a). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-13** (42 mg, 0.14 mmol). Methylene chloride (1 mL) was added and the mixture was cooled to 0 °C. Trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 25 min. The crude mixture was concentrated *in vacuo* to afford 41 mg (96%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, br, 1 H), 8.74 (s, br, 1 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 2 H), 6.72 (s, br, 1 H), 3.74 (s, 3 H), 3.28–3.18 (m, 1 H), 3.15–3.07 (m, 2 H), 3.00–2.86

(m, 2 H), 2.23–2.15 (m, 1 H), 2.14–2.05 (m, 1 H), 1.66–1.57 (m, 1 H), 0.99 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (q, J = 36.8 Hz), 158.8, 129.9, 127.6, 116.1 (q, J = 290.4 Hz), 114.2, 66.8, 55.1, 43.4, 38.3, 36.0, 32.2, 16.8; IR (film) 3502, 1690 cm^{-1}; MS (ESI): 206.1541 (206.1545 calculated for $C_{13}H_{19}NO$, M + H$^+$).

(±)–(2*R*,5*S*)-2-(3-Nitrobenzyl)-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (III-14). General procedure A was employed for the reaction of 1-bromo-3-nitrobenzene (122 mg, 0.6 mmol) with (1-phenylpent-4-enyl)carbamic acid *tert*-butyl ester (131 mg, 0.5 mmol). The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 151 mg (79%) of the title compound as a colorless oil with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.05 (m, 2 H), 7.72–7.52 (m, 1 H), 7.50–7.44 (m, 1 H), 7.36–7.16 (m, 5 H), 5.08–4.68 (m, 1 H), 4.28–4.09 (m, 1 H), 3.69–3.43 (m, 1 H), 2.88–2.76 (m, 1 H), 2.36–2.24 (m, 1 H), 2.01–1.92 (m, 1 H), 1.91–1.81 (m, 1 H), 1.75–1.66 (m, 1 H), 1.65–1.05 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 148.2, 144.3, 141.1, 135.7, 129.3, 128.2, 126.6, 125.5, 124.1, 121.4, 79.7, 63.0, 60.4, 40.6, 34.3, 28.1 (two aliphatic carbons are incidentally equivalent); IR (film) 1687, 1530 cm^{-1}. Anal calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.97; H, 6.98; N, 7.19.

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **III-14** with TFA, followed by

aqueous NaOH, to afford **III-14a** as shown below.



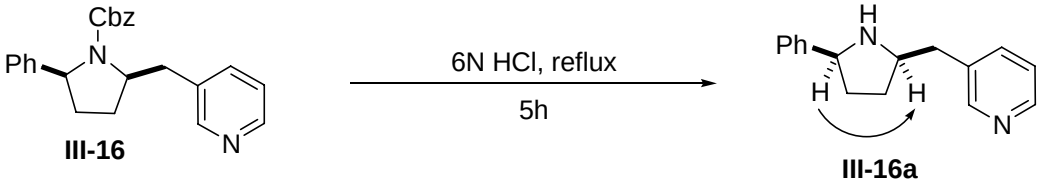
III-14 **III-14a**

(±)–(2*R*,5*S*)-2-(3-Nitrobenzyl)-5-phenylpyrrolidine (III-14a). Treatment of **III-14** (100 mg, 0.26 mmol) with TFA/CH_2Cl_2 was effected using a procedure analogous to that described above for the preparation of compound **III-13a**, with the following modification. The crude residue obtained upon removal of TFA/CH_2Cl_2 was dissolved in CH_2Cl_2 (10 mL), and washed with 1.0 M NaOH (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. This procedure afforded 65 mg (88%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.12 (m, 1 H), 8.09–8.02 (m, 1 H), 7.63–7.57 (m, 1 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.25–7.18 (m, 1 H), 4.15 (t, *J* = 7.4 Hz, 1 H), 3.55–3.44 (m, 1 H), 2.99–2.86 (m, 2 H), 2.20–2.09 (m, 1 H), 2.00–1.91 (m, 1 H), 1.85 (s, 1 H), 1.75–1.55 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.9, 142.3, 135.5, 129.1, 128.2, 126.8, 126.5, 123.9, 121.2, 62.2, 59.6, 42.9, 33.9, 30.9; IR (film) 1526 cm^{-1}; MS (ESI): 283.1435 (283.1447 calculated for $C_{17}H_{18}N_2O_2$, M + H^+).

(±)–(2*S*,5*R*)-2-Phenyl-5-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylic acid benzyl ester (III-16). General procedure A was employed for the reaction of 3-bromopyridine (60 μL, 0.6 mmol) with 1-phenylpent-4-enylcarbamate benzyl ester (148

mg, 0.5 mmol). The diastereoselectivity of the transformation was assessed by HCl-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 144 mg (78%) of the title compound as a colorless oil with >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59–8.31 (m, 2 H), 7.77–6.76 (m, 12 H), 5.29–4.85 (m, 3 H), 4.30–4.09 (m, 1 H), 3.67–3.27 (m, 1 H), 2.77–2.64 (m, 1 H), 2.35–2.24 (m, 1 H), 2.04–1.80 (m, 2 H), 1.76–1.65 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 150.5, 147.9, 143.6, 136.7, 136.5, 134.3, 128.4, 128.3, 127.5, 127.3, 126.8, 125.6, 123.4, 66.7, 63.0, 61.1, 38.1, 34.3, 28.6; IR (film) 1698 cm^{-1}; MS (ESI): 395.1736 (395.1735 calculated for $C_{24}H_{24}N_2O_2$, M + Na^+).

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **III-16** with 6N HCl, followed by aqueous NaOH, to afford **III-16a** as shown below.



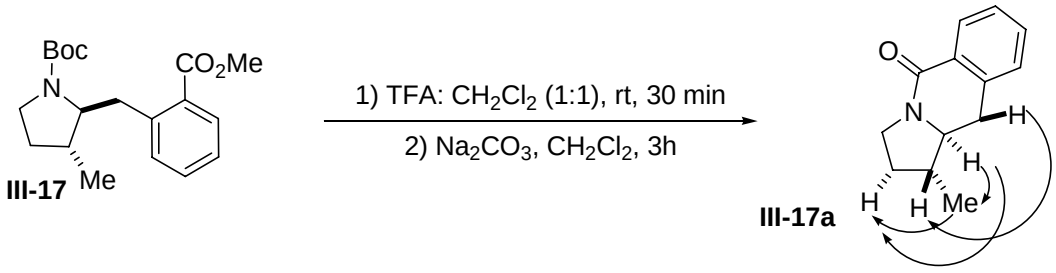
(±)–(2*R*,5*S*)-3-(5-Phenylpyrrolidin-2-ylmethyl)pyridine (III-16a). A flask was charged with **III-16** (40 mg, 0.11 mmol) and 6 N HCl (5 mL). The mixture was heated to reflux for 5 h, and then was cooled to rt. Distilled water was then added (2 mL), the crude

mixture was washed with ether (3 x 10 mL), and the ether layers were discarded. The aqueous layer was then basified with 1M NaOH to pH 11 and extracted twice with ether (10 mL). The combined ether layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography using 5% → 10% methanol/dichloromethane as the eluent to afford 22 mg (87%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55–8.42 (m, 2 H), 7.61–7.55 (m, 1 H), 7.43–7.36 (m, 2 H), 7.34–7.25 (m, 2 H), 7.24–7.17 (m, 2 H), 4.19 (t, *J* = 8.0 Hz, 1 H), 3.56–3.43 (m, 1 H), 3.25–2.89 (m, 1 H), 2.82 (d, *J* = 6.6 Hz, 2 H), 2.23–2.11 (m, 1 H), 2.02–1.90 (m, 1 H), 1.85–1.73 (m, 1 H), 1.72–1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 147.7, 136.6, 135.1, 128.3, 127.1, 126.7, 123.3, 62.3, 60.0, 39.7, 33.3, 30.6 (two aromatic carbons are incidentally equivalent); IR (film) 3410 cm^{-1}; MS (ESI): 239.1537 (239.1548 calculated for $C_{16}H_{18}N_2$, M + H$^+$).

(±)–(2*R*,3*S*)-*tert*-Butyl-2-(2-(Methoxycarbonyl)benzyl)-3-methylpyrrolidine-1-carboxylate (III-17). General procedure A was employed for the reaction of methyl-2-bromobenzoate (43 μL, 0.3 mmol) with **II-7** (50 mg, 0.25 mmol). The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be 14:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 63 mg (75%) of the title compound as a colorless oil with >20:1 dr. This compound was found to exist as a ~2.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.79 (m, 1 H),

7.44–7.33 (m, 1 H), 7.30–7.19 (m, 2 H), 3.89 (s, 3 H), 3.78–3.72 (m, 1 H), 3.60–3.50 (m, 0.6 H), 3.47–3.17 (m, 2.8 H), 3.08–3.01 (m, 0.6 H), 2.10–1.96 (m, 2 H), 1.52–1.25 (m, 10 H), 0.93–0.79 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 168.1, 155.0, 154.7, 140.9, 140.5, 131.8, 131.7, 131.6, 130.4, 130.2, 126.0, 125.9, 78.9, 65.8, 52.0, 45.1, 44.4, 37.6, 37.4, 35.9, 30.9, 30.0, 28.5, 28.3, 19.4, 19.3; IR (film) 1723, 1691 cm^{-1}. Anal calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.29; H, 8.12; N, 4.06.

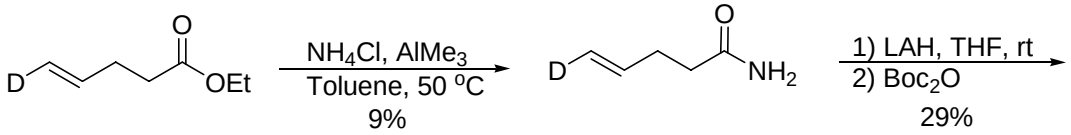
The stereochemistry of **III-17** was assigned by ^{1}H NMR nOe analysis of the corresponding derivative obtained from treatment of **III-17** with TFA/CH_2Cl_2, followed by Na_2CO_3, as shown below.

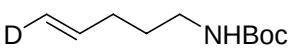


(±)–(1*R*,10a*S*)-1-Methyl-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (III-18). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-17** (67 mg, 0.2 mmol), and methylene chloride (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 37 mg (91%) of the title compound as a white solid, m.p. 152–154 ^{o}C. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 8.06 (dd, *J* = 1.2, 7.8, Hz, 1 H), 7.41 (td, *J* = 1.5, 7.3, Hz, 1 H), 7.34 (tt, *J* = 1.2, 7.6, Hz, 1 H), 7.22–7.19 (m, 1 H), 3.86–3.80 (m, 1 H), 3.64–3.57 (m, 1 H), 3.41–3.34 (m, 1 H), 3.05 (dd, *J* = 3.9, 15.1, Hz, 1 H), 2.78 (t, *J* = 3.9 Hz, 1 H), 2.22–2.15 (m, 1 H), 2.09–1.99 (m, 1 H), 1.60–1.50 (m, 1 H), 1.17 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 137.3, 131.5, 130.3, 127.6, 127.2, 127.1, 63.0, 44.2, 41.6, 33.6, 31.7, 15.9; IR (film) 1648 cm^{-1}; MS (EI): 201.1151 (201.1153 calculated for $C_{13}H_{15}NO$, M^+).

Deuterium-Labeling Experiment (Scheme 13)





III-19

(*E*)-*tert*-Butyl-5-*d*-pent-4-enylcarbamate (III-19). A flame-dried flask was cooled under a stream of nitrogen and charged with ammonium chloride (950 mg, 17.7 mmol), and toluene (40 mL) and was cooled to 0 °C. A solution of trimethylaluminum (1.7 mL, 17.7 mmol) in toluene (20 mL) was then added slowly to the ammonium chloride solution. The mixture was allowed to warm to rt and was stirred for 30 min (bubbling was observed). To another flame-dried flask cooled under a stream of nitrogen was added (*E*)-5-*d*-ethyl 4-pentenoate[25] (745 mg, 5.8 mmol), and toluene (10 mL), and this solution was cooled to 0 °C. The trimethylaluminum solution was then added dropwise to this mixture slowly. The resulting mixture was heated to 50 °C with stirring until the starting material was consumed as judged by TLC analysis (ca. 9h). The mixture was cooled to 0 °C and a 1 M solution of HCl was added slowly dropwise (60 mL). Ethyl

acetate was added and the layers were separated. The organic layer was washed with a solution of saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 50 mg (9%) of (*E*)-5-*d*-pent-4-enylamide that was used without further purification. ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (s, br, 1 H), 5.91–5.78 (m, 1 H), 5.72 (s, br, 1 H), 5.14–4.97 (m, 1 H), 2.45–2.24 (m, 4 H).

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with (*E*)-5-*d*-pent-4-enylamide (50 mg, 0.5 mmol). The flask was purged with nitrogen, THF (5 mL) was added, and the resulting solution was cooled to 0 ^oC. A solution of $LiAlH_4$ in THF (4 mL, 4 mmol, 1.0 M) was added dropwise. The reaction mixture was warmed to rt, and stirred for 21 h, then was cooled to 0 ^oC, quenched with H_2O (1 mL), and diluted with ether (5 mL). An aqueous solution of NaOH (2 mL, 10 M) was added followed by H_2O (0.2 mL), and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (15 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered to afford a solution of (*E*)-5-*d*-pent-4-en-1-yl-amine in diethyl ether (ca 0.1 M), which was used without purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of (*E*)-5-*d*-pent-4-en-1-yl-amine (5 mL, 0.5 mmol, 0.1M). Di-*tert*-butyl dicarbonate (200 mg, 0.75 mmol) was added to the solution. The resulting mixture was stirred for 3 h, and then aqueous NaOH (20 mL, 1.0 M) was added. The biphasic mixture was vigorously stirred for 12 h and then the layers were separated. The

aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 27 mg (29%) of the title compound as a colorless oil with ~80% deuterium incorporation as judged by ^{1}H NMR analysis. The data is for major compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85–5.75 (m, 1 H), 5.07–4.96 (m, 1 H), 4.56 (s, 1 H), 3.18–3.05 (m, 2 H), 2.13–2.04 (m, 2 H), 1.58 (p, J = 7.6 Hz, 2 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 137.7, 114.8 (t, J = 23.9 Hz), 79.0, 40.1, 30.9, 29.2, 28.4. MS (ESI): 209.1369 (209.1376 calculated for $C_{10}H_{18}DNO_2$, M + Na^+).

(±)–(1*R*,2*S*)-*tert*-Butyl-[2*d*(2-(methoxycarbonyl)phenyl)methyl]pyrrolidine-1-carboxylate (III-20). General procedure A was employed for the reaction of methyl 2-bromobenzoate (38 mg, 0.17 mmol) with **III-19** (27 mg, 0.14 mmol). This procedure afforded 30 mg (65%) of the title compound as a colorless oil with ~80% deuterium incorporation as judged by ^{1}H NMR analysis and as a single stereoisomer. This compound was found to exist as a 2:1 mixture of rotamers, the data is for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.78 (m, 1 H), 7.45–7.33 (m, 1.33 H), 7.30–7.18 (m, 1.66 H), 4.20–4.10 (m, 1 H), 3.89 (s, 3 H), 3.49–3.20 (m, 2.66 H), 3.07–2.97 (m, 0.33 H), 1.95–1.75 (m, 2.66 H), 1.74–1.61 (m, 1.33 H), 1.53–1.17 (m, 9 H).

(±)–(10*S*,10a*R*)-10-*d*-2,3,10,10a-Tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (III-21). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-20** (30 mg, 0.09 mmol) and methylene chloride (1 mL). The resulting solution was

cooled to 0 °C, trifluoroacetic acid (1 mL) was added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 19 mg (100%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, C_6D_6) δ 8.48–8.43 (m, 1 H), 7.15–7.12 (m, 1 H), 7.10–7.04 (m, 1 H), 6.80–6.74 (m, 1 H), 3.61–3.54 (m, 1 H), 3.45–3.37 (m, 1 H), 3.11–3.01 (m, 1 H), 2.18–2.10 (m, 1 H), 1.46–1.38 (m, 1 H), 1.39–1.27 (m, 1 H), 1.16–1.05 (m, 1 H), 0.98–0.88 (m, 1 H).

***tert*-Butyl-2-[2-(methoxycarbonyl)benzyl]pyrrolidine-1-carboxylate (III-22).** General procedure A was employed for the reaction of methyl 2-bromobenzoate (65 mg, 0.3 mmol) with **II-5** (47 mg, 0.25 mmol). This procedure afforded 57 mg (71%) of the title compound as a colorless oil and as a 2:1 mixture of rotamers. The data is for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.79 (m, 1 H), 7.45–7.34 (m, 1 H), 7.32–7.19 (m, 2 H), 4.22–4.10 (m, 1 H), 3.90 (s, 3 H), 3.48–3.21 (m, 3.33 H), 3.09–2.99 (m, 0.66 H), 1.95–1.75 (m, 2.66 H), 1.74–1.62 (m, 1.33 H), 1.52–1.23 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 154.6, 141.0, 131.9, 131.8, 130.4, 130.3, 126.0, 78.9, 58.9, 58.7, 52.0, 46.6, 45.9, 37.6, 36.1, 30.3, 28.5, 28.3, 23.5, 22.7; IR (film) 1719, 1694 cm^{-1}; MS (EI): 342.1674 (342.1681 calculated for $C_{18}H_{25}NO_4$, M $^+$).

2,3,10,10*a*-tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (III-23).[26] A flame-

dried flask was cooled under a stream of nitrogen and charged with **III-22** (39 mg, 0.12 mmol) and methylene chloride (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 16 mg (70%) of the title compound as a white solid; m.p. 102-104 ^oC (lit. m.p. 108 ^oC).[26] ^1H NMR (500 MHz, C_6D_6) δ 8.50–8.45 (m, 1 H), 7.09–7.04 (m, 2 H), 6.80–6.75 (m, 1 H), 3.62–3.54 (m, 1 H), 3.45–3.36 (m, 1 H), 3.12–3.02 (m, 1 H), 2.25 (dd, *J* = 4.2, 15.1 Hz, 1 H), 2.19–2.11 (m, 1 H), 1.47–1.39 (m, 1 H), 1.36–1.27 (m, 1 H), 1.16–1.04 (m, 1 H), 0.98–0.87 (m, 1 H).

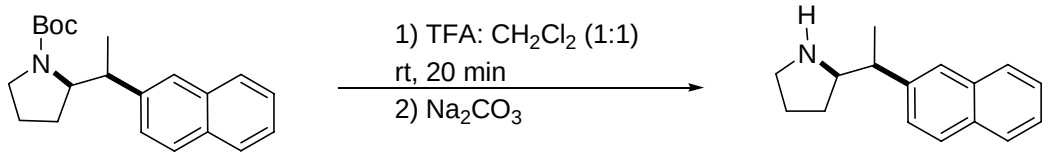
Synthesis of Functionalized Pyrrolidines via Coupling with Aryl Bromides (Tables 8–9, Equations 21, 23 and 24)

General Procedure B for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (5 mol %), Nixantphos (7.5 mol %) or (±)-BINAP (7.5 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (5 mL/mmol substrate) was then added. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous

NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

(±)–(1*R*,2*S*)-*tert*-Butyl-2-[1-(naphthalen-2-yl)ethyl]pyrrolidine-1-carboxylate (II-50). General procedure B with Nixantphos as ligand was employed for the reaction of 2-bromonaphthalene (63 mg, 0.3 mmol) with **II-49** (50 mg, 0.25 mmol). This procedure afforded 49 mg (60%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis and as a single diastereoisomer; data are for the mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3 H), 7.72–7.61 (m, 1 H), 7.54–7.34 (m, 3 H), 4.24–4.03 (m, 1 H), 3.85–3.71 (m, 0.4 H), 3.66–3.43 (m, 1.6 H), 3.38–3.25 (m, 1 H), 1.87–1.66 (m, 3 H), 1.65–1.53 (m, 1 H), 1.46 (s, 9 H), 1.32 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.0, 141.5, 133.4, 132.2, 127.7, 127.5, 126.9, 125.9, 125.3, 79.4, 62.6, 47.7, 47.2, 41.5, 40.5, 28.5, 26.8, 25.9, 24.4, 23.6, 13.2, 12.9; IR (film) 1690 cm^{-1}. MS (ESI): 348.1932 (348.1939 calculated for $C_{21}H_{27}NO_2$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.



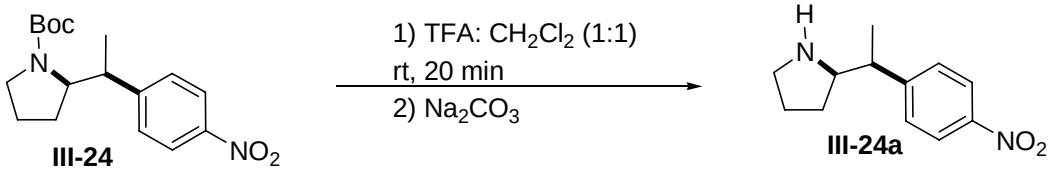
II-50 **II-50a**

(±)–(1*R*-2*S*)-2-[1-(Naphthalen-2-yl)ethyl]pyrrolidine (II-50a). A flame-dried flask was cooled under a stream of nitrogen and charged with **II-50** (33 mg, 0.1 mmol), and methylene chloride (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 24 mg (100%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.76 (m, 3 H), 7.67 (s, 1 H), 7.47–7.38 (m, 3 H), 3.22–3.14 (m, 1 H), 2.98–2.92 (m, 1 H), 2.80–2.70 (m, 2 H), 2.06–1.98 (m, 1 H), 1.88–1.72 (m, 2 H), 1.67–1.45 (m, 2 H), 1.34 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 133.6, 132.3, 128.1, 127.6, 127.6, 125.9, 125.8, 125.2, 65.1, 46.5, 46.1, 30.0, 24.6, 19.7; IR (film) 3340 cm^{-1}; MS (EI): 226.1591 (226.1596 calculated for $C_{16}H_{19}N$, M $^+$).

(±)–(1*R*,2*S*)-*tert*-Butyl-2-[1-(3-nitrophenyl)ethyl]pyrrolidine-1-carboxylate (III-24). General procedure B with Nixantphos as ligand was employed for the reaction of 1-bromo-3-nitrobenzene (61 mg, 0.3 mmol) with **II-49** (50 mg, 0.25 mmol) except that the reaction was conducted at 100 ^{o}C for 48 h. This procedure afforded 40 mg (50%) of

the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereoisomer and an 11:1 mixture of regioisomers. The NMR data is for the major regioisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–8.02 (m, 2 H), 7.70–7.42 (m, 2 H), 4.10–3.91 (m, 1 H), 3.67–3.39 (m, 2 H), 3.36–3.21 (m, 1 H), 1.88–1.59 (m, 4 H), 1.42 (s, 9 H), 1.29 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 148.1, 146.1, 146.0, 140.3, 134.6, 134.3, 133.4, 133.3, 133.0, 130.3, 129.6, 129.2, 128.9, 123.3, 122.5, 122.12, 122.08, 121.8, 121.7, 121.3, 121.1, 79.6, 79.2, 64.8, 62.3, 47.3, 46.9, 41.5, 40.9, 39.8, 28.5, 28.4, 28.2, 26.9, 26.4, 24.7, 24.2, 23.4, 22.0, 13.5; IR (film) 1691 cm^{-1}. MS (ESI): 343.1638 (343.1634 calculated for $C_{17}H_{24}N_2O_4$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.

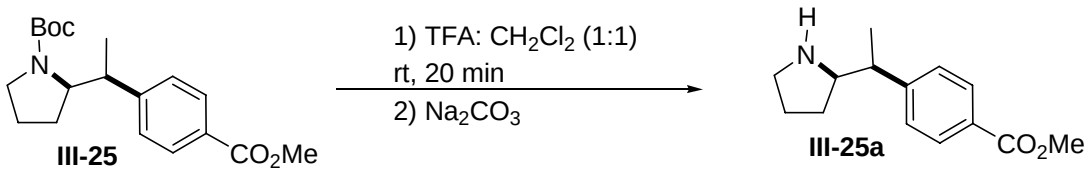


(±)–(1*R*,2*S*)-2-[1-(4-Nitrophenyl)ethyl]pyrrolidine (III-24a). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-24** (18 mg, 0.06 mmol), and methylene chloride (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture

was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo*. This procedure afforded 11 mg (89%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as an 11:1 mixture of regioisomer. The NMR data is for the major regioisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11–8.03 (m, 2 H), 7.60–7.54 (m, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 3.58–3.47 (m, 1 H), 3.18–3.08 (m, 1 H), 2.95–2.80 (m, 2 H), 2.30–2.20 (m, 1 H), 2.12–2.00 (m, 1 H), 1.98–1.87 (m, 1 H), 1.84–1.71 (m, 1 H), 1.33 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 144.6, 133.5, 129.8, 122.6, 122.2, 65.0, 44.8, 42.7, 29.5, 23.5, 19.8; IR (film) 1530 cm^{-1}; MS (EI): 221.1290 (221.1290 calculated for $C_{12}H_{16}N_2O_2$, M^+).

(±)–(1*R*,2*S*)-*tert*-Butyl-2-[1-(4-(methoxycarbonyl)phenyl)ethyl]pyrrolidine-1-carboxylate (III-25). General procedure B with (±)-BINAP as ligand was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.3 mmol) with **II-49** (50 mg, 0.25 mmol) except that the reaction was conducted at 100 ^{o}C for 48 h. This procedure afforded 38 mg (46%) of the title compound as a colorless oil and as a 5:1 mixture of regioisomers. The NMR data is for the major regioisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01–7.92 (m, 2 H), 7.41–7.22 (m, 2 H), 4.11–3.95 (m, 1 H), 3.90 (s, 3 H), 3.67–3.54 (m, 1 H), 3.50–3.40 (m, 1 H), 3.33–3.21 (m, 1 H), 1.81–1.55 (m, 4 H), 1.45 (s, 9 H), 1.24 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 166.9, 154.8, 149.4, 130.0, 129.5, 127.9, 127.1, 79.4, 62.4, 52.0, 51.9, 47.5, 47.1, 41.6, 40.8, 28.5, 26.8, 26.1, 24.2, 23.5, 13.1, 9.7; IR (film) 1724, 1693 cm^{-1}. MS (ESI): 356.1838 (356.1838 calculated for $C_{19}H_{27}NO_4$, $M + Na^+$).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.



(±)–(1*S*,2*R*)-Methyl-4-(1-pyrrolidin-2-yl)ethylbenzoate (III-25a). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-25** (15 mg, 0.04 mmol), and methylene chloride (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 10 mg (95%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a mixture of 5:1 mixture of regioisomers. The NMR data is for the major regioisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.85 (m, 2 H), 7.31–7.21 (m, 2 H), 3.87 (s, 3 H), 3.63–3.52 (m, 1 H), 3.10–2.94 (m, 1 H), 2.82–2.69 (m, 2 H), 2.29–2.18 (m, 1 H), 2.05–1.94 (m, 1 H), 1.93–1.82 (m, 1 H), 1.79–1.71 (m, 1 H), 1.27 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 147.8, 130.0, 129.1, 127.4, 64.7, 52.1, 45.0, 43.3, 29.7, 23.6, 20.1; IR

(film) 1721 cm^{-1}; MS (EI): 234.1485 (234.1494 calculated for $C_{14}H_{19}NO_2$, M^+).

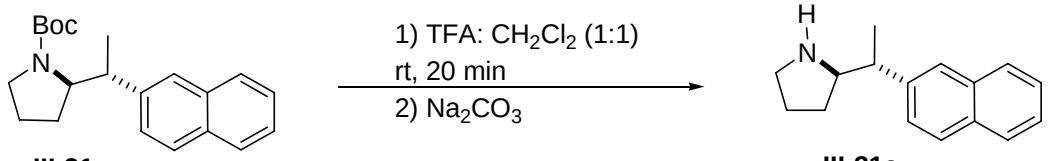
(±)–(1*R*,2*S*)-Benzyl-2-[1-(4-(methoxycarbonyl)phenyl)ethyl]pyrrolidine-1-carboxylate (III-27). General procedure B with (±)-BINAP as ligand was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.3 mmol) with **III-26** (59 mg, 0.25 mmol) except that the reaction was conducted at 100 ^oC for 72 h. This procedure afforded 39 mg (43%) of the title compound as a colorless oil and as a single diastereoisomer. This compound exists as a 1.5:1 mixture of rotamers as judged by ^1H NMR analysis; data are for the mixture. ^1H NMR (500 MHz, $CDCl_3$) δ 8.00–7.85 (m, 2 H), 7.41–7.28 (m, 6 H), 7.20–7.13 (m, 1 H), 5.19–5.07 (m, 1.6 H), 5.01–4.93 (m, 0.4 H), 4.18–4.02 (m, 1 H), 3.90 (s, 3 H), 3.71–3.51 (m, 1.6 H), 3.43–3.32 (m, 1.4 H), 1.85–1.57 (m, 4 H), 1.29–1.19 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 155.2, 149.2, 137.0, 136.6, 130.0, 129.4, 129.2, 128.5, 128.1, 127.9, 127.7, 67.1, 66.5, 63.1, 62.6, 52.0, 47.5, 47.4, 41.8, 40.7, 29.7, 26.9, 26.0, 24.3, 23.5, 13.4, 13.1; IR (film) 1719, 1702 cm^{-1}. MS (ESI): 390.1670 (390.1681 calculated for $C_{22}H_{25}NO_4$, $M + Na^+$).

(±)–(1*R*,2*S*)-Benzyl-2-[1-(3-formylphenyl)ethyl]pyrrolidine-1-carboxylate (III-28). General procedure B with (±)-BINAP as ligand was employed for the reaction of 3-bromobenzaldehyde (93 mg, 0.5 mmol) with **III-26** (59 mg, 0.25 mmol) except that 10 mol % palladium and 15 mol % of ligand were used and the reaction was conducted at 100 ^oC for 72 h. This procedure afforded 38 mg (45%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereoisomer. This compound exists as a 1:1 mixture of rotamers as judged by ^1H

NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05–9.84 (m, 1 H), 7.83–7.54 (m, 3 H), 7.51–7.28 (m, 6 H), 5.16–4.89 (m, 2 H), 4.19–4.01 (m, 1 H), 3.72–3.54 (m, 1.5 H), 3.46–3.32 (m, 1.5 H), 1.91–1.58 (m, 4 H), 1.32–1.20 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 192.4, 155.2, 144.8, 136.3, 134.5, 134.1, 128.8, 128.5, 128.1, 127.9, 127.7, 67.1, 66.6, 63.1, 62.7, 47.4, 47.3, 41.5, 40.4, 26.9, 26.0, 24.3, 23.5, 13.6, 13.2; IR (film) 1698 cm^{-1}. MS (ESI): 360.1584 (360.1576 calculated for $C_{21}H_{23}NO_3$, M + Na^+).

(±)–(1*R*,2*R*)-*tert*-Butyl 2-[1-(naphthalen-2-yl)ethyl]pyrrolidine-1-carboxylate (III-31). General procedure B with (±)-BINAP as ligand was employed for the reaction of 2-bromonaphthalene (62 mg, 0.3 mmol) with **III-30** (50 mg, 0.25 mmol). This procedure afforded 50 mg (61%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereoisomer. This compound exists as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.73 (m, 3 H), 7.64–7.58 (m, 1 H), 7.49–7.39 (m, 2 H), 7.38–7.29 (m, 1 H), 4.19–4.03 (m, 1 H), 3.54–3.44 (m, 0.5 H), 3.43–3.33 (m, 0.5 H), 3.31–3.18 (m, 1 H), 3.14–2.98 (m, 0.5 H), 2.93–2.82 (m, 0.5 H), 1.79–1.63 (m, 2.5 H), 1.62–1.47 (m, 11 H), 1.39 (d, J = 7.0 Hz, 3 H), 1.31–1.10 (m, 1.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 141.2, 133.4, 132.3, 127.8, 127.6, 127.5, 127.4, 127.1, 126.7, 126.6, 126.3, 125.9, 125.8, 125.3, 125.2, 79.4, 79.0, 62.6, 62.5, 46.7, 46.1, 42.6, 41.3, 29.8. 29.7, 28.6, 28.4, 28.2, 27.6, 26.5, 25.5, 23.5; IR (film) 1690 cm^{-1}. MS (ESI): 348.1626 (348.1939 calculated for $C_{21}H_{27}NO_2$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.



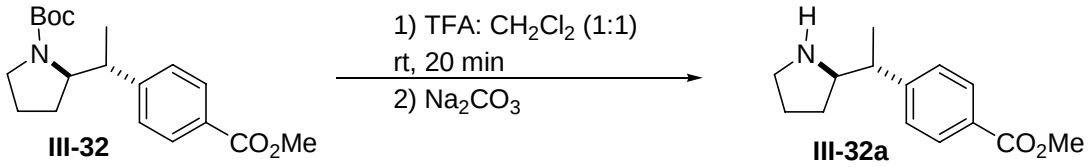
III-31 **III-31a**

(±)–(1*R*,2*R*)-2-[1-(Naphthalen-2-yl)ethyl]pyrrolidine (III-31a). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-31** (40 mg, 0.1 mmol), and methylene chloride (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 28 mg (100%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.77 (m, 3 H), 7.64 (s, 1 H), 7.48–7.41 (m, 2 H), 7.38–7.34 (m, 1 H), 3.33–3.27 (m, 1 H), 3.15–3.08 (m, 1 H), 3.02–2.95 (m, 1 H), 2.92–2.84 (m, 1 H), 2.28 (s br, 1 H), 1.81–1.72 (m, 1 H), 1.71–1.63 (m, 1 H), 1.61–1.53 (m, 1 H), 1.48 (d, *J* = 7.1 Hz, 3 H) 1.40–1.31 (m, 1 H); MS (EI): 226.1591 (226.1596 calculated for $C_{16}H_{19}N$, M^+).

(±)–(1*R*,2*R*)-*tert*-Butyl-2-[1-(4-(methoxycarbonyl)phenyl)ethyl]pyrrolidine-1-carboxylate (III-32). General procedure B with (±)-BINAP as ligand was employed for

the reaction of methyl 4-bromobenzoate (130 mg, 0.6 mmol) with **III-30** (100 mg, 0.5 mmol). This procedure afforded 98 mg (59%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereoisomer. This compound exists as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.93 (m, 2 H), 7.27–7.22 (m, 2 H), 4.10–3.96 (m, 1 H), 3.91 (s, 3 H), 3.52–3.32 (m, 1 H), 3.29–3.13 (m, 1 H), 3.05–2.96 (m, 0.5 H), 2.89–2.80 (m, 0.5 H), 1.81–1.69 (m, 1 H), 1.64–1.45 (m, 11 H), 1.30 (d, J = 7.2 Hz, 3 H), 1.20–1.00 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 155.0, 149.0, 129.4, 129.2, 128.3, 128.1, 79.5, 79.1, 62.4, 62.3, 52.0, 46.7, 46.2, 42.4, 40.9, 28.5, 27.3, 26.1, 23.4, 22.5, 17.9, 17.2; IR (film) 1724, 1694 cm^{-1}. MS (ESI): 356.1837 (356.1838 calculated for $C_{19}H_{27}NO_4$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.



III-32 **III-32a**

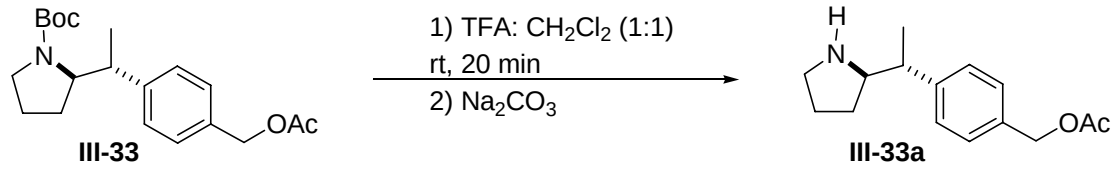
(±)–(1*R*,2*R*)-Methyl 4-(1-pyrrolidin-2-yl-ethyl)benzoate (III-32a). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-32** (60 mg, 0.18 mmol), and methylene chloride (2 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (2 mL) was then added slowly and the resulting mixture was stirred at

rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (1.2 g, 8 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 41 mg (98%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 3.90 (s, 3 H), 3.16–3.09 (m, 1 H), 3.05–2.98 (m, 1 H), 2.97–2.85 (m, 1 H), 2.71–2.62 (m, 1 H), 2.00 (s br, 1 H), 1.77–1.58 (m, 2 H), 1.55–1.46 (m, 1 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.27–1.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 151.2, 129.6, 128.1, 127.6, 64.8, 51.9, 46.7, 46.2, 30.3, 25.2, 19.7; IR (film) 1721 cm^{-1}; MS (EI): 234.1496 (234.1494 calculated for $C_{14}H_{19}NO_2$, M^+).

(±)–(1*R*,2*R*)-*tert*-Butyl-2-[1-(4-(acetoxymethyl)phenyl)ethyl]pyrrolidine-1-carboxylate (III-33). General procedure B with (±)-BINAP as ligand was employed for the reaction of 4-bromobenzyl acetate (69 mg, 0.3 mmol) with **III-30** (50 mg, 0.25 mmol). ^{1}H NMR analysis of the crude reaction mixture indicated that the reaction went to 94% conversion. After purification, 52 mg (60%) of the title compound was obtained as a colorless oil and as a single diastereoisomer. This compound exists as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2 H), 7.22–7.14 (m, 2 H), 5.08 (s, 2 H), 4.08–3.92 (m, 1 H), 3.44–3.19 (m, 1.5 H), 3.15–2.85 (m, 1.5 H), 2.10 (s, 3 H), 1.78–1.66 (m, 1 H), 1.65–1.45 (m, 11 H), 1.27 (d, *J* = 7.2 Hz, 3 H), 1.24–1.09 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.1, 143.7, 134.0, 133.8, 128.4, 128.2, 128.1, 79.4, 79.0, 66.1, 62.5, 62.4, 46.7,

46.1, 42.1, 41.0, 28.6, 27.5, 26.4, 23.4, 22.6, 21.0, 18.2, 17.7; IR (film) 1742, 1691 cm^{-1}. MS (ESI): 370.1979 (370.1994 calculated for $C_{20}H_{29}NO_4$, M + Na^+).

The diastereoselectivity of the transformation was assessed by TFA-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis.



III-33 **III-33a**

(±)–(1*R*,2*R*)-4-(1-Pyrrolidin-2-yl-ethyl)benzyl acetate (III-33a). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-33** (25 mg, 0.07 mmol), and methylene chloride (1 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (1 mL) was then added slowly, and the resulting mixture was stirred at rt for 30 min. The crude mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and solid Na_2CO_3 (636 mg, 4 mmol) was added. The resulting mixture was stirred at rt for 3 h, filtered through a plug of celite, and the filtrate was concentrated *in vacuo.* This procedure afforded 30 mg (100%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.3 Hz, 2 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 5.08 (s, 2 H), 3.61–3.54 (m, 1 H), 3.41–3.30 (m, 2 H), 3.09–3.01 (m, 1 H), 2.11 (s, 3 H), 2.08–1.99 (m, 1 H), 1.96–1.85 (m, 1 H), 1.80–1.72 (m, 1 H), 1.67–1.57 (m, 1 H), 1.44 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 142.6, 135.1, 128.8, 127.3, 66.2, 65.8, 45.2, 42.7, 30.2, 23.6, 21.0, 20.0; IR (film) 1678 cm^{-1}; MS (EI): 248.1644

(248.1651 calculated for $C_{15}H_{21}NO_2$, M^+).

(±)–(1*R*,2*R*)-*tert*-Butyl-2-(1-pyridin-3-yl-ethyl)pyrrolidine-1-carboxylate (III-34). General procedure B with (±)-BINAP as ligand was employed for the reaction of methyl 3-bromopyridine (48 mg, 0.3 mmol) with **III-30** (50 mg, 0.25 mmol) except that this reaction was conducted at 100 ^oC for 48 h. This procedure afforded 39 mg (56%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereoisomer. This compound exists as a 1:1 mixture of rotamers as judged by ^1H NMR analysis; data are for the mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 8.54–8.37 (m, 2 H), 7.57–7.42 (m, 1 H), 7.25–7.19 (m, 1 H), 4.08–3.95 (m, 1 H), 3.53–3.34 (m, 1 H), 3.31–3.21 (m, 0.5 H), 3.20–3.09 (m, 0.5 H), 3.05–2.95 (m, 0.5 H), 2.91–2.81 (m, 0.5 H), 1.87–1.73 (m, 1.5 H), 1.68–1.48 (m, 11.5 H), 1.31 (d, J = 7.2 Hz, 3 H), 1.23–1.13 (m, 0.5 H), 1.11–0.99 (m, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.1, 149.6, 148.0, 147.8, 138.3, 135.5, 135.4, 123.1, 79.6, 79.3, 62.1, 46.8, 46.3, 40.1, 38.3, 28.6, 28.4, 27.3, 25.9, 23.5, 22.6, 17.6, 16.8; IR (film) 1692 cm^{-1}. MS (ESI): 277.1909 (277.1916 calculated for $C_{16}H_{24}N_2O_2$, $M + Na^+$).

(±)–(1*R*,2*R*)-Benzyl-2-[1-(4-(methoxycarbonyl)phenyl)ethyl]pyrrolidine-1-carboxylate (III-36). General procedure B with (±)-BINAP as ligand was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.3 mmol) with **III-35** (59 mg, 0.25 mmol). This procedure afforded 46 mg (50%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereoisomer. This compound exists as a 2:1 mixture of rotamers as judged by ^1H NMR analysis; data are for

the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2 H), 7.47–7.29 (m, 5 H), 7.24–7.14 (m, 2 H), 5.31–5.14 (m, 2 H), 4.15–4.05 (m, 1 H), 3.91 (s, 3 H), 3.49–3.39 (m, 1 H), 3.38–3.29 (m, 0.66 H), 3.26–3.17 (m, 0.33 H), 3.06–2.91 (m, 1 H), 1.83–1.71 (m, 1 H), 1.67–1.50 (m, 2 H), 1.35–1.23 (m, 3 H), 1.20–1.04 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 155.3, 148.6, 148.5, 137.1, 136.8, 129.4, 129.3, 128.5, 128.3, 128.12, 128.06, 127.9, 127.8, 67.0, 66.6, 63.0, 62.4, 52.0, 46.8, 46.6, 42.1, 40.9, 27.2, 26.1, 23.4, 22.6, 17.7, 17.4; IR (film) 1721, 1702 cm^{-1}. MS (ESI): 390.1670 (390.1681 calculated for $C_{22}H_{25}NO_4$, M + Na^+).

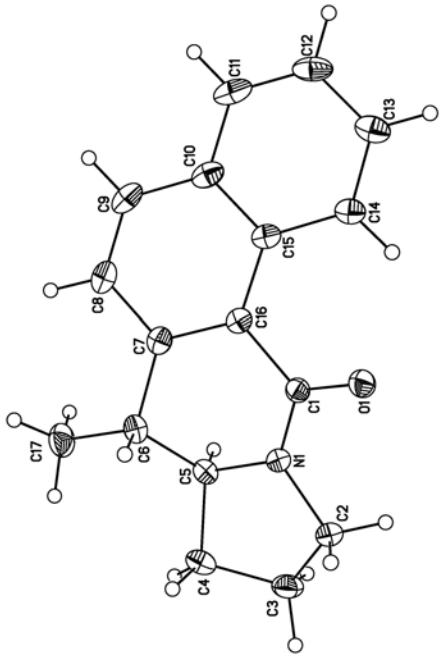
(±)–(1*R*,2*R*)-Benzyl-2-[1-(3-formylphenyl)ethyl]pyrrolidine-1-carboxylate (III-37). General procedure B with (±)-BINAP as ligand was employed for the reaction of 3-bromobenzaldehyde (93 mg, 0.5 mmol) with **III-35** (59 mg, 0.25 mmol) except that the amounts of palladium and ligand were doubled and that this reaction was conducted at 100 ^{o}C for 72 h. This procedure afforded 39 mg (46%) of the title compound as a colorless oil. NMR analysis indicated that the product was obtained as a single diastereoisomer. This compound exists as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1 H), 7.78–7.61 (m, 2 H), 7.49–7.30 (m, 6 H), 5.33–5.12 (m, 2 H), 4.17–4.07 (m, 1 H), 3.54–3.43 (m, 1 H), 3.42–3.31 (m, 0.66 H), 3.30–3.19 (m, 0.33 H), 3.03–2.88 (m, 1 H), 1.86–1.74 (m, 1 H), 1.67–1.52 (m, 2 H), 1.39–1.25 (m, 3 H), 1.23–1.09 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 155.4, 144.2, 137.1, 136.3, 134.7, 129.2, 128.9, 128.8, 128.7, 128.5, 128.14, 128.14, 128.07, 127.9, 127.8, 67.0, 66.6, 62.8, 62.3, 46.8, 46.6, 41.8, 40.5,

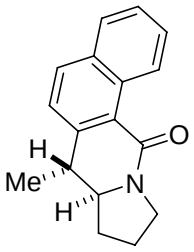
27.3, 26.1, 23.4, 22.6, 17.7, 17.4; IR (film) 1698 cm^{-1}. MS (ESI): 360.1578 (360.1576 calculated for $C_{21}H_{23}NO_3$, M + Na^+).

***tert*-Butyl-2-(2-chlorophenethyl)pyrrolidine-1-carboxylate (III-38).** General procedure B with (±)-BINAP as ligand was employed for the reaction of 2-bromo chlorobenzene (48 mg, 0.3 mmol) with **III-30** (50 mg, 0.25 mmol) except that this reaction was conducted at 100 ^oC for 35 h. This procedure afforded 58 mg (75%) of the title compound as a colorless oil that contained ~8% of an unidentified impurity. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.02 (m, 4 H), 4.00–3.73 (m, 1 H), 3.48–3.25 (m, 2 H), 2.79–2.62 (m, 2 H), 2.13–1.72 (m, 5 H), 1.69–1.54 (m, 1 H), 1.49–1.37 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 139.5, 133.8, 130.2, 129.5, 127.2, 126.8, 79.1, 56.8, 46.5, 46.1, 34.7, 34.1, 30.5, 29.9, 28.5, 28.4, 23.8, 23.1; IR (film) 1693 cm^{-1}. MS (ESI): 332.1398 (332.1393 calculated for $C_{17}H_{24}ClNO_2$, M + Na^+).

(±)–(10*S*,10a*R*)-10-Methyl-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-5(1H)-one (III-39). A flame-dried flask was cooled under a stream of nitrogen and charged with **II-50** (70 mg, 0.22 mmol), P_2O_5 (184 mg, 0.65 mmol) and $POCl_3$ (2 mL). The resulting mixture was heated to 100 °C for 13 h. The crude mixture was concentrated *in vacuo* and cooled to 0 °C. The crude material was diluted with water, and aqueous Na_2CO_3 was added until bubbling stopped. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were then washed with saturated Na_2CO_3, brine and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 12 mg (22%) of the title compound as a white solid; mp 135-137 ^oC. ^1H NMR

(400 MHz, $CDCl_3$) δ 9.39 (d, *J* = 8.8 Hz, 1 H), 7.94 (d, *J* = 8.6 Hz, 1 H), 7.81 (dd, *J* = 8.2, 0.6 Hz, 1 H), 7.60–7.55 (m, 1 H), 7.50–7.44 (m, 2 H), 3.93–3.85 (m, 1 H), 3.79–3.70 (m, 1 H), 3.53–3.44 (m, 1 H), 3.02–2.92 (m, 1 H), 2.44–2.35 (m, 1 H), 2.18–2.09 (m, 1 H), 1.96–1.73 (m, 2 H), 1.46 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 132.8, 132.2, 131.3, 127.8, 127.5, 127.0, 125.7, 121.6, 61.6, 45.6, 39.4, 33.3, 23.3, 14.6 (two aromatic carbons are accidentally equivalent); IR (film) 1639 cm^{-1}. MS (ESI): 274.1202 (274.1208 calculated for $C_{17}H_{17}NO$, $M + Na^+$).





39

(±)–(10*R*,10a*R*)-10-Methyl-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinolin-

5(1H)-one (III-40). A flame-dried flask was cooled under a stream of nitrogen and charged with **III-31** (64 mg, 0.20 mmol), P_2O_5 (168 mg, 0.59 mmol) and $POCl_3$ (2 mL). The resulting mixture was heated to 100 °C for 13 h. The crude mixture was concentrated *in vacuo* and cooled to 0 °C. The crude material was diluted with water, and aqueous Na_2CO_3 was added until bubbling stopped. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were then washed with sat. Na_2CO_3 (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 12 mg (24%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 8.8 Hz, 1 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 7.80 (dd, *J* = 8.3, 0.7 Hz, 1 H), 7.60–7.55 (m, 1 H), 7.49–7.45 (m, 1 H), 7.30–7.27 (m, 1 H), 4.09–4.02 (m, 1 H), 3.91–3.84 (m, 1 H), 3.71–3.63 (m, 1 H), 3.10–3.04 (m, 1 H), 2.16–2.07 (m, 2 H), 2.04–1.95 (m, 1 H), 1.94–1.86 (m, 1 H), 1.17 (dd, *J* = 7.1, 0.7, Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 133.1, 132.4, 131.6, 128.0, 127.5, 126.8, 125.7, 125.1, 58.3, 45.8, 37.7, 28.6, 23.7, 14.9 (two aromatic carbons are incidentally equivalent); IR (film) 1638 cm^{-1}. MS (ESI): 252.1388 (252.1393 calculated for $C_{17}H_{17}NO$, $M + H^+$).

Synthesis of Functionalized Pyrrolidines via Coupling with Aryl Bromides (Table 10)

General Procedure C for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (2 mol %), Nixantphos (4 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (5

mL/mmol substrate) was then added. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

***tert*-Butyl-2-methyl-2-(naphthalen-2-ylmethyl)pyrrolidine-1-carboxylate (III-43)**. General procedure C was employed for the reaction of 2-bromonapthalene (63 mg, 0.30 mmol) with **III-41** (50 mg, 0.25 mmol). This procedure afforded 62 mg (77%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.70 (m, 3 H), 7.65–7.56 (m, 1 H), 7.48–7.39 (m, 2 H), 7.36–7.26 (m, 1 H), 3.70–3.64 (m, 0.5 H), 3.47–3.37 (m, 1 H), 3.35–3.26 (m, 0.5 H), 3.19–3.11 (m, 0.5 H), 2.98–2.89 (m, 1.5 H), 2.12–2.03 (m, 1 H), 1.65–1.48 (m, 14 H), 1.23–1.11 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 153.8, 136.6, 136.3, 133.4, 132.0, 129.2, 128.9, 128.8, 128.7, 127.6, 127.5, 127.2, 125.8, 125.7, 125.4, 125.2, 79.6, 78.6, 63.6, 63.1, 48.50, 48.46, 44.5, 43.2, 39.0, 37.8, 28.8, 28.7, 27.1, 26.1, 21.7, 21.3; IR (film) 1690 cm^{-1}. MS (ESI): 348.1940 (348.1939 calculated for $C_{21}H_{27}NO_2$, M + Na^+).

***tert*-Butyl-2-methyl-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate (III-44)**. General procedure C was employed for the reaction of 3-bromopyridine (48 mg, 0.30

mmol) with **III-41** (50 mg, 0.25 mmol) except that 10 mol % palladium and 15 mol % ligand were used. This procedure afforded 55 mg (80%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49–8.40 (m, 2 H), 7.51–7.42 (m, 1 H), 7.23–7.16 (m, 1 H), 3.56–3.50 (m, 0.6 H), 3.48–3.41 (m, 0.4 H), 3.38–3.31 (m, 0.6 H), 3.28–3.21 (m, 0.4 H), 3.18–3.11 (m, 0.4 H), 3.00–2.93 (m, 0.6 H), 2.82–2.73 (m, 1 H), 1.99–1.88 (m, 1 H), 1.70–1.45 (m, 14 H), 1.26–1.15 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 153.7, 151.4, 151.3, 147.8, 147.5, 137.7, 137.3, 135.7, 134.2, 134.0, 123.2, 123.0, 121.7, 79.8, 78.9, 63.2, 62.7, 48.5, 48.4, 41.6, 40.4, 39.0, 37.6, 29.7, 28.7, 28.6, 28.39, 28.36, 26.9, 25.8, 21.6, 21.2; IR (film) 1687 cm^{-1}. MS (ESI): 299.1738 (299.1735 calculated for $C_{16}H_{24}N_2O_2$, M + Na^+).

***tert*-Butyl-2-(3-methoxybenzyl)-2-methylpyrrolidine-1-carboxylate (III-45)**. General procedure C was employed for the reaction of 3-bromoanisole (57 mg, 0.30 mmol) with **III-41** (50 mg, 0.25 mmol). This procedure afforded 52 mg (68%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (q, J = 7.8 Hz, 1 H), 6.79–6.67 (m, 3 H), 3.78 (s, 3 H), 3.46–3.38 (m, 1 H), 3.36–3.29 (m, 0.5 H), 3.28–3.23 (m, 0.5 H), 3.21–3.13 (m, 0.5 H), 3.09–3.01 (m, 0.5 H), 2.80–2.69 (m, 1 H), 2.06–1.97 (m, 1 H), 1.60–1.45 (m, 14 H), 1.27–1.13 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 159.3, 154.3, 153.7, 140.6, 140.3, 129.0, 128.7, 123.0, 122.7, 116.1, 115.7, 111.8, 111.5, 79.5, 78.6, 63.5, 63.0, 55.2, 48.6, 48.5, 44.3, 43.2, 39.1,

37.8, 28.73, 28.69, 27.2, 26.0, 21.7, 21.3, 18.6; IR (film) 1693 cm^{-1}. MS (ESI): 328.1881 (328.1889 calculated for $C_{18}H_{27}NO_3$, M + Na^+).

Benzyl 2-(4-*tert*-butylbenzyl)-2-methylpyrrolidine-1-carboxylate (III-46). General procedure C was employed for the reaction of 4-*tert*-butyl bromobenzene (64 mg, 0.30 mmol) with **III-42** (50 mg, 0.21 mmol). This procedure afforded 58 mg (74%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^1H NMR analysis; data are for the mixture. ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.30 (m, 5 H), 7.27–7.18 (m, 2 H), 7.05–6.95 (m, 2 H), 5.28–5.22 (m, 1.4 H), 5.13–5.05 (m, 0.6 H), 3.53–3.40 (m, 1 H), 3.37–3.31 (m, 0.6 H), 3.26–3.12 (m, 1.4 H), 2.88–2.82 (m, 0.6 H), 2.79–2.73 (m, 0.4 H), 2.08–1.98 (m, 1 H), 1.64–1.53 (m, 2 H), 1.48 (s, 2 H), 1.40 (s, 1 H), 1.34–1.24 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 153.8, 149.1, 148.9, 137.5, 135.4, 135.2, 130.1, 129.9, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 125.0, 124.8, 67.0, 65.9, 64.2, 63.6, 49.1, 48.1, 43.9, 42.5, 38.9, 37.6, 34.3, 31.4, 31.4, 26.9, 25.7, 21.8, 21.4; IR (film) 1701 cm^{-1}. MS (ESI): 388.2256 (388.2252 calculated for $C_{24}H_{31}NO_2$, M + Na^+).

Benzyl-2-(4-(methoxycarbonyl)benzyl)-2-methylpyrrolidine-1-carboxylate (III-47). General procedure C was employed for the reaction of methyl 4-bromobenzoate (65 mg, 0.30 mmol) with **III-42** (59 mg, 0.25 mmol). This procedure afforded 63 mg (68%) of the title compound as a colorless oil. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^1H NMR analysis; data are for the mixture. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92–7.84 (m, 2 H), 7.46–7.32 (m, 5 H), 7.16–7.06 (m, 2 H), 5.30–

5.20 (m, 1.25 H), 5.12–5.06 (m, 0.75 H), 3.90 (s, 3 H), 3.57–3.51 (m, 0.75 H), 3.50–3.39 (m, 1 H), 3.30–3.25 (m, 0.25 H), 3.23–3.16 (m, 0.25 H), 3.12–3.05 (m, 0.75 H), 2.86–2.79 (m, 1 H), 2.04–1.93 (m, 1 H), 1.67–1.54 (m, 2 H), 1.51 (s, 2.25 H), 1.42 (s, 0.75 H), 1.27–1.13 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 153.9, 144.1, 143.8, 137.3, 130.4, 130.2, 129.4, 129.2, 128.54, 128.45, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8, 67.1, 66.1, 64.0, 63.4, 52.0, 49.1, 48.1, 44.4, 43.0, 39.0, 37.6, 27.2, 26.0, 21.8, 21.4, 18.9; IR (film) 1721, 1698 cm^{-1}. MS (ESI): 390.1683 (390.1681 calculated for $C_{22}H_{25}NO_4$, M + Na^+).

Synthesis of Functionalized Pyrrolidines via Coupling with Aryl Triflates (Table 11)

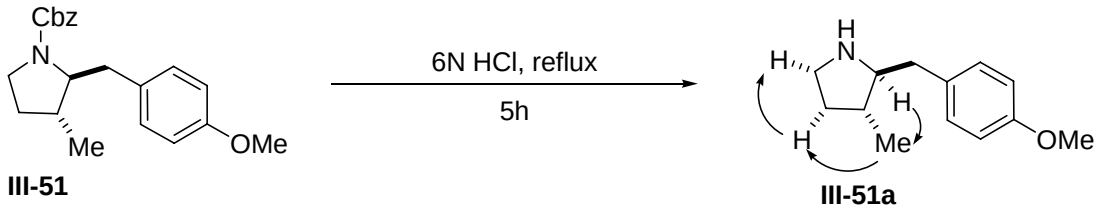
General Procedure D for Pd-Catalyzed Carboamination Reactions of Aryl Triflates. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (4 mol %), dpe-phos (8 mol %) and K_3PO_4 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (4 mL/mmol substrate) was then added. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

2-(4-Formylbenzyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (III-49). General procedure D was employed for the reaction of 4-formylphenyl trifluoromethanesulfonate (82 mg, 0.30 mmol) with **II-5** (47 mg, 0.25 mmol). This procedure afforded 49 mg (68%) of the title compound as a colorless oil. This material gave spectral data to those obtained for the synthesis of this product from the analogous aryl bromide (see above). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98–9.96 (s, 1 H), 7.83–7.77 (d, *J* = 8.0 Hz, 2 H), 7.41–7.29 (m, 2 H), 4.13–3.92 (m, 1 H), 3.46–3.01 (m, 3 H), 2.74–2.58 (m, 1 H), 1.85-1.60 (m, 4 H), 1.52–1.45 (s, 9 H).

2-(2-Methylbenzyl)pyrrolidine-1-carboxylic acid benzyl ester (III-50). General procedure D was employed for the reaction of *o*-tolyl trifluoromethanesulfonate (145 mg, 0.3 mmol) with **III-11** (110 mg, 0.5 mmol). This procedure afforded 120 mg (78%) of the title compound as a pale yellow oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.27 (m, 5 H), 7.20–6.98 (m, 4 H), 5.23–5.07 (m, 2 H), 4.17–4.00 (m, 1 H), 3.56–3.31 (m, 2.5 H), 3.15–3.03 (m, 0.5 H), 2.52–2.38 (m, 2.5 H), 2.14 (s, 1.5 H), 2.01–1.78 (m, 2 H), 1.77–1.68 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 137.2, 137.0, 136.6, 130.4, 130.33, 130.28, 128.5, 128.4, 128.1, 127.8, 127.7, 126.4, 125.73, 125.67, 67.1, 66.5, 58.1, 57.3, 46.7, 46.5, 37.8, 36.9, 29.4, 28.6, 23.4, 22.6, 19.5, 19.2; IR (film) 1698 cm^{-1}. MS (ESI): 332.1618 (332.1626 calculated for $C_{20}H_{23}NO_2$, M + Na^+).

(±)– (2*R*,3*S*)-2-(4-Acetylbenzyl)-3-methylpyrrolidine-1-carboxylic acid benzyl ester (III-51). General procedure D was employed for the reaction of 4-acetylphenyl trifluoromethanesulfonate (41 mg, 0.15 mmol) with **III-15** (30 mg, 0.125 mmol). The diastereoselectivity of the transformation was assessed by HCl-mediated deprotection of the crude product obtained in a duplicate reaction, and was found to be 12:1 dr as judged by ^{1}H NMR analysis. The minor diastereomer was separated upon chromatographic purification to afford 31 mg (71%) of the title compound as a colorless oil with >20:1 dr. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91–7.78 (m, 2 H), 7.44–7.30 (m, 5 H), 7.29–7.23 (m, 1 H), 7.20–7.10 (m, 1 H), 5.26–5.08 (m, 2 H), 3.76–3.49 (m, 2 H), 3.35–3.12 (m, 1.5 H), 3.07–2.97 (m, 0.5 H), 2.92–2.82 (m, 0.5 H), 2.78–2.68 (m, 0.5 H), 2.62–2.53 (m, 3 H), 2.11–1.96 (m, 1 H), 1.95–1.76 (m, 1 H), 1.51–1.36 (m, 1 H), 0.88 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 197.8, 155.0, 154.9, 144.5, 144.4, 137.0, 136.6, 135.3, 129.8, 129.6, 128.5, 128.42, 128.37, 128.0, 127.9, 127.8, 67.0, 66.6, 65.7, 65.5, 45.4, 45.3, 40.2, 38.6, 37.0, 36.1, 31.1, 30.2, 26.5, 19.2, 19.0; IR (film) 1698 cm^{-1}. MS (EI): 374.1728 (374.1732 calculated for $C_{22}H_{25}NO_3$, M + Na^+).

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **III-51** with 6N HCl, followed by aqueous NaOH, to afford **III-51a** as shown below.



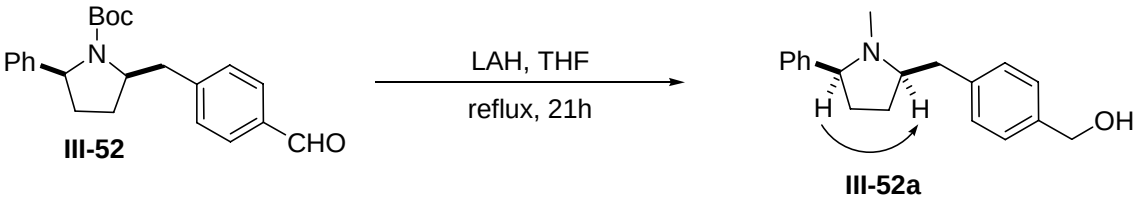
III-51 **III-51a**

(±)– (2*S*,3*R*)-2-(4-Acetylbenzyl)-3-methylpyrrolidine (III-51a). The product **III-51** (70 mg, 0.20 mmol) was deprotected with 6 N HCl (10 mL) using a procedure analogous to that described above for the preparation of **III-21a**. This procedure afforded 40 mg (92%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 2.98–2.91 (m, 2 H), 2.88–2.81 (m, 1 H), 2.78–2.71 (m, 1 H), 2.67–2.59 (m, 1 H), 2.57 (s, 3 H), 2.06–1.97 (m, 1 H), 1.91 (s, br, 1 H), 1.77–1.68 (m, 1 H), 1.41–1.32 (m, 1 H), 0.99 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 146.1, 135.2, 129.2, 128.5, 67.2, 44.7, 41.2, 39.1, 34.0, 26.5, 18.1; IR (film) 3435, 1645 cm^{-1}. MS (ESI): 218.1548 (218.1545 calculated for $C_{14}H_{19}NO$, M + H^+).

(±)–(2*R*,5*S*)-2-(4-Formylbenzyl)-5-phenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (III-52). General procedure D was employed for the reaction of 4-formylphenyl trifluoromethanesulfonate (82 mg, 0.30 mmol) with **II-21** (66 mg, 0.25 mmol). The diastereoselectivity of the transformation was assessed by LAH reduction of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 63 mg (69%) of the title compound as a colorless oil with >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1 H), 7.87–7.80 (m, 2 H), 7.55–7.37 (m, 2 H), 7.35–7.29 (m, 2 H), 7.28–7.19 (m, 3 H),

5.05–4.60 (m, 1 H), 4.30–4.08 (m, 1 H), 3.71–3.44 (m, 1 H), 2.82–2.69 (m, 1 H), 2.33–2.23 (m, 1 H), 2.00–1.90 (m, 1 H), 1.88–1.77 (m, 1 H), 1.73–1.66 (m, 1 H), 1.60–1.03 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 154.9, 146.6, 144.5, 134.8, 130.1, 130.0, 128.3, 126.6, 125.5, 79.7, 63.1, 60.6, 41.3, 34.6, 28.2 (two aliphatic carbons are incidentally equivalent); IR (film) 1690, 1606 cm^{-1}. MS (EI): 388.1886 (388.1889 calculated for $C_{23}H_{27}NO_3$, M + Na^+).

The stereochemistry of the above compound was determined by ^{1}H NMR nOe analysis of the product obtained through LAH reduction of **52** to afford **52a** as shown below.



(±)–(2*S*,5*R*)-4-(1-Methyl-5-phenylpyrrolidin-2-ylmethyl)phenylmethanol (III-52a). A flame-dried flask was cooled under a steam of nitrogen and charged with **III-52** (95 mg, 0.26 mmol) and tetrahydrofuran (3 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (2.6 mL, 2.6 mmol, 1 M in tetrahydrofuran) was added dropwise via syringe. The resulting mixture was heated to reflux until the starting material was consumed as judged by TLC analysis (ca. 21 h). The reaction mixture was cooled to 0 °C, slowly quenched with water (0.3 mL) and diluted with diethyl ether (5 mL). Aqueous NaOH (0.3 mL, 10 M) and water (0.3 mL) were added sequentially and an insoluble white precipitate formed. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with diethyl ether. The combined organic extracts

were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil obtained was purified by flash chromatography using 10% → 20% methanol/dichloromethane as the eluent to afford 54 mg (74%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 6 H), 7.26–7.21 (m, 3 H), 4.66 (s, 2 H), 3.23 (t, *J* = 7.8 Hz, 1 H), 3.10–3.02 (m, 1 H), 2.66–2.56 (m, 2 H), 2.20 (s, 3 H), 2.03–1.95 (m, 1 H), 1.88 (s, br 1 H), 1.79–1.70 (m, 1 H), 1.66–1.56 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 139.4, 138.5, 129.6, 128.3, 127.4, 127.0, 126.9, 72.4, 68.1, 65.2, 40.7, 39.1, 33.2, 29.3 (two aromatic carbons are incidentally equivalent); IR (film) 3339 cm^{-1}; MS (EI): 282.1847 (282.1858 calculated for $C_{19}H_{23}NO$, M + H^+).

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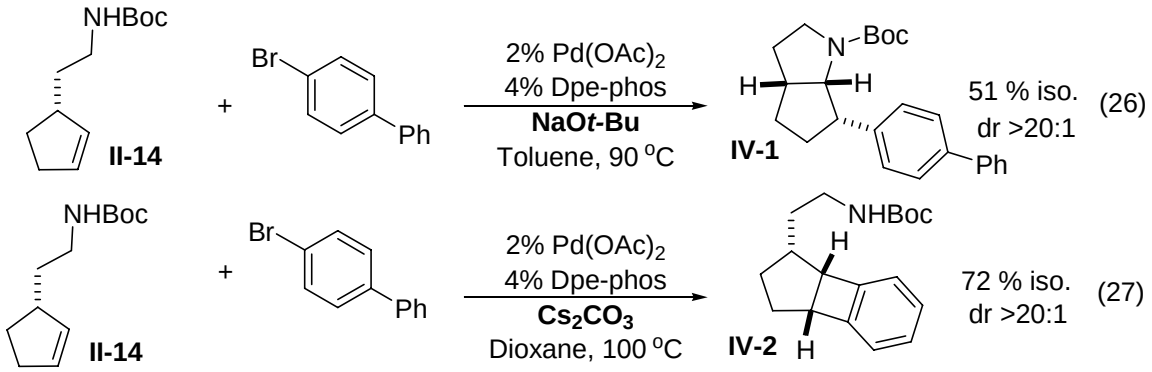
Chapter IV

Palladium-Catalyzed Synthesis of Cyclopentane-Fused Benzocyclobutenes via Tandem Directed Carbopalladation/C-H Bond Functionalization[1]

During the course of our studies on Pd-catalyzed carboamination reactions of *N*-protected γ-aminoalkenes,[2] we observed that the use of the weak base Cs_2CO_3 in transformations of terminal alkene substrates provided 2-benzylpyrrolidine derivatives in yields that were comparable to those obtained with the stronger base NaO*t*-Bu (Chapters II and III).[3] However, when the Cs_2CO_3 conditions were employed with cyclopentene-derived substrate **II-14**, a surprising result was obtained. As shown in equation 27, the Pd-catalyzed reaction of **II-14** with 4-bromobiphenyl in the presence of Cs_2CO_3 did not provide the expected product **IV-1**, but instead generated benzocyclobutene derivative[4] **IV-2** in 72% yield and >20:1 dr. This result is in marked contrast with the reaction of **II-14** with 4-bromobiphenyl in the presence of NaO*t*-Bu,[2b] which affords the expected heterocycle **IV-1** in 51% yield and >20:1 dr (eq 26).



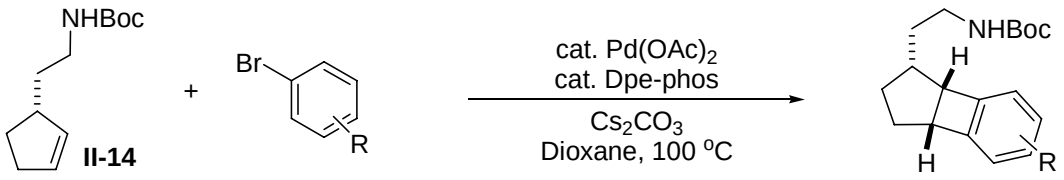
The generation of benzocyclobutene **IV-2** is both synthetically and mechanistically interesting.[5] Benzocyclobutenes are widely employed as precursors to *ortho*-quinodimethides, which are known to undergo facile [4+2] cycloaddition reactions,[6] and can also be employed in polymerizations.[7] Moreover, the surprising effect of base on the reactivity of **II-14** raises questions about the mechanistic relationship between the reactions shown in equations 26-27 and the carboamination reactions of acyclic *N*-protected aminoalkene substrates. This chapter contains a description of our studies in the preparation of benzocyclobutenes via coupling of **II-14** with aryl bromides, preliminary studies in expanding the scope of this new transformation and a presentation of a mechanistic hypothesis that accounts for the observed effect of base.

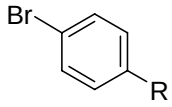
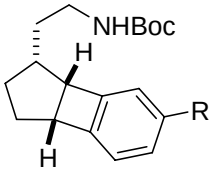
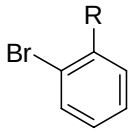
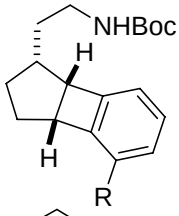
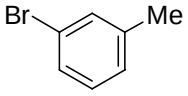
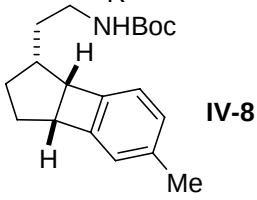
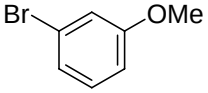
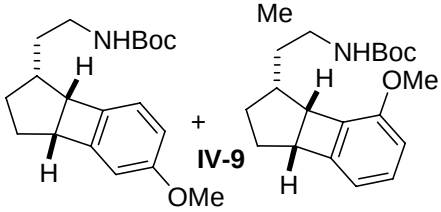
Scope and Diastereoselectivity

To explore the scope of the Pd-catalyzed benzocyclobutene forming process, we examined reactions of **II-14** with various *p*-, *m*- and *o*-substituted aryl bromides. As shown in Table 1, reactions of *p*-substituted starting materials afforded products

substituted exclusively at the 2-position of the aromatic ring (entries 1–4). Similarly high regioselectivity was obtained in reactions of *o*-substituted aryl bromides, which afforded products bearing substituents at the 5-position (entries 5–6). The regioselectivities observed in reactions of *m*-substituted aryl bromides were dependent on the nature of the substituent. Although the reaction of **II-14** with *m*-bromotoluene proceeded with good regioselectivity (entry 7), the coupling of **II-14** with *m*-bromoanisole afforded a 2:1 mixture of regioisomers (entry 8).

Table 12. Synthesis of Benzocyclobutenes from **II-14**[a]



Entry	Aryl bromide	Product	Yield (%)[b,c]
1			R = CH_2OAc: 74, **IV-3**
2			R = Ph: 72, **IV-2**
3			R = Cl: 70, **IV-4**
4			R = OMe: 58, **IV-5**
5			R = Me: 85, **IV-6**
6			R = Ph: 80, **IV-7**
7		 **IV-8**	68
8		 **IV-9**	66 (2:1)

[a]Conditions: 1.0 equiv **II-14**, 1.2. equiv ArBr, 2.3 equiv Cs_2CO_3, 4 mol % $Pd(OAc)_2$, 8 mol % Dpe-phos, dioxane (0.25 M), 100 °C. [b]Yields refer to average isolated yields obtained in two or more experiments. [c]All products were obtained with >20:1 dr and >20:1 regioselectivity unless otherwise noted.

The major side products formed in reactions between **II-14** and either electron-rich or -neutral aryl bromides were arylated cyclopentanes (**IV-10**), although in many reactions trace amounts of bicyclic products **IV-11**–**IV-13** were detected by ^{1}H NMR analysis of the crude reaction mixtures (Figure 5).[8]

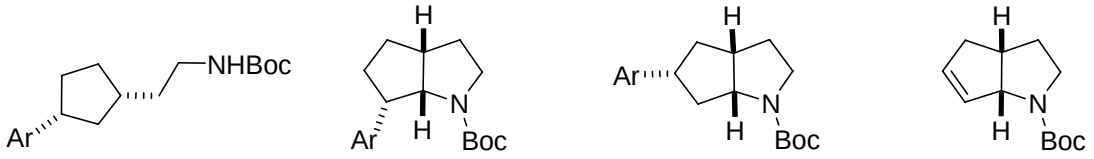
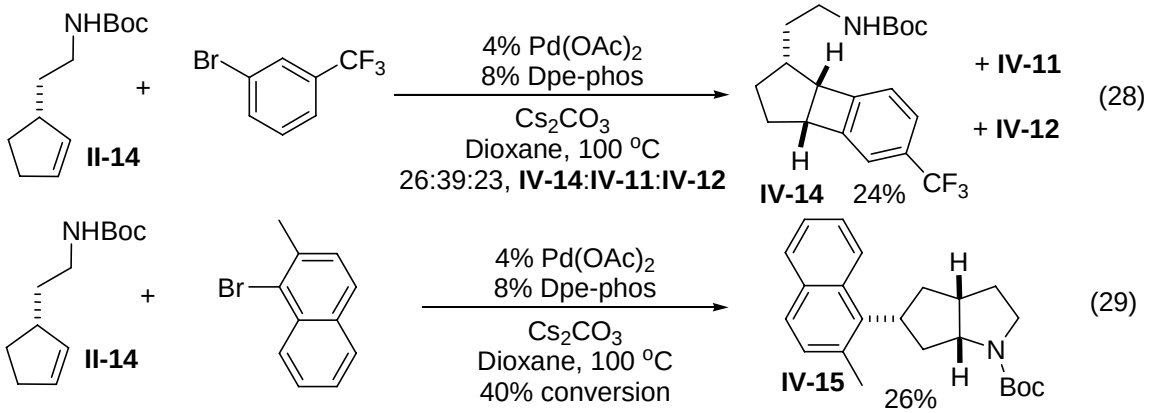
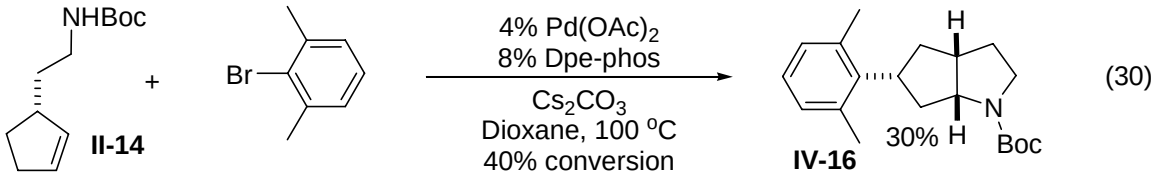


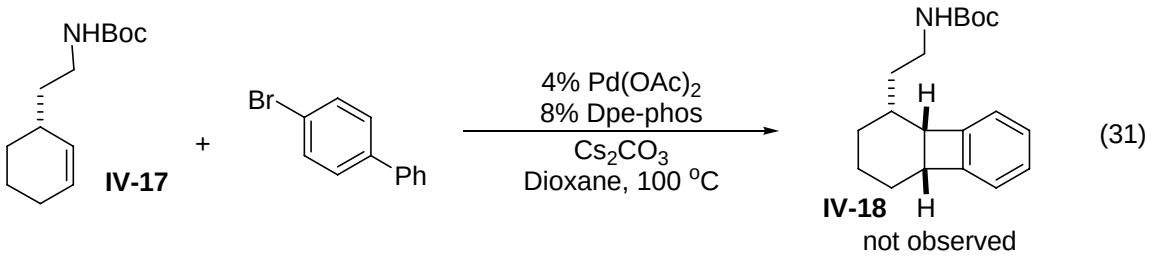
Figure 5. Side-products.

Although the benzocyclobutene-forming reactions proceeded smoothly with many aryl bromides, the Pd-catalyzed coupling of **II-14** with the electron-poor substrate 3-bromobenzotrifluoride afforded a 26:39:23 mixture of **IV-14**:**IV-11**:**IV-12** (eq 28);[9] upon purification **IV-14** was obtained in 24% yield. In addition, the Pd-catalyzed reaction of **II-14** with 1-bromo-2-methylnaphthalene proceeded slowly and in low conversion (ca. 40%) to afford 5-aryl azabicyclo[3.3.0]octane **IV-15** in 26% isolated yield (eq 29). A similar result was obtained with 2-bromo-*m*-xylene, which afforded a 5-aryl azabicyclo[3.3.0]octane **IV-16** in 30% yield (ca. 40% conversion, eq 30). Efforts to extend this transformation to cyclohexene-derived substrate **IV-17** were unsuccessful (eq 31).[10] In addition, when the reaction of **II-14** with 4-bromobiphenyl was conducted under a CO atmosphere, the aryl bromide was consumed, but **II-14** was recovered unchanged.





(30)

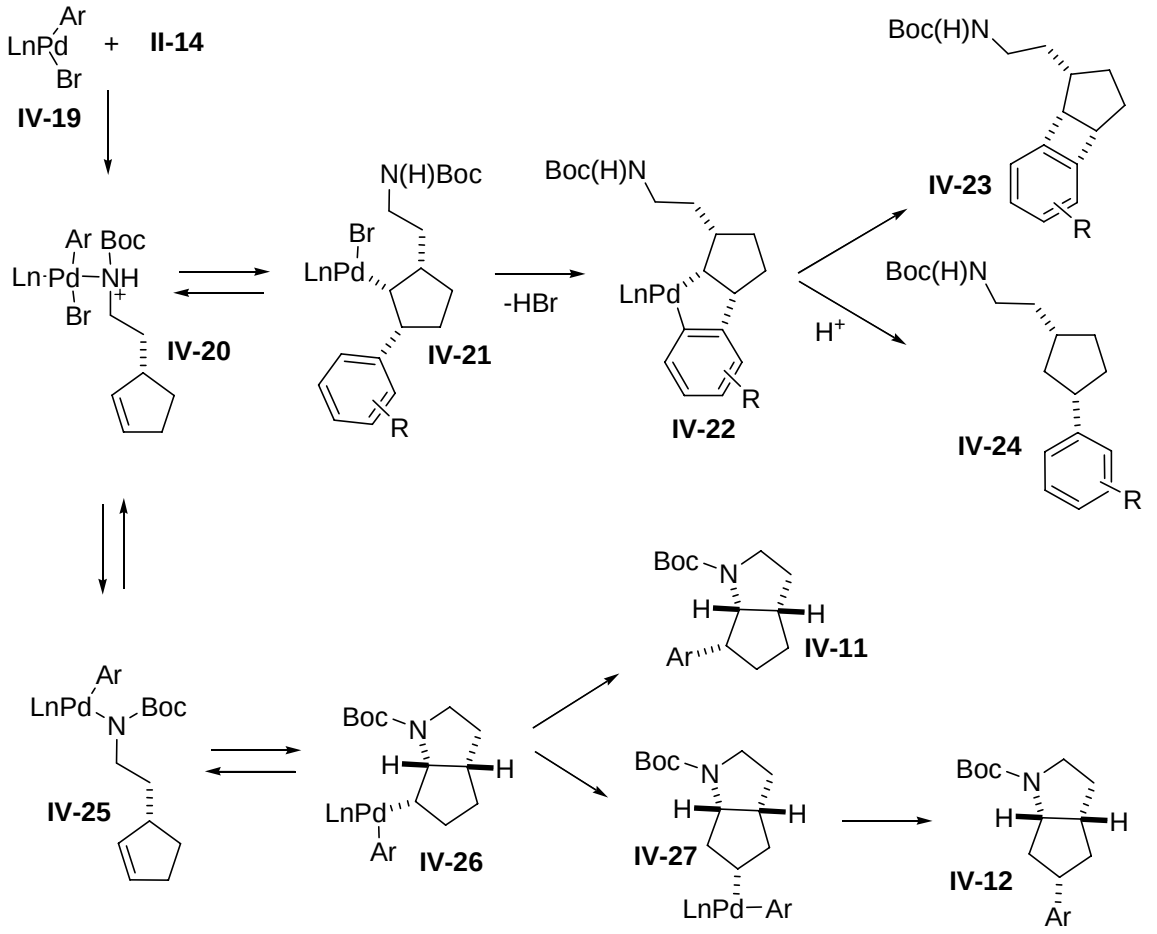


(31)

Mechanistic Considerations

The dependence of base on the outcome of Pd-catalyzed reactions of **II-14** with aryl bromides (Scheme 18) likely results from differences in reactivity of palladium *amino* complexes vs. palladium *amido* complexes.[11] As shown in Scheme 18, oxidative addition of the aryl bromide to Pd(0) would generate **IV-19**, which can bind the carbamate to provide **IV-20**. In the presence of a base, *amino* complex **IV-20** can potentially be converted to *amido* complex **IV-25**. However, with the weak base Cs_2CO_3 this process should be relatively slow due to the low solubility of Cs_2CO_3,[11] and the equilibrium between **IV-20** and **IV-25** may favor **IV-20**. In contrast, when the relatively strong, soluble base NaO*t*-Bu is employed, the conversion of **IV-20** to **IV-25** is relatively fast, and the equilibrium favors amido complex **IV-25**.[11,12]

Scheme 18. Proposed Mechanism for the Tandem Directed Carbopalladation/C-H Bond Functionalization



The benzocyclobutene products formed when Cs_2CO_3 is used as base are likely generated via directed carbopalladation[13,14] of *amino* complex **IV-20** to provide the sterically hindered alkylpalladium intermediate **IV-21**, which lacks β–hydrogen atoms *syn* to the metal. Intramolecular aryl C–H bond activation[5,15] of **IV-21** provides **IV-22** and an equivalent of HBr, which is neutralized by Cs_2CO_3. Complex **IV-22** is then converted to benzocyclobutene **IV-23** via C–C bond-forming reductive elimination.[5,16] The arylated cyclopentane side-product **IV-24** may result from competing protonation of

the Pd–C bond(s) of **IV-21** or **IV-22**.

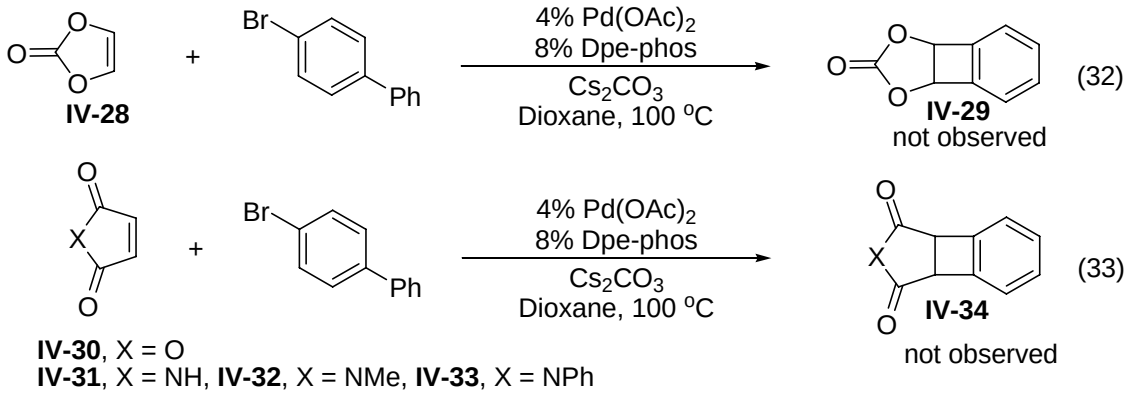
The conversion of the electron-poor *m*-bromobenzotrifluoride to a mixture of **IV-14**, **IV-11**, and **IV-12** is likely due to enhancement of the N–H proton acidity of **IV-20** when the complex bears an electron-withdrawing aryl substituent, which would shift the **IV-20**/**IV-25** equilibrium towards **IV-25**. Under conditions that facilitate rapid and/or thermodynamically favorable formation of *amido* complex **IV-25**, the reactions likely proceed via *syn*-amidopalladation as described previously to generate **IV-26**,[2] which is converted to **IV-11** via C–C bond-forming reductive elimination. Alternatively, **IV-26** can also be transformed to **IV-12** via β-hydride elimination/reinsertion processes.[2a,c]

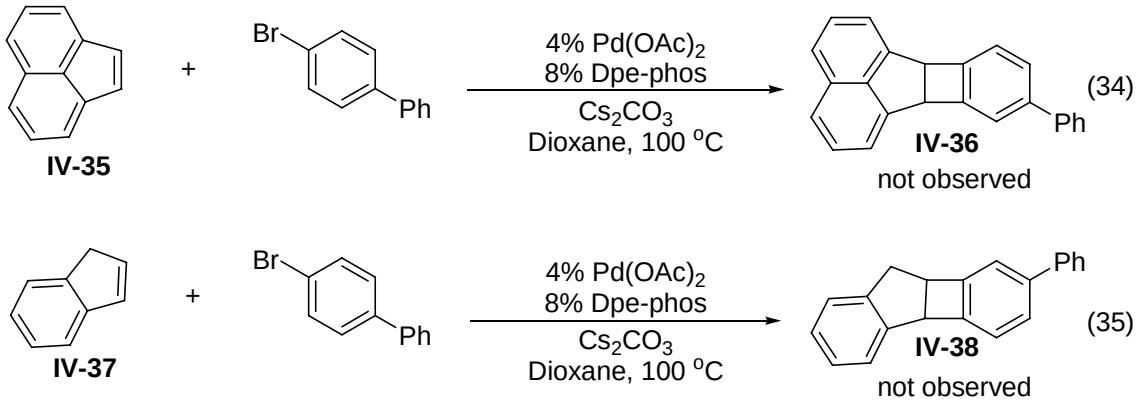
The differences in reactivity observed between substrates bearing terminal alkenes (e.g., **II-5**) and cycloalkene substrate **II-14** may be due either to the influence of alkene size on the position of the **IV-25**/**IV-26** equilibrium, the influence of substrate sterics on the rate of C–C bond-forming reductive elimination from **IV-26**, or the influence of alkene substitution on the relative rates of alkene insertion into the Pd–C bond of **IV-20** vs. the Pd–N bond of **IV-25**. In addition, the fact that Pd-catalyzed reactions of **II-14** with aryl halides lacking *o*-hydrogen atoms are converted to azabicyclooctanes (e.g., **IV-15**) in the presence of Cs_2CO_3 suggests that the carbopalladation of **IV-20** is either reversible,[17] or very slow with bulky aryl groups. Our current data do not allow us to differentiate between these two possibilities.

Studies Towards the Development of Non-Directed Benzocyclobutene-Forming Reactions and Other Tandem Reactions

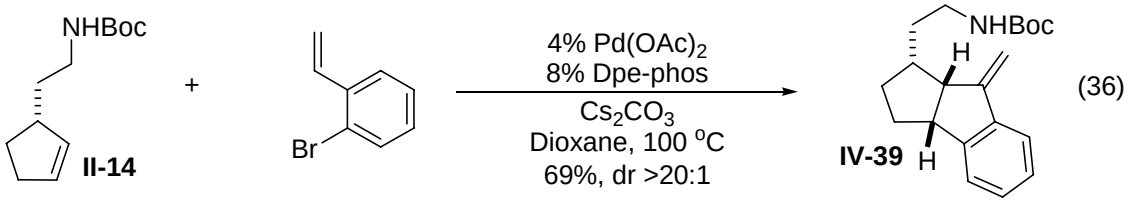
The mechanistic hypothesis outlined above suggested that it may be possible to

expand the scope of this chemistry in two manners. First of all, it could be possible to employ other alkene substrates that lack a directing group, provided that the intermediate generated upon carbopalladation lacks *syn* β-hydrogen atoms. To probe this hypothesis, olefin substrates **IV-28**, **IV-30**, **IV-31**, **IV-32**, **IV-33**, **IV-35** and **IV-37** were treated with 4-bromobiphenyl and Cs_2CO_3 using several Pd-catalysts (eqs 32-35).[21] Unfortunately, none of these reactions provided the desired benzocyclobutene products, and starting material was recovered in all cases. The absence of a directing group such as a Boc-protected secondary amine could explain the low reactivity of these olefinic substrates.

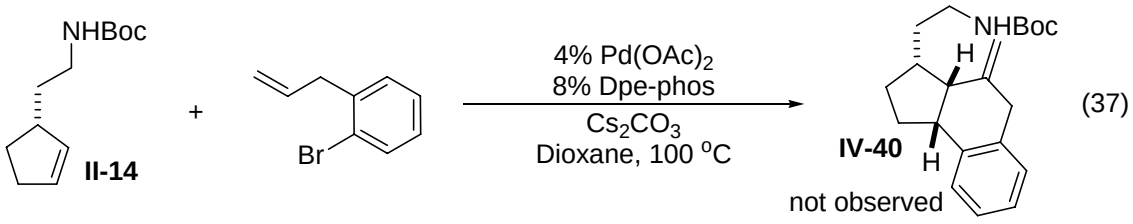




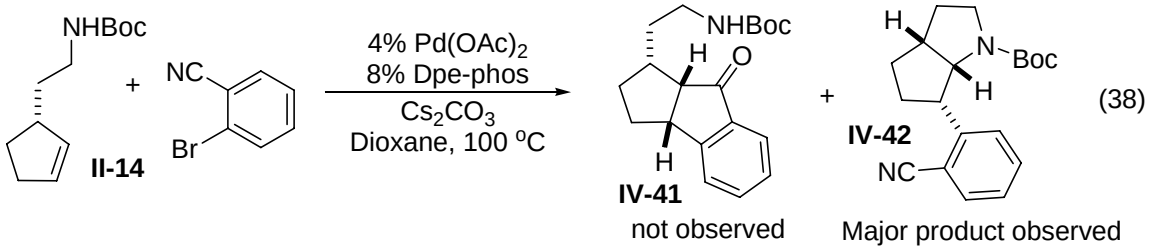
A second study that would expand the scope of this process would involve capture of intermediate **IV-21** by a pendant alkene, nitrile or heteroatom present on the aryl bromide substrate. As shown in eq 36, treatment of **II-14** with *ortho*-vinyl bromobenzene under the optimized reaction conditions afforded product **IV-39** in 69% yield and high diastereoselectivity.[18] However, use of *ortho*-allyl bromobenzene under the same reaction conditions led to a complex mixture of products and **IV-40** was not observed (eq 37), presumably due to relatively slow formation of the six-membered ring. Similarly, reaction of **II-14** with 2-bromobenzonitrile did not afford any of the ketone product **IV-41** but instead lead to the formation of bicyclic structure **IV-42** as a major product (eq 38).[19] Pyrrole-containing aryl bromide **IV-43** was recently used in a similar C-H activation/annulation reaction by Lautens and coworkers (eq 39).[20] Unfortunately, use of the substrate also failed to produce **IV-44**, and all starting material was recovered. Attempts to extend the methodology to heteroatom nucleophiles (**IV-45**, **IV-47** and **IV-48**) did not produce any of the desired products; starting material was usually recovered (eqs 40-41).[21] It is possible that heteroatom chelation to the palladium catalyst could prevent the desired reaction pathway from occuring.



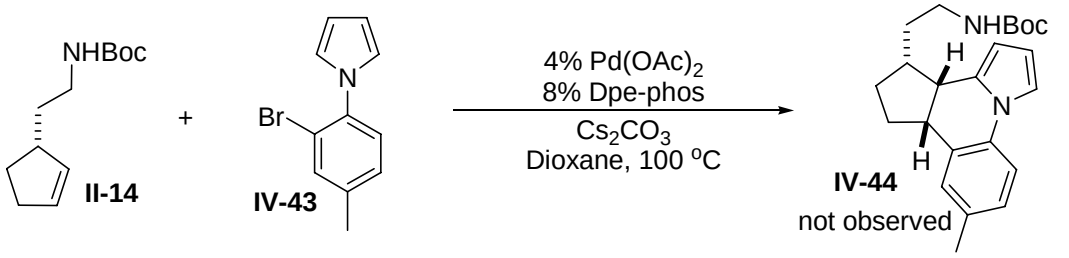
(36)



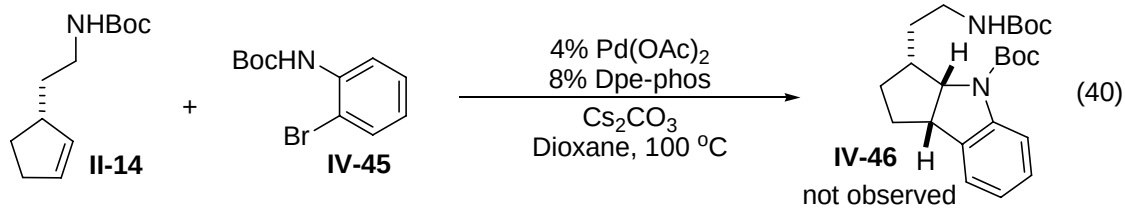
(37)



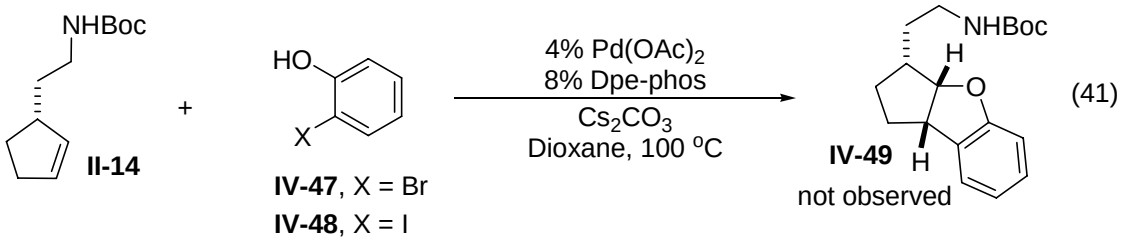
(38)



(39)



(40)



(41)

Conclusion

In conclusion, we have developed a new transformation for the conversion of **II-14** to cyclopentane-fused benzocyclobutenes via an unprecedented sequence of heteroatom-directed carbopalladation followed by intramolecular aryl C–H bond

activation. These are the first examples of reactions that exploit directed carbopalladation for the generation and functionalization of alkylpalladium intermediates that lack *syn*-β-hydrogen atoms. Importantly, the results described above illustrate that differences in reactivity between Pd-*amino* and Pd-*amido* complexes can be exploited to allow the construction of strikingly different products from common starting materials.

Experimental Section

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. $Pd(OAc)_2$, Dpe-phos, anhydrous dioxane, and all starting materials were obtained from commercial sources and used without further purification except 2-cyclopent-2-enylethyl carbamic acid *tert*-butyl ester (**II-14**),[22] **IV-17**,[23] 2-allyl bromobenzene,[24] **IV-43**,[25] **IV-45**,[26] and 4-bromobenzyl acetate,[27] which were prepared according to published procedures. Ratios of regioisomers and/or diastereomers were determined by ^{1}H NMR and/or capillary GC analysis of crude reaction mixtures. 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, whereas the yields reported in Table 12 are the average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 12. The stereochemistry of **IV-2** was assigned by x-ray crystallographic analysis. The stereochemistry of the other benzocyclobutene products was assigned based on analogy to **IV-2**.

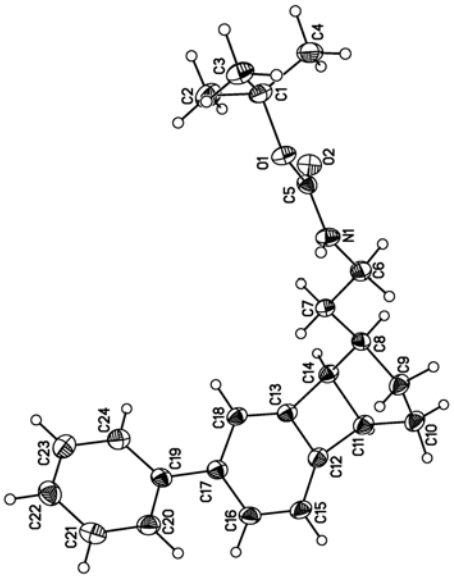
Synthesis of Benzocyclobutene Derivatives and Cyclized Products via Coupling with Aryl Bromides (Table 12, eqs 28–30)

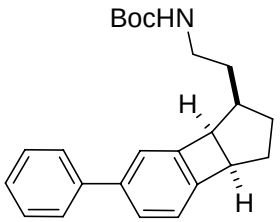
General Procedure. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (4 mol %), Dpe-phos (8 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate **II-14** (1.0 equiv) in dioxane (4 mL/mmol **II-14**) was then added via syringe. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel. All reactions provided the benzocyclobutene derivatives with >20:1 dr.

(±)-(3a*R*,6*S*,6a*S*)-6-Biphenyl-4-yl-hexahydrocyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (IV-1).[22] The general procedure was employed for the reaction of 4-bromobiphenyl (140 mg, 0.60 mmol) with **II-14** (106 mg, 0.50 mmol) except that NaO*t*-Bu (111 mg, 1.15 mmol) was used as a base instead of Cs_2CO_3. This procedure afforded 92 mg (51%) of the title compound as a white solid, m.p. 126–128 °C. This compound was found to exist as a ~2:1 mixture of rotamers as judged by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58–7.52 (m, 2 H), 7.53–7.45 (m, 2 H),

7.42 (t, *J* = 7.6 Hz, 2 H), 7.28–7.20 (m, 3 H), 4.58–4.48 (m, 0.3 H), 4.43–4.34 (m, 0.7 H), 3.86–3.75 (m, 0.7 H), 3.57–3.45 (m, 0.3 H), 3.39–3.19 (m, 1.3 H), 3.12–3.01 (m, 0.7 H), 3.00–2.81 (m, 1 H), 2.16–2.02 (m, 1 H), 2.01–1.77 (m, 3 H), 1.76–1.62 (m, 2 H), 1.21–0.93 (m, 9 H).

(±)-(1*R*,3a*R*,7b*S*)-2-[6-Phenyl-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (IV-2). The general procedure was employed for the reaction of 4-bromobiphenyl (70 mg, 0.30 mmol) with **II-14** (53 mg, 0.25 mmol). This procedure afforded 71 mg (75%) of the title compound as a white solid, m.p. 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2 H), 7.46–7.38 (m, 3 H), 7.34–7.27 (m, 2 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 4.56 (s, br, 1 H), 3.85 (d, *J* = 4.6 Hz, 2 H), 3.41–3.28 (m, 1 H), 3.29–3.17 (m, 1 H), 1.95–1.83 (m, 2 H), 1.81–1.59 (m, 4 H), 1.46 (s, 9 H), 1.13–1.02 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 146.3, 144.4, 142.2, 140.4, 128.6, 127.2, 126.8, 122.2, 121.8, 79.0, 50.7, 47.6, 40.2, 38.6, 32.1, 30.2, 28.7, 28.4 (two aromatic carbons are incidentally equivalent); IR (film) 1700 cm^{-1}. MS (ESI): 386.2092 (386.2096 calculated for $C_{24}H_{29}NO_2$, M + Na^+).

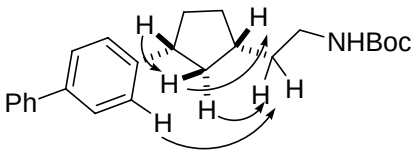




IV-2

(±)-(1*S*,3*R*)-2-[3-Biphenyl-4-yl-cyclopentyl)-ethyl]-carbamic acid *tert*-butyl ester (**IV-10, Ar = *p*-biphenyl**). This compound was isolated as a side-product formed in the reaction of **II-14** with 4-bromobiphenyl described above (10 mg, 5% yield, ca. 90% purity). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.56 (m, 2 H), 7.51 (d, J = 8.2 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.35–7.28 (m, 3 H), 4.52 (s, br, 1 H), 3.21–3.04 (m, 3 H), 2.29–2.21 (m, 1 H), 2.16–1.92 (m, 3 H), 1.77–1.68 (m, 1 H), 1.66–1.54 (m, 3 H), 1.45 (s, 9 H), 1.35–1.24 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 145.2, 141.1, 138.8, 128.7, 127.4, 127.1, 127.0, 126.8, 79.1, 45.4, 42.1, 39.9, 37.7, 36.7, 33.3, 31.8, 28.4; IR (film) 1699 cm^{-1}. MS (ESI): 388.2247 (388.2252 calculated for $C_{24}H_{31}NO_2$, M + Na^+).

The stereochemistry of **IV-10** was determined by ^{1}H NMR nOe analysis as shown below.



IV-10

(±)-(3*R*,3a*S*,7b*R*)-3-(2-*tert*-Butoxycarbonylamino-ethyl)-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-5-yl-acetic acid methyl ester (IV-3). The general procedure was employed for the reaction of 4-bromobenzyl acetate (69 mg, 0.30 mmol) with II-14 (53 mg, 0.25 mmol). This procedure afforded 68 mg (76%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (m, 1 H), 7.07–6.97 (m, 2 H), 5.05 (q, *J* = 11.9 Hz, 2 H), 4.58 (s, br, 1 H), 3.79 (d, *J* = 6.6 Hz, 2 H), 3.35–3.17 (m, 2 H), 2.09 (s, 3 H), 1.93–1.79 (m, 2 H), 1.78–1.51 (m, 4 H), 1.46 (s, 9 H), 1.08–0.94 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.9, 147.5, 144.3, 134.7, 128.1, 123.6, 121.8, 79.1, 67.1, 50.9, 47.6, 40.3, 38.7, 32.0, 30.1, 28.7, 28.4, 21.1; IR (film) 1740, 1713 cm^{-1}. Anal calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.31; H, 8.21; N, 3.88.

(±)-(1*R*,3a*R*,7b*S*)-2-[6-Chloro-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl] ethyl-carbamic acid *tert*-butyl ester (IV-4). The general procedure was employed for the reaction of 4-bromochlorobenzene (115 mg, 0.60 mmol) with **II-14** (106 mg, 0.50 mmol). This procedure afforded 120 mg (71%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 1.7, 7.8 Hz, 1 H), 7.03 (s, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 4.63 (s, br, 1 H), 3.76 (p, *J* = 3.9 Hz, 2 H), 3.32–3.14 (m, 2 H), 1.92–1.77 (m, 2 H), 1.72–1.63 (m, 2 H), 1.64–1.51 (m, 2 H),

1.46 (s, 9 H), 1.04–0.94 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 145.2, 132.7, 127.9, 123.7, 123.1, 79.1, 50.8, 47.3, 40.1, 38.6, 31.9, 30.0, 28.6, 28.4 (two aromatic carbons are incidentally equivalent); IR (film) 1695 cm^{-1}. Anal calcd for $C_{18}H_{24}ClNO_2$: C, 67.17; H, 7.52; N, 4.35. Found: C, 67.10; H, 7.55; N, 4.38.

(±)-(1*R*,3a*R*,7b*S*)-2-6-Methoxy-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (IV-5). The general procedure was employed for the reaction of 4-bromoanisole (113 mg, 0.60 mmol) with **II-14** (106 mg, 0.50 mmol). This procedure afforded 98 mg (62%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, J = 8.1 Hz, 1 H), 6.75 (dd, J = 2.2, 8.1Hz, 1 H), 6.71 (s, 1 H), 4.60 (s, br, 1 H), 3.78 (s, 3 H), 3.73 (d, J = 6.3 Hz, 2 H), 3.38–3.27 (m, 1 H), 3.24–3.15 (m, 1 H), 1.89–1.76 (m, 2 H), 1.75–1.62 (m, 2 H), 1.61–1.52 (m, 2 H), 1.45 (s, 9 H), 1.07–0.96 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 155.9, 144.7, 138.8, 122.6, 114.0, 109.3, 79.1, 55.4, 50.2, 47.0, 40.3, 38.6, 32.1, 30.2, 28.9, 28.4; IR (film) 1700 cm^{-1}. Anal calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.06; H, 8.59; N, 4.36.

(±)-(1*R*,3a*R*,7b*S*)-2-[4-Methyl-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (IV-6). The general procedure was employed for the reaction of 2-bromotoluene (103 mg, 0.60 mmol) with **II-14** (106 mg, 0.50 mmol). This procedure afforded 130 mg (87%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 7.6 Hz, 1 H), 6.98 (d, J = 7.8 Hz, 1 H), 6.83 (d, J = 7.0 Hz, 1 H), 4.56 (s, br, 1 H), 3.83–3.72 (m, 2 H),

3.36–3.16 (m, 2 H), 2.17 (s, 3 H), 1.90–1.79 (m, 2 H), 1.75–1.62 (m, 2 H), 1.61–1.51 (m, 2 H), 1.45 (s, 9 H), 1.07–0.95 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 145.2, 143.5, 131.9, 128.2, 127.3, 120.5, 79.1, 50.4, 47.0, 40.3, 38.5, 31.9, 30.2, 28.4, 27.6, 16.2; IR (film) 1696 cm^{-1}. Anal calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.61; H, 9.04; N, 4.64.

(±)-(1*R*,3a*R*,7b*S*)-2-[4-Phenyl-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (IV-7). The general procedure was employed for the reaction of 2-bromobiphenyl (70 mg, 0.30 mmol) with **II-14** (53 mg, 0.25 mmol). This procedure afforded 68 mg (75%) of the title compound as a white solid (m.p. 118–120 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.4 Hz, 2 H), 7.48 (d, *J* = 8.2 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.33–7.23 (m, 2 H), 6.98 (d, *J* = 7.2 Hz, 1 H), 4.58 (s, br, 1 H), 4.18–4.10 (m, 1 H), 3.89–3.81 (m, 1 H), 3.37–3.17 (m, 2 H), 1.96–1.86 (m, 1 H), 1.85–1.79 (m, 1 H), 1.78–1.70 (m, 1 H), 1.69–1.54 (m, 3 H), 1.46 (s, 9 H), 1.09–0.96 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 144.7, 143.8, 138.0, 134.4, 128.7, 128.0, 127.2, 126.9, 125.2, 122.2, 79.1, 50.6, 48.9, 40.3, 38.8, 31.8, 30.2, 28.4, 27.7; IR (film) 1699 cm^{-1}. Anal calcd for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.01; H, 8.05; N, 3.84.

(±)-[(1*R*,3a*R*,7b*S*)-2-[5-Methyl-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (IV-8). The general procedure was employed for the reaction of 3-bromotoluene (52 mg, 0.30 mmol) with **II-14** (53 mg, 0.25 mmol). This procedure afforded 56 mg (75%) of the title

compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 7.2 Hz, 1 H), 6.79 (s, 1 H), 4.51 (s, br, 1 H), 3.72 (m, 2 H), 3.31–3.11 (m, 2 H), 2.28 (s, 3 H), 1.86–1.73 (m, 2 H), 1.71–1.48 (m, 4 H), 1.41 (s, 9 H), 1.03–0.90 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 147.3, 140.6, 137.1, 127.7, 123.0, 122.4, 79.1, 50.5, 47.6, 40.3, 38.6, 32.0, 30.1, 28.7, 28.4, 22.1; IR (film) 1699 cm^{-1}. Anal calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.53; H, 9.02; N, 4.47.

(±)-(1*R*,3a*R*,7b*S*)-2-[5-Methoxy-2,3,3a,7b-tetrahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (IV-9). The general procedure was employed for the reaction of 3-bromoanisole (113 mg, 0.6 mmol) with **II-14** (106 mg, 0.5 mmol). This procedure afforded 107 mg (67%) of the title compound as an inseparable 2:1 mixture of regioisomers (colorless oil). Data are for the mixture ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.6 Hz, 0.33 H), 6.93 (d, *J* = 8.0 Hz, 0.67 H), 6.77–6.70 (m, 1 H), 6.69–6.63 (m, 0.33 H), 6.62–6.58 (m, 0.67 H), 5.02 (s, br, 0.33 H), 4.62 (s, br, 0.67 H), 3.89–3.83 (m, 0.33 H), 3.82–3.68 (m, 4.67 H), 3.39–3.14 (m, 2 H), 1.89–1.75 (m, 2 H), 1.74–1.51 (m, 4 H), 1.46 (s, 9 H), 1.18–1.07 (m, 0.33 H), 1.06–0.94 (m, 0.67 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 156.1, 155.9, 154.0, 149.1, 148.0, 135.4, 129.7, 129.2, 124.2, 114.6, 113.4, 109.4, 107.5, 79.0, 78.7, 55.3, 55.0, 50.0, 49.9, 47.7, 47.1, 40.6, 40.2, 40.0, 38.6, 31.9, 30.5, 30.1, 28.6, 28.43, 28.39, 28.0 (two aliphatic carbons are incidentally equivalent); IR (film) 1699 cm^{-1}. Anal calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.99; H, 8.72; N, 4.34.

(±)-(1*R*,3a*R*,7b*S*)-2-[5-Trifluoromethyl-2,3,3a,7b-tetrahydro-1*H*-

cyclopenta[3,4]cyclobuta[1,2]benzen-1-yl]ethyl-carbamic acid *tert*-butyl ester (IV-14). The general procedure was employed for the reaction of 3-bromobenzotrifluoride (270 mg, 1.2 mmol) with **II-14** (212 mg, 1.0 mmol). This procedure afforded 84 mg (24%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 1 H), 7.25 (s, 1 H), 7.16 (d, *J* = 7.3 Hz, 1 H), 4.60 (s, br, 1 H), 3.85 (d, *J* = 6.3 Hz, 2 H), 3.37–3.27 (m, 1 H), 3.26–3.15 (m, 1 H), 1.97–1.83 (m, 2 H), 1.76–1.61 (m, 3 H), 1.60–1.51 (m, 1 H), 1.46 (s, 9 H), 1.04–0.92 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 148.2, 147.7, 129.8 (q, *J* = 31.8 Hz), 124.6 (q, *J* = 272.5 Hz), 124.3, 123.5, 118.7, 79.2, 51.2, 47.8, 40.2, 38.6, 32.0, 30.1, 28.6, 28.4; IR (film) 1699 cm^{-1}. Anal calcd for $C_{19}H_{24}F_3NO_2$: C, 64.21; H, 6.81; N, 3.94. Found: C, 64.19; H, 7.00; N, 3.94.

(±)-(3a*R*,5*R*,6a*R*)-5-(2-Methylnaphthalen-1-yl)hexahydrocyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (IV-15). The general procedure was employed for the reaction of 1-bromo-2-methylnaphthalene (67 mg, 0.30 mmol) with **II-14** (53 mg, 0.25 mmol). This procedure afforded 23 mg (26%) of the title compound as a colorless oil and as a ~2:1 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.64–7.57 (m, 1 H), 7.48–7.34 (m, 2 H), 7.30–7.23 (m, 1 H), 4.36–4.21 (m, 1 H), 4.02–3.87 (m, 1 H), 3.84–3.77 (m, 0.7 H), 3.74–3.67 (m, 0.3 H), 3.65–3.55 (m, 1 H), 2.92–2.82 (m, 1 H), 2.57–2.42 (m, 5 H), 2.30–2.16 (m, 1 H), 2.10–1.97 (m, 2 H), 1.87–1.79 (m, 1 H), 1.54–1.36 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 135.1, 133.6, 133.4, 131.7, 129.7, 129.2, 126.8, 126.7, 125.3, 124.8, 124.3, 124.2, 124.1, 79.1, 63.3, 62.9, 45.6, 45.1, 44.8, 44.0,

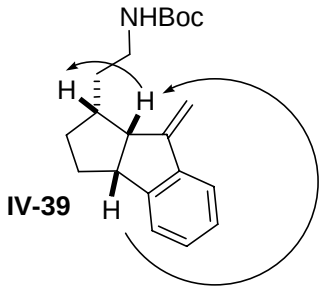
41.3, 39.5, 38.1, 36.3, 29.4, 28.8, 28.6, 28.5, 21.8; IR (film) 1692 cm^{-1}. MS (ESI): 374.2087 (374.2096 calculated for $C_{23}H_{29}NO_2$, M + Na^+).

(±)-(3a*R*,5*R*,6a*R*)-5-(2,4,6-Trimethylphenyl)hexahydrocyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (IV-16). The general procedure was employed for the reaction of 2-bromomesitylene (60 mg, 0.30 mmol) with **II-14** (53 mg, 0.25 mmol). This procedure afforded 25 mg (30%) of the title compound as a colorless oil and as a ~2:1 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86–6.78 (m, 2 H), 4.23–4.10 (m, 1 H), 3.73–3.65 (m, 0.7 H), 3.62–3.55 (m, 0.3 H), 3.52–3.36 (m, 2 H), 2.79–2.67 (m, 1 H), 2.42–2.29 (m, 7 H), 2.23 (s, 3 H), 2.11–1.82 (m, 4 H), 1.78–1.70 (m, 1 H), 1.52–1.39 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 136.7, 135.4, 135.3, 130.3, 130.2, 79.0, 62.6, 62.3, 45.5, 44.9, 44.3, 43.3, 41.4, 39.0, 37.4, 35.1, 29.7, 28.9, 28.5, 21.4, 21.2, 20.6; IR (film) 1695 cm^{-1}. MS (ESI): 352.2249 (352.2252 calculated for $C_{21}H_{31}NO_2$, M + Na^+).

***tert*-butyl 2-((1*R*,3a*R*,8a*S*)-8-methylene-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]inden-1-yl)ethylcarbamate (IV-39).** The general procedure was employed for the reaction of 2-bromostyrene (55 mg, 0.30 mmol) with **II-14** (53 mg, 0.25 mmol). This procedure afforded 58.4 mg (74%) of the title compound as a colorless oil and as a single diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38 (m, 1 H), 7.25–7.14 (m, 3 H), 5.56 (s, 1 H), 4.96 (s, 1 H), 4.48 (s, 1 H), 3.75–3.68 (m, 1 H), 3.39–3.32 (m, 1), 3.23–3.04 (m, 2 H), 2.07–1.97 (m, 1 H), 1.92–1.86 (m, 2 H), 1.85–1.77 (m, 1 H), 1.70–1.64 (m, 1 H), 1.44 (s, 9 H), 1.29–1.20 (m, 1 H), 0.87–0.77 (m, 1 H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 155.9, 150.4, 149.8, 142.1, 128.6, 126.6, 124.5, 119.6, 105.5, 79.0, 50.3, 48.5, 41.4, 40.3, 33.0, 31.9, 30.3, 28.4; IR (film) 1699, 1636 cm^{-1}. MS (ESI): 313.2036 (313.2042 calculated for $C_{20}H_{27}NO_2$, M + Na^+).

The stereochemistry of the above compound was determined by ^1H NMR nOe analysis of the product as shown below.



IV-39

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[1] Reproduced in part with permission from Beaudoin Bertrand, M.; Wolfe, J. P. "Palladium-Catalyzed Synthesis of Cyclopentane-Fused Benzocyclobutenes via Tandem Directed Carbopalladation/C-H Bond Functionalization" *Org. Lett.* **2007**, *9*, 3073–3075. © 2007 American Chemical Society.

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[4] This proposed structure of **IV-2** was confirmed by X-ray crystallography. See experimental section for details.

[5] For Pd-catalyzed reactions of aryl bromides with norbornene and related bicyclo[2.2.n]alkenes that afford benzocyclobutene products, see: (a) Catellani, M.; Chiusoli, G. P.; Ricotti, S. *J. Organomet. Chem.* **1985**, *296*, C11–C15. (b) Catellani, M.; Chiusoli, G. P.; Ricotti, S.; Sabini, F. *Gazz. Chim. Ital.* **1985**, *115*, 685–689. (c) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769–772.

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[8] Products **IV-11–IV-13** were identified by comparison with similar compounds reported in previous reports from our laboratory. See references 2b and 2c.

[9] The remainder of the mixture consisted of 5% *N*-arylated substrate and 8% of unidentified products.

[10] There are no examples of a directed Heck reaction on a cyclohexene system. Few examples of Heck reactions on cyclohexene derivatives have been reported in the literature. For a recent example under similar reaction conditions, see: Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 1221–1225.

[11] *Amino* complex refers to coordination of the neutral carbamate, whereas *amido* complex refers to coordination of the deprotonated, anionic carbamate. For discussion of kinetic and thermodynamic effects in amido complex formation, see: a) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemiere, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010–6017. b) Driver, M. S.; Hartwig, J. F. *Organometallics* **1997**, *16*, 5706–5715.

[12] When NaO*t*-Bu is employed as base, the amido complex could also be generated via reaction of **II-14** with deprotonated carbamate, or through reaction of the carbamate with a $L_nPd(Ar)(O$*t*-Bu) complex. See: Shekhar, S.; Hartwig, J. F *Organometallics* **2007**, *26*, 340–351.

[13] For early examples, see: a) Kasahara, A.; Izumi, T.; Takeda, T.; Imamura, H. *B. Chem. Soc. Jpn.* **1974**, *47*, 183–185. b) Andersson, C. –M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757–5761.

[14] For a recent review see: Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783–792.

[15] For recent reviews, see: a) Campeau, L. –C.; Fagnou, K. *Chem. Commun.* **2006**, 1253–1264. b) Catellani, M. *Synlett* **2003**, 298–313.

[16] For tandem intermolecular carbopalladation/C–H functionalization processes involving alkenylpalladium intermediates, see: a) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927–4930. b) Furuta, T.; Asakawa, T.; Iinuma, M.; Fujii, S.; Tanaka, K.; Kan, T. *Chem. Commun.* **2006**, 3648–3650.

[17] a) Campora, J.; Gutierrez-Puebla, E.; Lopez, J. A.; Monge, A.; Palma, P.; del Rio, D.; Carmona, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3641–3644. b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119–122.

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[21] Emrich, D. E.; Larock, R. C. *J. Organomet. Chem.* **2004**, *689*, 3756–3766.

[22] Bertrand, M. B.; Wolfe, J. P. *Tetrahedron*, **2005**, *61*, 6447–6459.

[23] Made by Joshua E. Ney.

[24] Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. I*, **1989**, 979–984.

[25] Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761–1764.

[26] Kessler, A.; Coleman, C. M.; Charoenying, P.; O'Shea, D. F. *J. Org. Chem.* **2004**, *69*, 7836–7846.

[27] Bertrand, M. B.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457–460.

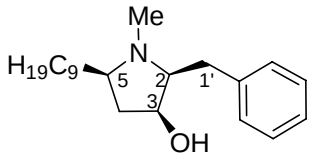
Chapter V

Stereoselective Synthesis of Preussin via Pd-Catalyzed Carboamination Reaction[1]

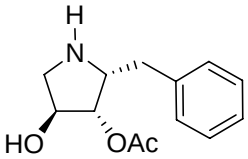
With the aim of demonstrating an application of the carboamination methodology described in Chapter II, the synthesis of an alkaloid natural product alkaloid was undertaken. Preussin (**V-1**), a 2-benzyl pyrrolidine derivative, was chosen as a target to accomplish this task. In this chapter our two routes for the synthesis of preussin and analogs are described.

Background

The natural product preussin (**V-1**) was first isolated in 1988 by Schwartz and coworkers from the fermentation extracts of *Preussia sp*. and *Aspergillus ochraceus* (Figure 6).[2] Initial screens revealed that this compound had significant antifungal activity,[2,3] and more recent work has demonstrated that preussin induces apoptosis in a number of human cancer cell lines and is a potent (IC_{50} = 500 nm) inhibitor of cyclin-E kinase.[4] Preussin has also shown antiviral activity, and is believed to inhibit –1 ribosomal frameshifting of RNA-based viruses.[5] Interestingly, all eight stereoisomers of preussin exhibit biological activity.[6]



Preussin (**V-1**)



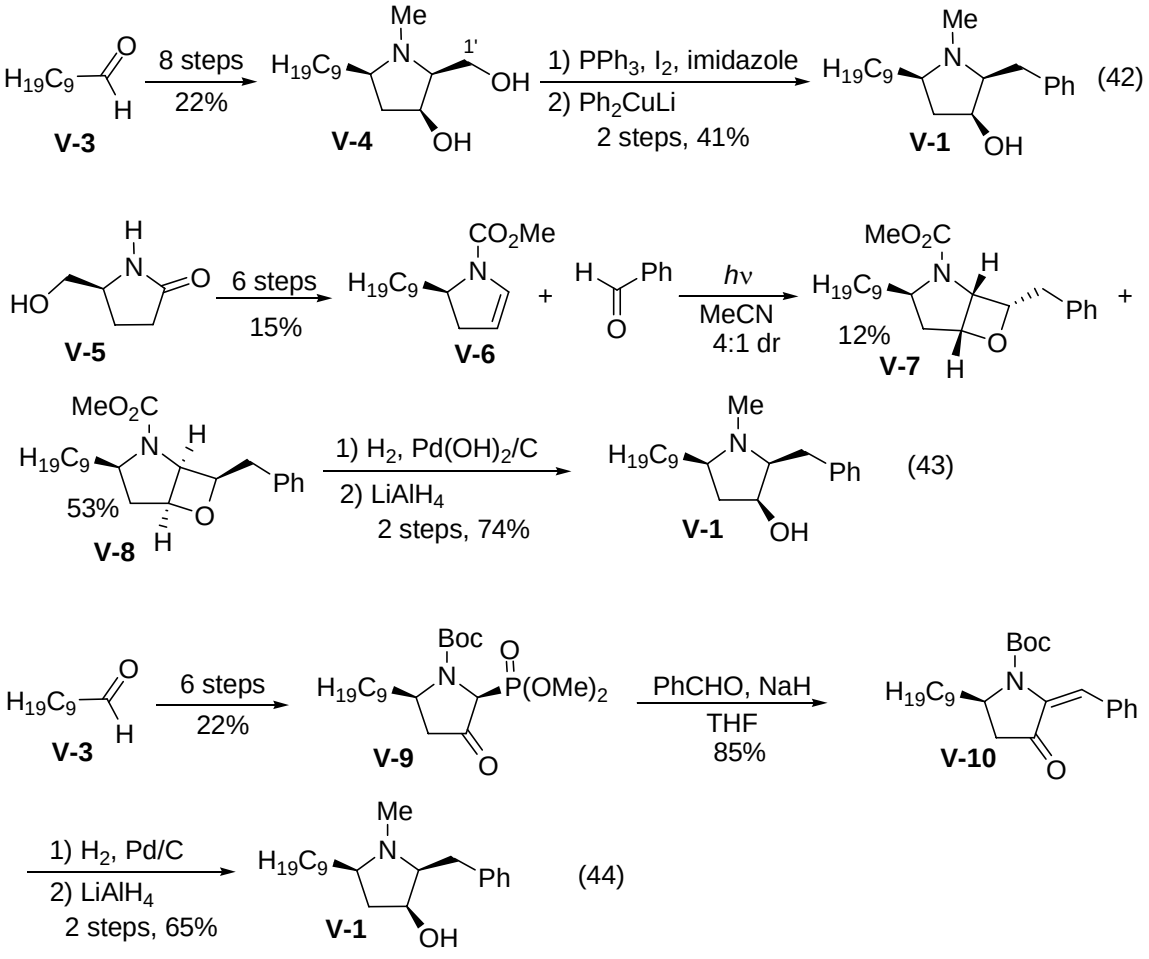
Anisomycin (**V-2**)

Figure 6. Preussin and Anisomycin

Owing to its interesting biological properties, preussin has been a popular target for total synthesis, and has been prepared via 23 different routes ranging from five steps to over 23 steps.[7,8,9,10] We felt that the majority of these routes were limited in that the synthetic sequences were not easily amenable to the preparation of analogs. In particular, introduction of the C5 alkyl side-chain is generally accomplished by addition of the corresponding organometallic reagent to an electrophilic site[8] towards the beginning of the sequence.[11] Additionally, a large majority of these syntheses employ phenylalanine as the source of the C1'-phenyl group, and most other routes also install this group early in the synthetic sequence.[7] Three strategies allow installation of the aryl moiety within 1–3 steps of the final target. As shown in Scheme 19, equation 42, Davis generated the C1'-phenyl group as the final step in his asymmetric synthesis of preussin via reaction of lithium diphenyl cuprate with a pyrrolidinylmethyl iodide (40% yield, single diastereomer; 10 steps total, 9% overall yield).[10c] In the second example presented in equation 43, Bach employed a Paternò-Büchi reaction of benzaldehyde with dihydropyrrole **V-6** (4:1 dr, 53% yield after separation of diastereomers) followed by a two-step deprotection sequence to generate the C1'-phenyl substituent (39% yield over 3 steps; 9 steps total, 11% overall yield).[12] More recently, Davis and coworkers described an asymmetric synthesis of Preussin where the aromatic portion is introduced via a

Horner-Wadsworth-Emmons reaction between phosphonate **V-9** and benzaldehyde (85% yield, eq 44).[10a] This strategy allowed the authors to synthesize a *p*-methoxy aryl analog of preussin by using *p*-anisaldehyde in this key transformation (70% yield). The final two steps of the synthesis involved hydrogenation and $LiAlH_4$ reduction of enone **V-10** (55% over three steps; 9 steps total, 28% overall yield).

Scheme 19. Preussin Syntheses



Although the three strategies described above do effect installation of the aryl

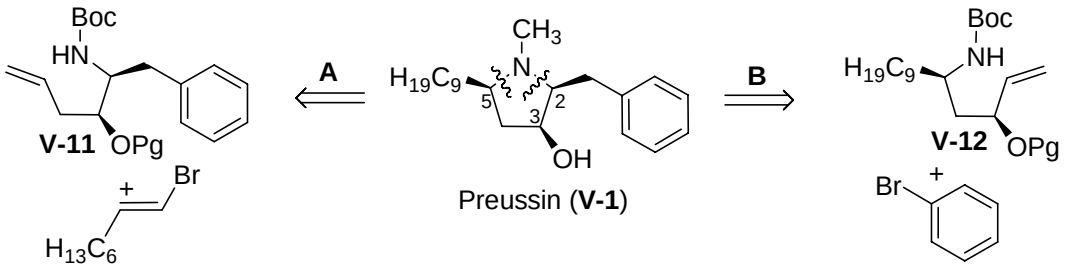
group towards the end of the synthetic sequence, they are limited by the need for highly reactive reagents (e.g. $LiAlH_4$ or aryllithium reagents) in the final steps that limit functional group tolerance. A concise approach to preussin that involves the installation of the alkyl side-chain or aryl group near the end of the synthetic route under mild conditions would be of great value, particularly if the alkyl group or arene could be incorporated in a manner that would permit synthesis of functionalized and/or heteroaryl analogs from readily available precursors.

Due to the limitations of existing synthetic routes, very little work has been conducted on the synthesis and study of preussin analogs.[13] Schaumann[14] and Bach[15] have reported the synthesis of analogs where the C5 alkyl chain was replaced with a (*Z*)-non-1-enyl group or a benzyl group, but the testing of these compounds in biological assays was not reported. Other than the *p*-methoxyphenyl analog reported recently by Davis,[10a] no aryl analogs of preussin have been prepared that are modified on the aromatic ring. However, limited studies on the effect of arene substitution on the activity of the related alkaloid anisomycin (**V-2**) have been performed. These studies demonstrated that the nature of the C1' aryl group has a profound effect on biological activity.[16,17] For example, an anisomycin analog bearing a phenyl group in place of the *p*-methoxyphenyl moiety showed 40-fold less cytotoxic potency than **V-2** against a human KB cell line.[17] For these reasons we felt that a short synthetic route to preussin that would allow facile modification of the alkyl side-chain or arene moiety would be of significant biological interest.

Synthetic Studies

We envisioned that the trisubstituted pyrrolidine alkaloid preussin (**V-1**) could be potentially generated via two different carboamination disconnections: route **A** and route **B** (Scheme 20). Route **A** would involve coupling of a 1,2-amino alcohol derivative (**V-11**) with (*E*)-1-bromooct-1-ene. Route **B**, on the other hand, would involve coupling of a 1,3-amino alcohol derivative (**V-12**) with bromobenzene.

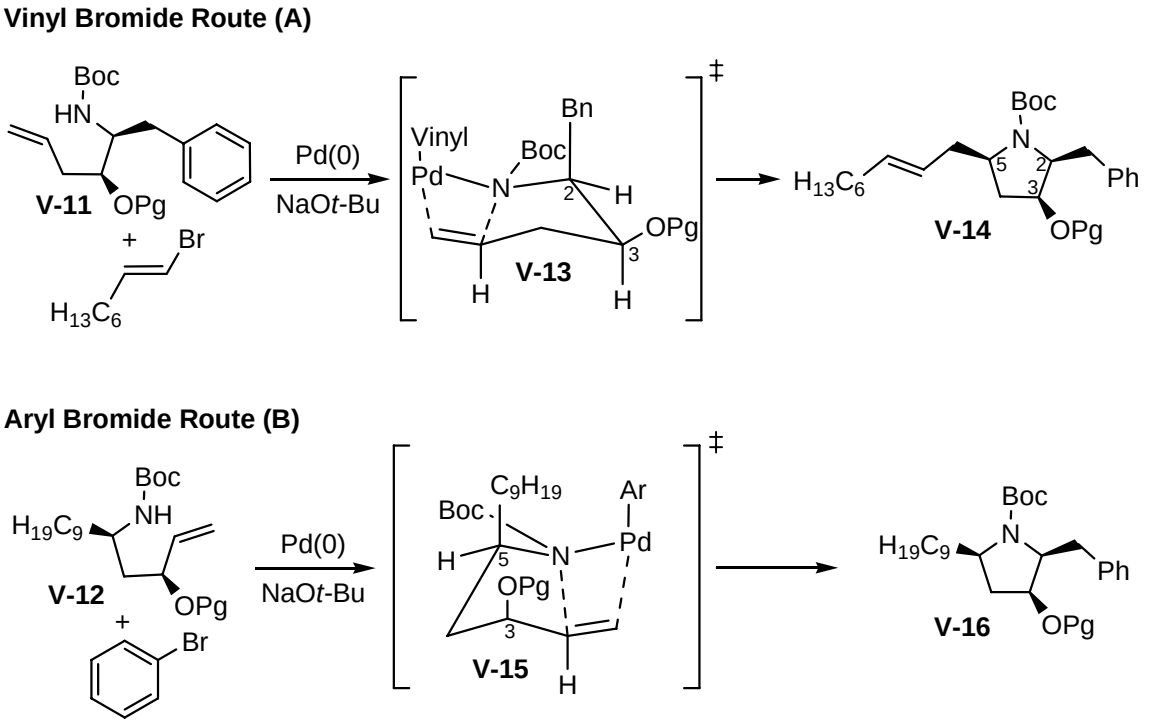
Scheme 20. Preussin Synthetic Strategies



The key steps proposed for the synthesis of trisubstituted pyrrolidines **V-14** and **V-16** would challenge our previously developed methodology as well as our proposed stereochemical model (Scheme 21). In the vinyl bromide route (**A**), analysis of transition state model **V-13** for the formation of the required 2,5-*cis* pyrrolidine **V-14** revealed a O-Pg substituent at C3 lying in the pseudoequatorial position. The effects of this polar side chain on the cyclization yield and selectivity were unknown at the time of our study.[18] In the aryl bromide route (**B**), analysis of transition state **V-15** required to afford the desired 2,5-*cis* pyrrolidine product **V-16** revealed an O-Pg at C3 that would lie in the pseudoaxial position. It is possible that this O-Pg substituent at C3 and the alkyl side chain at C5 would suffer from unfavorable 1,3-diaxial interactions,[19] leading to diminished yield

and/or selectivity for the key reaction. Thus, we opted to start our synthetic studies with the vinyl bromide route (**A**).

Scheme 21. Stereochemical Analysis

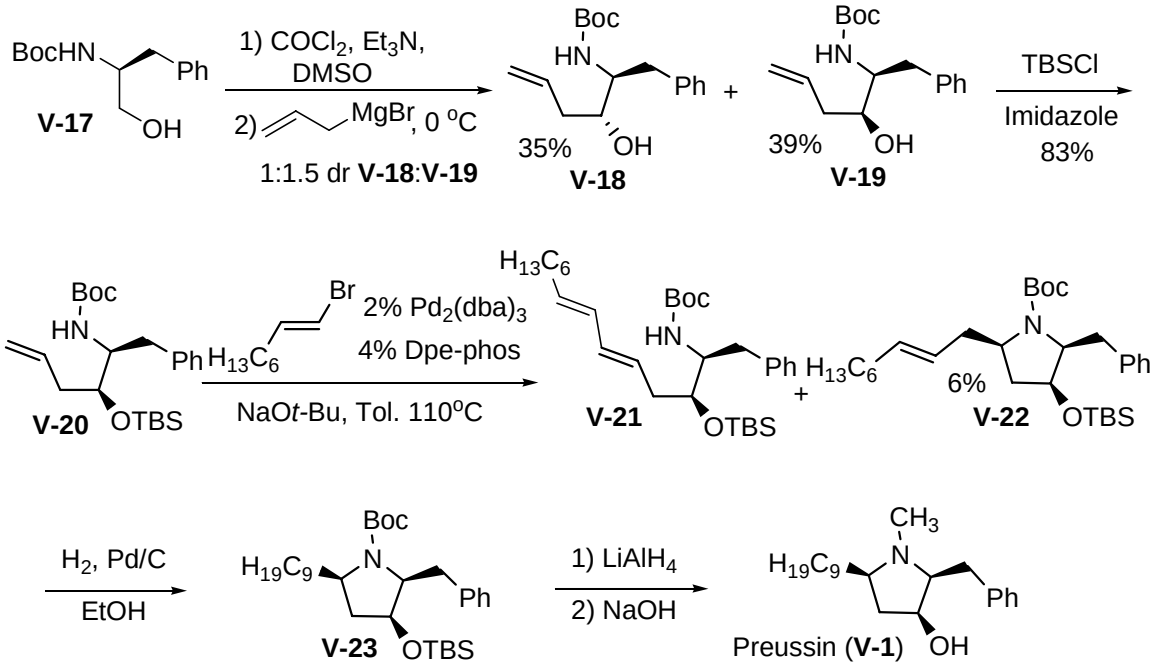


Vinyl Bromide Route (A)

Our synthetic plan involved a five-step sequence to preussin (Scheme 22), which would be equal in length to the shortest reported synthesis of the natural product.[20] Additionally, it would enable the installation of various alkyl side chains at C5 two steps from the end of the sequence, which would permit the facile construction of a number of preussin analogs. Following a literature procedure,[21] oxidation of commercially available (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenyl-1-propanol (**V-17**) followed by *in situ* addition of allyl MgBr afforded a 1.5:1 mixture of *syn:anti* 1,2-amino alcohol isomers **V-**

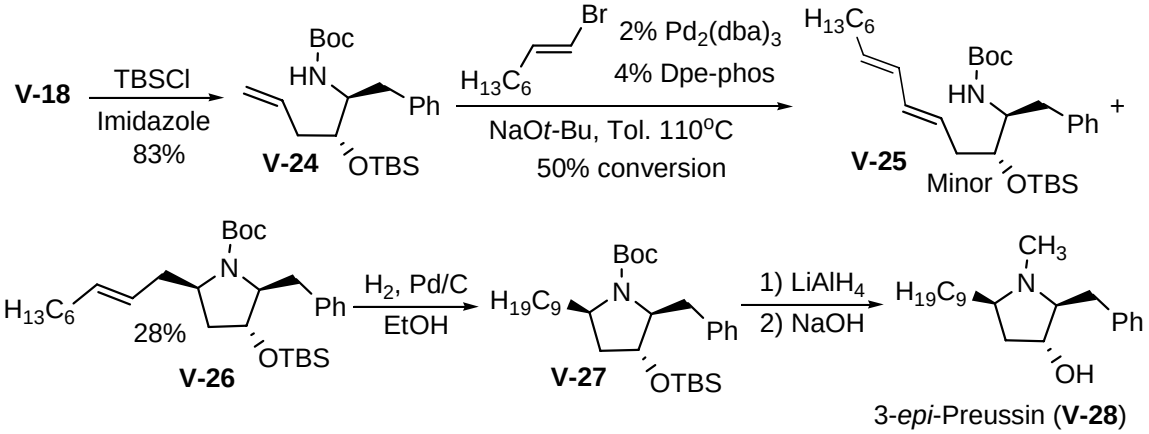
18:**V-19** that were separable by column chromatography. Protection of **V-19** with TBS-Cl afforded substrate **V-20** that was used in the key cyclization. Under optimized reaction conditions,[22] the Pd-catalyzed carboamination reaction of **V-20** afforded only 6% of **V-22** as a single diastereomer. The majority of the starting material was converted to Heck-type side-product **V-21**. Other reaction parameters that could influence the carboamination reaction such as solvent and base were investigated, but none provided significant improvements in the key reaction. Pyrrolidine **V-22** was then converted in two steps to preussin (**V-1**) via hydrogenation of the internal olefin and reduction of the Boc protecting group with concomitant TBS deprotection.[21] The ^{1}H NMR spectra obtained for **V-1** matched the literature data available for preussin.[15] Thus, the key reaction was found to be selective for the formation of 2,5-*cis* pyrrolidine **V-22**, albeit in low yield.

Scheme 22. Synthesis of Preussin via Coupling with a Vinyl Bromide (Route **A**)



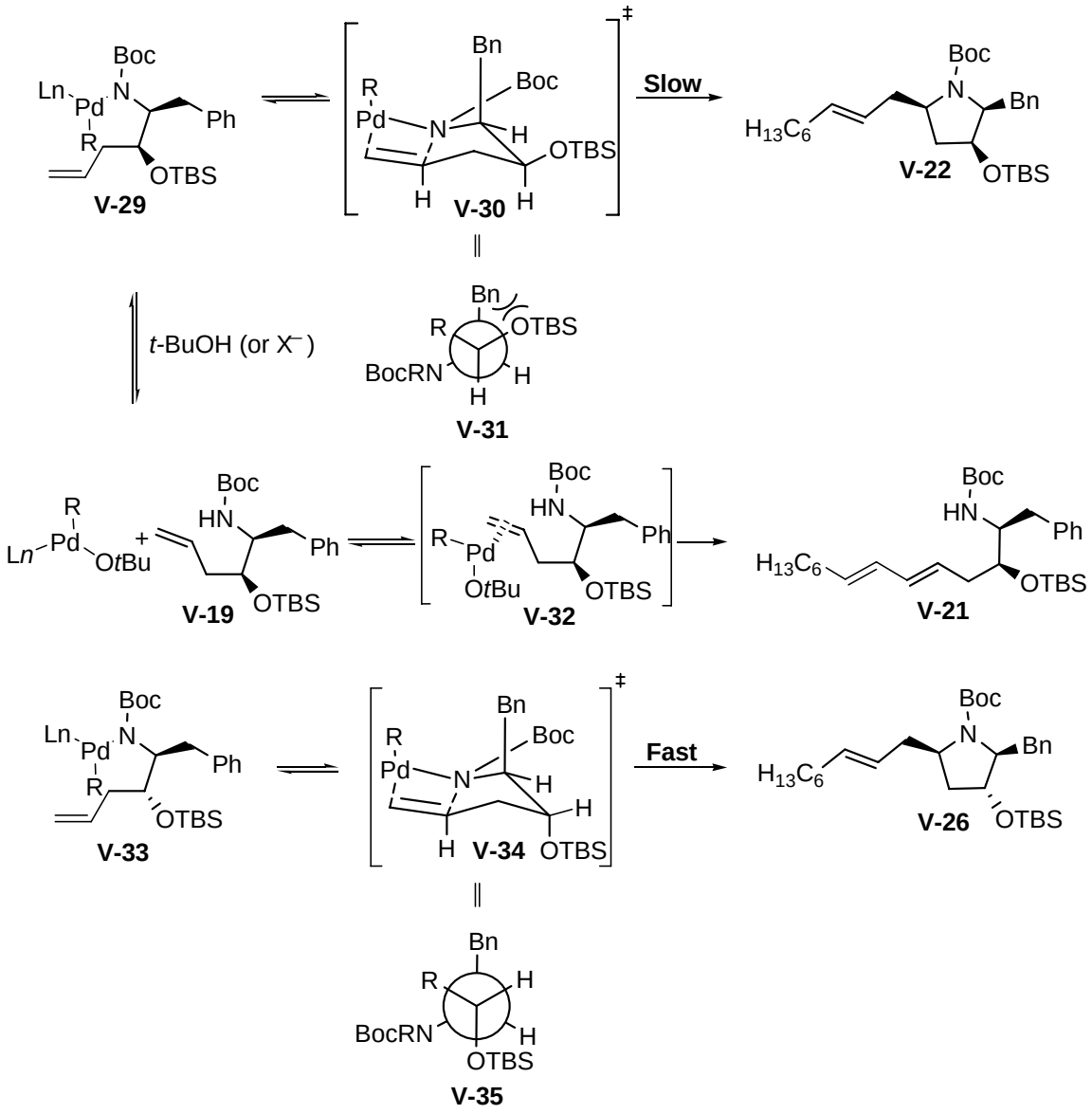
With the *anti* 1,2-aminoalcohol substrate **V-18** in hand, we were interested in examining the outcome of its cyclization, as this would lead to the generation of a biologically active stereoisomer of the natural product, and would also indicate the importance of the C3 stereochemical configuration on the yield and selectivity of the carboamination. Interestingly, the use of *anti* 1,2-aminoalcohol substrate **V-24** in the key cyclization step afforded product **V-26** in 28% isolated yield, although the reaction proceeded to only ~50% conversion (Scheme 23).[23] The minor product observed resulted from a Heck-type side-reaction (**V-25**).[24] The pyrrolidine product **V-26** was then converted in two steps (hydrogenation and $LiAlH_4$ reduction) to 3-*epi*-preussin (**V-28**), and the ^1H NMR spectra obtained matched the literature data.[6,9d] Thus, the key reaction of **V-24** was found to be highly selective for the formation of the 2,5-*cis* pyrrolidine isomer. Additionally, a much higher yield of the pyrrolidine **V-26** was obtained (28% yield, 50% conversion), which is in sharp contrast to the cyclization of **V-20** where pyrrolidine **V-22** was obtained in only 6% yield.

Scheme 23. Synthesis of 3-*epi*-Preussin via Coupling with a Vinyl Bromide (Route **A**)



The different product distribution observed in the reaction of *syn* substrate **V-20** and *anti* substrate **V-24** could be due to differences in the relative rates of aminopalladation versus Heck arylation (Scheme 24). Transition state analysis for the cyclization of *syn* substrate **V-30** via the Newman projection **V-31** reveals a gauche interaction between the pseudoaxial benzyl group and the pseudoequatorial TBS-protected oxygen, which would result in a higher energy transition state **V-30** and thus a slower cyclization. Conversely, transition state analysis of the *anti* substrate **V-34** reveals both Bn and OTBS groups in a pseudoaxial position, and a Newman projection of this configuration (**V-35**) reveals a *gauche* interaction between the OTBS group and *N*-Boc group. However, since a higher ratio of pyrrolidine **V-26** to Heck product was obtained with **V-24**, it is believed that this *gauche* interaction was not as severe as in **V-31** and rendered olefin insertion faster for this particular stereoisomer. This hypothesis implied that reducing the steric bulk on the oxygen substituent (**V-31**) could facilitate the cyclization of *syn* substrate **V-20**.

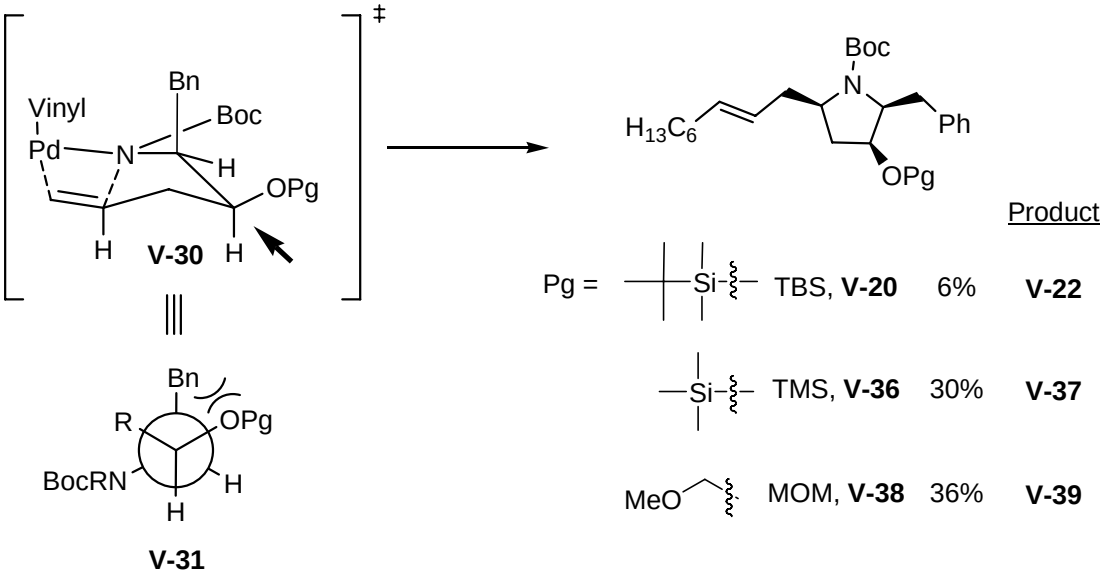
Scheme 24. Possible Origin of Heck Side-Products



This idea was tested by studying the carboamination of substrates containing various oxygen protecting groups TBS, TMS and MOM (**V-20**, **V-36** and **V-38**, Scheme 25). The trend observed was consistent with the hypothesis: the smallest oxygen protecting group (**V-38**) provided the highest yield of **V-39**. Although this result was encouraging, we were aware that the use of this protecting group would increase the

number of steps to the final target molecule, as an extra deprotection step would be necessary. [25] Additionally, removal of a MOM group often requires harsh acidic conditions incompatible with numerous functional groups.[26] It is important to note that when no protecting groups were used on the substrate, some conversion to a ketone product was observed, presumably via Pd(II)-catalyzed oxidation of the secondary alcohol functionality.[27]

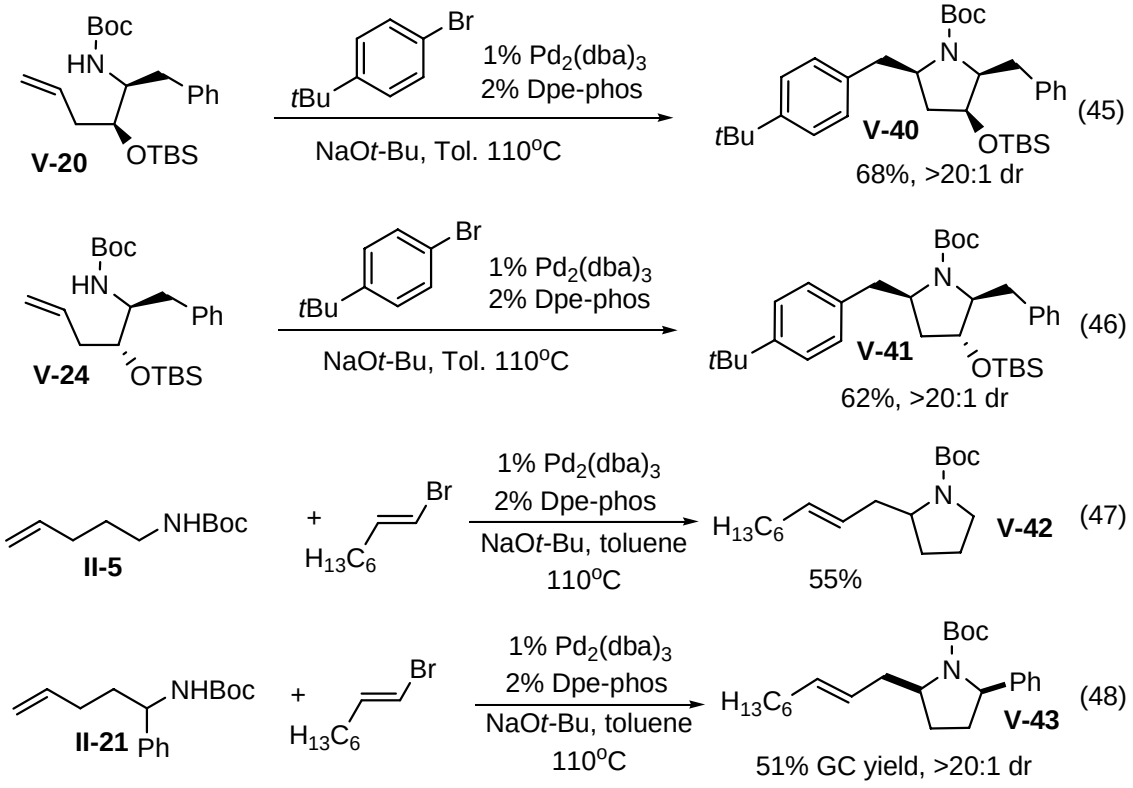
Scheme 25. Oxygen Protecting Group Study



In order to better understand the reasons behind the low yields and different chemoselectivities obtained in the coupling of **V-20** with **V-24**, we examined the reactions of unsaturated amines **V-20**, **V-24**, **II-5** and **II-21** with 4-*t*-butyl bromobenzene and (*E*)-1-bromooct-1-ene (Scheme 26). As shown in eqs 45 and 46, treatment of substrates **V-20** and **V-24** with 4-*t*-butyl bromobenzene and NaO*t*-Bu in the presence of the $Pd_2(dba)_3$/Dpe-phos catalysts afforded moderate to good yields of the pyrrolidine

products **V-40** and **V-41** with excellent diastereoselectivity. Surprisingly, contrary to their reaction with (*E*)-1-bromooct-1-ene, the two substrates **V-20** and **V-24** afforded similar product yields with 4-*t*-butyl bromobenzene. The coupling of (*E*)-1-bromooct-1-ene with less substituted substrates **II-5** and **II-21** provided moderate but comparable yields of the pyrrolidine products **V-42** and **V-43** under the same reaction conditions (eqs 47 and 48). The major side-product observed resulted from *N*-vinylation of the substrates. This side-reaction was previously observed in the reaction of **II-5** and β-bromostyrene under the same condition. Use of dppe as a ligand improved the yield of **II-35** to 75% (Chapter II).[28] Together these results suggested that the low yields originally obtained in the preussin synthesis (Schemes 22 and 23) could be attributed to a combination of two factors: use of a vinyl bromide and the reactant's high degree of substitution. It was more difficult to identify the reason behind the different chemoselectivities that were observed with the use of (*E*)-1-bromooct-1-ene (6% vs 56% yields) but that were not observed with the use of an aryl bromide (yields: 68% and 62%). Such results suggested that the energy of transition states **V-30** and **V-34** in Scheme 24 was closer when R = aryl than when R = vinyl. These results also implied that olefin insertion in the Pd-N bond was in general faster when R = aryl, since higher yields of pyrrolidine products were obtained, although the reasons for this effect are unclear.

Scheme 26. Additional Experiments

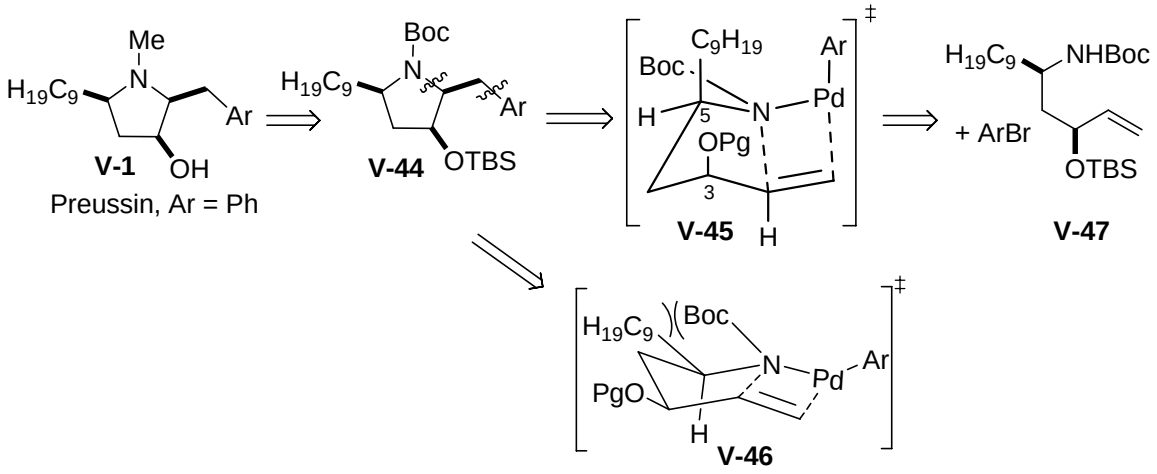


Aryl Bromide Route (B)

Since our first approach to preussin was not satisfying, we decided to investigate the aryl bromide route (**B**) (Scheme 27). The key disconnection in this route is the retrosynthetic cleavage of both the C–N bond and C1'–aryl bond to yield starting amino alcohol **V-47** and aryl bromide. This strategy had two significant implications for the construction of the molecule. It would allow the installation of a variety of different functionalized arenes one step from the end of the sequence, which would permit the facile construction of a number of preussin analogs. It could also allow control of the relative stereochemistry at C2 through use of $A^{(1,3)}$-strain [29] in conjunction with a favorable eclipsed orientation of the Pd–N and alkene C–C bonds during the

stereochemistry determining step of the carboamination reaction to afford 2,5-*cis* pyrrolidine **V-44**. The cyclization would occur through transition state **V-45** in which the C3 O-Pg substituent and C5 alkyl chain are oriented in a pseudoaxial position. Although we favored transition state **V-45** on the basis of minimizing $A^{(1,3)}$-strain, we were concerned that the two axial substituents would suffer from unfavorable 1,3-diaxial interactions[19] thus leading to lower yields and/or selectivity.

Scheme 27. Key Disconnection and Stereocontrol

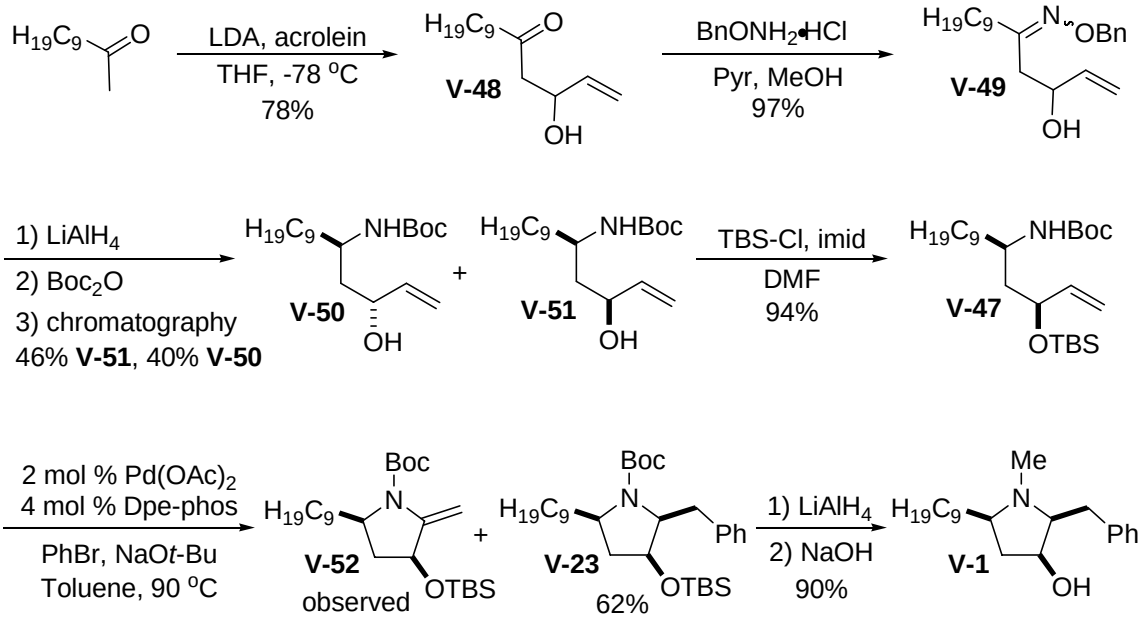


In order to probe the feasibility of the key Pd-catalyzed carboamination reaction, our initial studies focused on the development of a synthesis of (±)-preussin (**V-1**). As outlined in Scheme 28, aldol reaction between commercially available 2-undecanone and acrolein provided keto-alcohol **V-48** in 78% yield. Conversion of **V-48** to the *O*-benzyl oxime **V-49** proceeded smoothly, and was followed by a one-pot sequence of $LiAlH_4$ reduction and Boc-protection to provide an 86% yield of a 1:1.2 mixture of readily separable amino alcohol diastereomers **V-50** and **V-51**. Although stereoselective reductions of β–hydroxy oxime ethers have been previously described,[30] we elected to

employ non-selective conditions to allow access to both *syn*- and *anti*-amino alcohol substrates **V-50** and **V-51** for the Pd-catalyzed cyclization reactions, which would ultimately provide two different biologically active pyrrolidine derivatives (**V-1** and **V-28**).

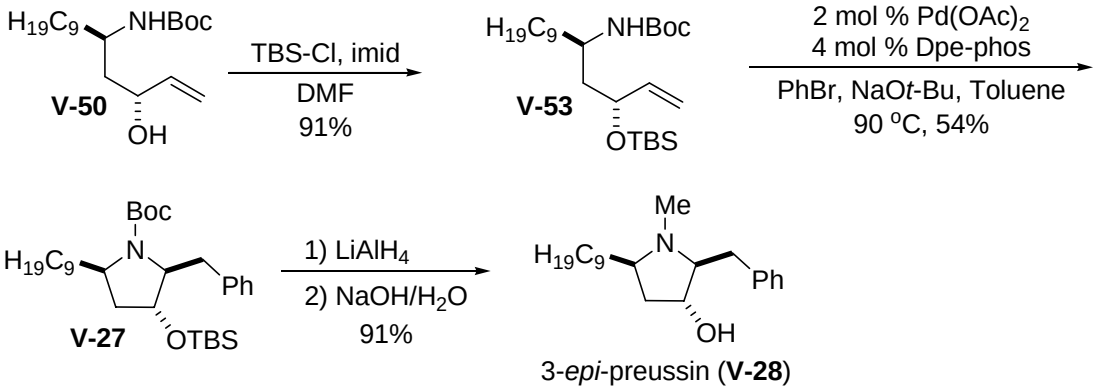
TBS-protection of amino alcohol **V-51** provided **V-47**, the substrate for the key Pd-catalyzed carboamination reaction. In the event, treatment of **V-47** with bromobenzene and NaO*t*-Bu in the presence of catalytic $Pd(OAc)_2$/Dpe-phos provided pyrrolidine **V-23** in 62% isolated yield with >20:1 diastereoselectivity. A major side-product observed was **V-52**, which likely derives from competing β-hydride elimination from intermediate **II-54** (Scheme 10). One-pot reduction and deprotection of **V-23** afforded (±)–Preussin (**V-1**) in 90% yield as a single diastereomer. This six-step sequence proceeded with an overall yield of 15% from 2-undecanone.

Scheme 28. Synthesis of (±)-Preussin



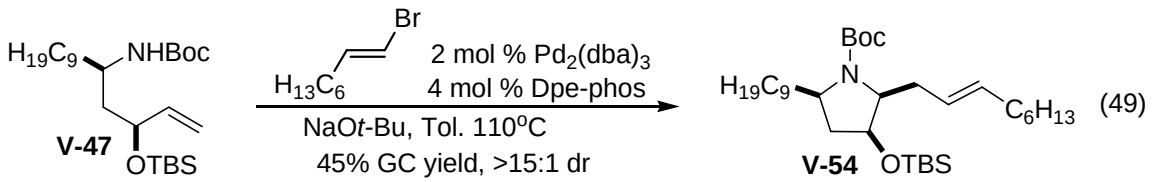
Amino alcohol **V-50** was converted to (±)-3-*epi*-preussin (**V-28**)[9a,c] using a sequence of reactions analogous to that described above (Scheme 29). The stereoselectivity of the Pd-catalyzed cyclization of **V-53** was high, although the chemical yield obtained in the reaction of **V-53** (54%) was slightly lower than that achieved for the reaction of **V-47** (62%). This route provided the desired pyrrolidine **V-28** as a single isomer in an overall yield of 15%. Thus, the strategy described herein provides straightforward access to both racemic preussin diastereomers in comparable yields and stereoselectivities.[31]

Scheme 29. Synthesis of (±)-3-*epi*-Preussin.

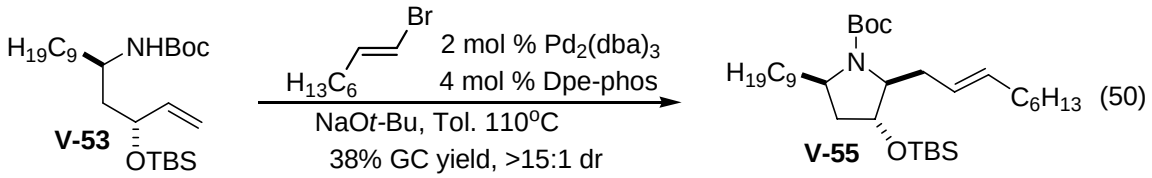


We were encouraged by these results, as our initial stereochemical hypothesis was confirmed (Scheme 27). Additionally, the stereochemistry at C3 did not appear to have an important effect on the yield and selectivity of the key reaction. However, these overall results differ greatly from the vinyl bromide route (**A**) where the cyclization yields where much lower, and a substantial difference in chemoselectivity was observed between the stereoisomeric substrates **V-20** and **V-24**. Interestingly, when substrates **V-**

47 and **V-53** were treated with vinyl bromide (*E*)-1-bromooct-1-ene under the same reaction conditions as with **V-20** and **V-24**, moderate but similar GC yields of products **V-54** and **V-55** were obtained (eqs 8 and 9).[32]



(49)

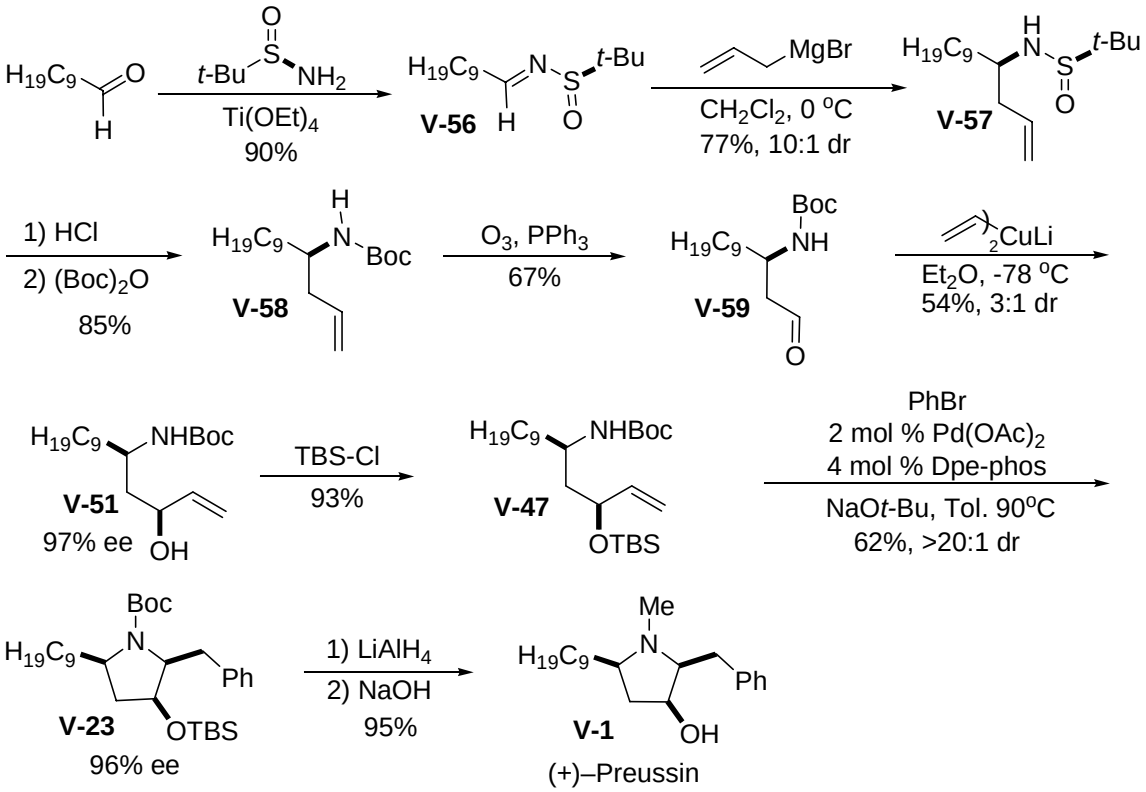


(50)

Having demonstrated the feasibility of the Pd-catalyzed carboamination for the construction of preussin, we turned our attention towards the development of an asymmetric synthesis of the naturally occurring (+)-enantiomer. As shown in Scheme 30, addition of allylmagnesium bromide to enantiopure sulfinylimine **V-56** under Ellman's conditions[33] afforded **V-57**, which was isolated in 77% yield as a single diastereomer upon purification.[34] Cleavage of the chiral auxiliary and protection of the resulting primary amine afforded **V-58** in 85% yield. Ozonolysis of **V-58** (63%) followed by vinylcuprate addition[35] to the resulting β-amino aldehyde **V-59** generated (+)-**V-51** with 3:1 diastereoselectivity; the desired pure *anti*-diastereomer was obtained in 54% yield after chromatographic separation. The remaining three steps proceeded with similar yields and selectivities to those obtained from the racemic route, and provided (+)-

preussin (**V-1**) {$[\alpha]^{23}_D$ +21.2° (*c* 1.0, $CHCl_3$) [lit.[3] $[\alpha]^{25}_D$ +22.0° (*c* 1.0, $CHCl_3$)]} with an overall yield of 12% in nine steps from commercially available decanal.

Scheme 30. Synthesis of (+)-Preussin (**V-1**)

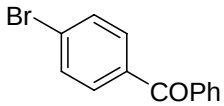
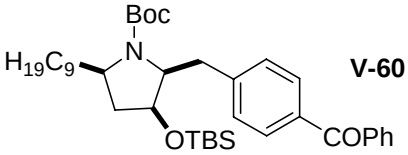
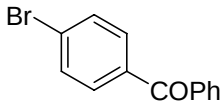
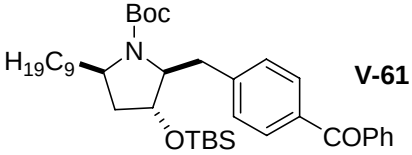
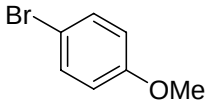
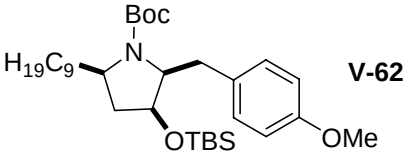
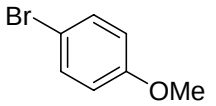
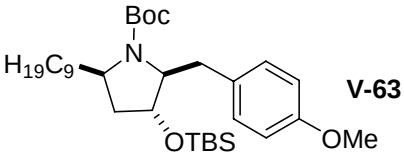
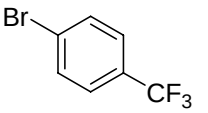
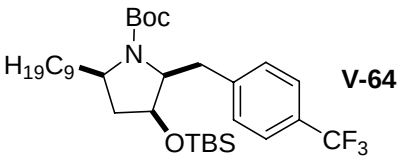
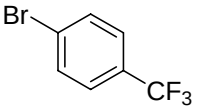
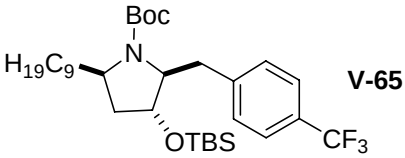


In order to demonstrate the amenability of this strategy toward the synthesis of differentially arylated preussin analogs, Pd-catalyzed reactions of **V-47** and **V-53** were conducted with a variety of different aryl bromide coupling partners. To illustrate the utility of this method for the rapid generation of useful quantities of analogs, the $Pd(OAc)_2$/Dpe-phos catalyst was employed for all substrate combinations. Previous studies indicated that other ligands may provide superior results for certain aryl bromide coupling partners,[28] thus the yields obtained in these transformations were not optimized

on a case-by-case basis. As shown in Tables 13 and 14, the cyclization reactions proceeded in moderate to good yields for a variety of different aryl bromides including substrates that are electron-rich (Table 13, entries 3–4),[36] electron-poor (Table 13, entries 1–2, 5–6 and Table 14, entries 3–6), or sterically hindered (Table 14, entry 2). Several functional groups were tolerated, and heterocyclic aryl bromides could also be employed (Table 14, entries 4–5). In most cases examined, the cyclizations of amino alcohol derivative **V-47** proceeded in higher yield than the analogous reactions of amino alcohol derivative **V-53**. In all cases the reactions proceeded with >20:1 diastereoselectivity as judged by ^{1}H and ^{13}C NMR analysis.

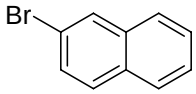
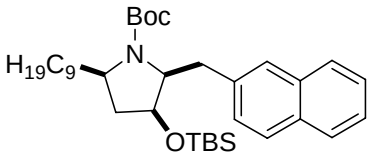
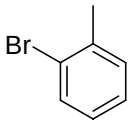
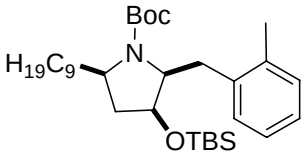
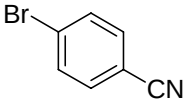
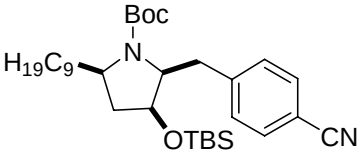
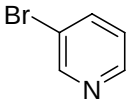
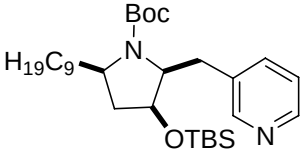
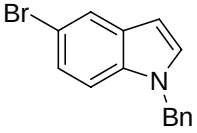
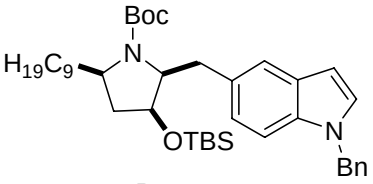
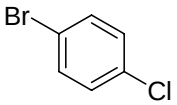
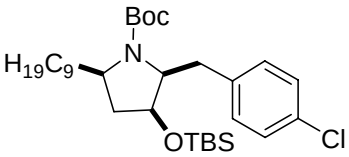
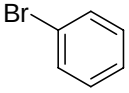
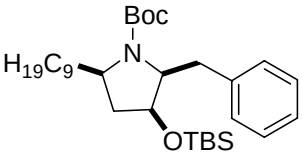
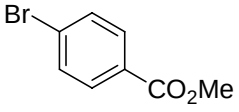
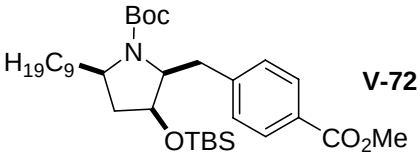
Substrate **V-47** was also efficiently transformed to the corresponding pyrrolidine product using the mild reaction conditions described in Chapter III. As shown in Table 14 (entries 7–8), Pd-catalyzed reactions of **V-47** with bromobenzene or methyl-4-bromobenzoate with Cs_2CO_3 as a base proceeded smoothly to provide preussin intermediate **V-23** and preussin analog **V-72** with excellent diastereoselectivity.

Table 13. Synthesis of *N*-Boc-*O*-TBS-Preussin and *N*-Boc-*O*-TBS-3-*epi*-Preussin Analogs[a]

Entry	Substrate	ArBr	Product	Yield (%)[b]
1	**V-47**		 **V-60**	70
2	**V-53**		 **V-61**	65
3	**V-47**		 **V-62**	52
4	**V-53**		 **V-63**	49
5	**V-47**		 **V-64**	69
6	**V-53**		 **V-65**	52

[a]Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 2.3 equiv NaO*t*-Bu, 2 mol % $Pd(OAc)_2$, 4 mol % Dpephos, toluene, 90 °C. [b]Yield refers to average isolated yield obtained in two or more experiments.

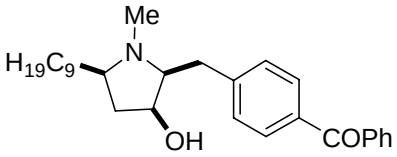
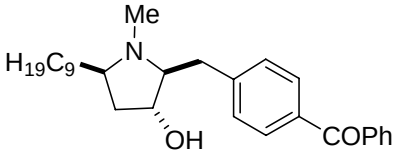
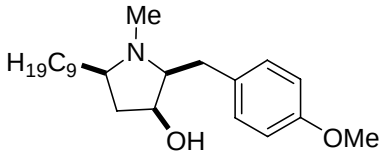
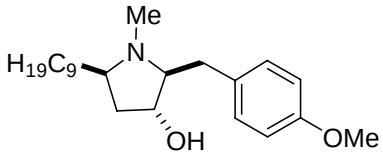
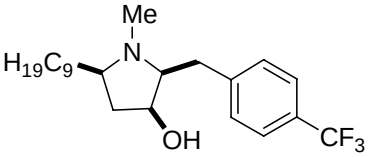
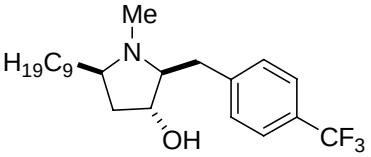
Table 14. Synthesis of *N*-Boc-*O*-TBS-Preussin Analogs[a]

Entry	ArBr	Product		Yield (%)
1			**V-66**	69
2			**V-67**	57
3			**V-68**	62
4			**V-69**	54
5			**V-70**	40
6			**V-71**	70
7			**V-23**	71[c]
8			**V-72**	73[c]

[a]Conditions: 1.0 equiv substrate **V-47**, 1.2 equiv ArBr, 2.3 equiv NaO*t*-Bu, 2 mol % $Pd(OAc)_2$, 4 mol % Dpe-phos, toluene, 90 °C. [b]Yield refers to average isolated yield obtained in two or more experiments. [c]Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 2.3 equiv Cs_2CO_3, 2 mol % $Pd(OAc)_2$, 4 mol % Dpe-phos, dioxane, 100 °C.

To illustrate that the *N*-Boc-*O*-TBS-preussin and *N*-Boc-*O*-TBS-3-*epi*-preussin analogs could be converted to *N*-methyl-3-hydroxy-2-(arylmethyl)pyrrolidines that are closely related to the natural product, the products shown in Table 13 were deprotected in a 1–2 step sequence. As shown in Table 15, deprotection was effected using $LiAlH_4$ followed by treatment with aqueous base or TBAF for products bearing unreactive aromatic functionality. Alternatively, deprotection was also achieved through one-pot Boc-cleavage and reductive amination with formic acid/formaldehyde followed by treatment with TBAF. The latter conditions tolerate functional groups (e.g., ketones, trifluoromethyl substituents) that would be reduced by $LiAlH_4$. Both deprotection protocols provided the desired products in excellent yields.

Table 15. Deprotection of *N*-Boc-*O*-TBS-Preussin and *N*-Boc-*O*-TBS-3-*epi*-Preussin Analogs[a]

Entry	Substrate	Method	Product		Yield (%)[b]
1	**V-60**	B		**V-73**	83
2	**V-61**	B		**V-74**	84
3	**V-62**	A		**V-75**	85
4	**V-63**	A		**V-76**	89
5	**V-64**	B		**V-77**	80
6	**V-65**	B		**V-78**	81

[a]Conditions: Method A: i) $LiAlH_4$, THF, 60 °C; ii) H_2O or TBAF. Method B: i) HCO_2H, HCHO; ii) TBAF, THF. [b]Yield refers to average isolated yield obtained in two or more experiments.

Conclusion

In conclusion, application of the carboamination methodology to the synthesis of preussin was achieved. Two major synthetic routes were studied and ultimately one was

successful. A concise, stereoselective route to (+)-preussin, (±)-preussin and (±)-3-*epi*-preussin was developed. This route features a new strategy for the synthesis of 2-benzylpyrrolidine alkaloids that allows the construction of both the C-N and the C1'-Ar bonds in a single step near the end of the synthetic sequence. It also allows the facile synthesis of differentially arylated preussin analogs, and provides straightforward access to derivatives that cannot be easily and rapidly prepared using previously developed routes. This strategy is potentially applicable to the synthesis of other pyrrolidine alkaloid natural products, and further studies in this area are presented in Chapter VI.

Experimental section

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. Palladium acetate 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 except (*E*)-1-bromooct-1-ene,[37] which were prepared according to published procedures. Toluene, ether, and THF were purified using a GlassContour solvent purification system. Ratios of regioisomers and/or diastereomers were determined by either ^{1}H NMR or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, and either capillary GC (known compounds), combustion analysis (new compounds). The yields reported in the supporting information describe the result of a single experiment, whereas the yields

reported in Tables 13–15 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 13–15.

Vinyl Bromide Route (A) (Schemes 22, 23, 25 and 26)

(2*S*,3*R*)-*tert*-Butyl-3-hydroxy-1-phenylhex-5-en-2-ylcarbamate (V-18).[21] Following a literature procedure, this product was obtained as a white solid (m.p.: 137–139 ^{o}C, lit m.p.: 136–138 ^{o}C) and was the second diastereoisomer to elute from purification by column chromatography (10% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 3 H), 7.23–7.20 (m, 2 H), 5.90–5.82 (m, 1 H), 5.20–5.16 (m, 2 H), 4.58 (s, br, 1 H), 3.82 (s, 1 H), 3.72 (s, 1 H), 3.00–2.91 (m, 1 H), 2.84–2.78 (m, 1 H), 2.60 (s, 1 H), 2.40–2.36 (m, 1 H), 2.28–2.23 (m, 1 H), 1.35 (s, 9 H).

(2*S*,3*S*)-*tert*-Butyl-3-hydroxy-1-phenylhex-5-en-2-ylcarbamate (V-19).[21] Following a literature procedure, this product was obtained as an oil and was the first diastereoisomer to elute from purification by column chromatography (10% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5 H), 7.81–5.70 (m, 1 H), 5.14–5.10 (m, 2 H), 4.87–4.84 (m, 1 H), 3.79–3.74 (m, 1 H), 3.61–3.57 (m, 1 H), 2.96–2.85 (m, 2 H), 2.28–2.22 (m, 2 H), 2.05–1.92 (m, 1 H), 1.44–1.28 (m, 9 H).

(2*S*,3*S*)-*tert*-Butyl-3-(tert-butyldimethylsilyloxy)-1-phenylhex-5-en-2-ylcarbamate (V-20). A flame-dried flask was cooled under a steam of nitrogen and charged with **V-19** (1.5 g, 5.0 mmol), dimethylformamide (30 mL), imidazole (463 mg,

6.8 mmol) and TBS-Cl (820 mg, 5.4 mmol). The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 24 h). The reaction mixture was diluted with water (20 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 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 using 5% ethyl acetate/hexanes as the eluent to afford 1.5 g (74%) of the title compound as a colorless oil. This compound was found to exist as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (m, 2 H), 7.22–7.13 (m, 3 H), 5.74–5.60 (m, 1 H), 5.08–4.98 (m, 2 H), 4.78–4.72 (m, 0.66 H), 4.66–4.59 (m, 0.33 H), 3.96–3.87 (m, 0.66 H), 3.80–3.72 (m, 0.33 H), 3.70–3.64 (m, 1 H), 2.79–2.74 (m, 1.33 H), 2.72–2.66 (m, 0.66 H), 2.39–2.24 (m, 1 H), 2.23–2.14 (m, 1 H), 1.37 (s, 6 H), 1.21 (s, 3 H), 0.95 (s, 9 H), 0.10 (d, J = 11.0 Hz, 6 H).

(*E*)-(2*S*,3*S*,5*R*)-*tert*-Butyl-2-benzyl-3-(*tert*-butyldimethylsilyloxy)-5-(non-2-enyl)pyrrolidine-1-carboxylate (V-22). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **V-20** (102 mg, 0.25 mmol), $Pd_2(dba)_3$ (4.8 mg, 0.005 mmol, 2 mol %), Dpe-phos (5.6 mg, 0.01 mmol, 4 mol %), NaO*t*-Bu (30 mg, 0.30 mmol) and (*E*)-1-bromooct-1-ene (60 mg, 0.30 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring for 16 hours until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added.

The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 2.5% ethyl/hexanes as the eluent to afford 7.7 mg (6%) of the title compound as a colorless oil in ~60% purity. This compound was identified by comparison of ^{1}H NMR data to that reported for the known pyrrolidine compound **V-23**.[38] Also isolated from this reaction was Heck product **V-21**; data are provided below.

(*E*)-(2*S*,3*S*)-*tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-1-phenyldodec-5-en-2-ylcarbamate (V-21). The title compound was isolated as an oil in ~80% purity and was found to exist as a 1:1 mixture of rotamers. The data is for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.11 (m, 5 H), 6.05–5.91 (m, 1 H), 5.71–5.30 (m, 2 H), 4.77–4.57 (m, 1 H), 3.96–3.84 (m, 1 H), 3.79–3.62 (m, 1 H), 2.81–2.65 (m, 2 H), 2.38–2.12 (m, 1.5 H), 2.10–1.98 (m, 1.5 H), 1.43–1.09 (m, 21 H), 0.99–0.79 (m, 9 H), 0.16–-0.02 (m, 6 H).

(2*S*,3*S*,5*R*)–2-Benzyl-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-23).[38] A flame-dried flask was cooled under a stream of nitrogen and charged with 5% Pd/C (33 mg) followed by **V-22** (7.7 mg, 0.015 mmol) and EtOH (1 mL). The resulting mixture was purged with H_2 and, a balloon filled with H_2 was attached. The reaction was stirred at rt until the starting material was consumed as judged by crude ^{1}H NMR analysis (ca. 2 h). The reaction mixture was then filtered through a pad of celite/sand and the pad was washed with EtOH (3 x 5 mL). The combined organics were concentrated *in vacuo*. The title compound was obtained in

~60% purity and was identified by comparison of ^{1}H NMR data to that reported of known compound **V-23**. This mixture was used in the following transformation without further purification.

(±)–Preussin (V-1).[15] A flame-dried flask was cooled under a stream of nitrogen and charged with **V-23** (16 mg, 0.031 mmol) and tetrahydrofuran (4 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (1 mL, 0.1 mmol, 1 M in tetrahydrofuran) was added dropwise. The resulting mixture was heated to reflux with stirring until the starting material was consumed as judged by TLC analysis (ca. 15h). The reaction mixture was cooled to 0 °C, slowly quenched with water (0.2 mL) and diluted with diethyl ether (5 mL). Aqueous NaOH (0.2 mL, 10 M) and water (0.2 mL) were added sequentially and an insoluble white precipitate formed. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil obtained contained ~60% of the title compound that was identified by comparison of ^{1}H NMR data with ^{1}H NMR data previously reported in the literature.

(2*S*,3*R*)-*tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-1-phenylhex-5-en-2-ylcarbamate (V-24). A flame-dried flask was cooled under a stream of nitrogen and charged with **V-18** (400 mg, 1.4 mmol), dimethylformamide (10 mL), imidazole (191 mg, 2.8 mmol) and TBS-Cl (338 mg, 2.2 mmol). The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 24 h). The reaction mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The layers

were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% → 10% ethyl acetate/hexanes as the eluent to afford 460 mg (83%) of the title compound as a colorless oil. This compound was found to exist as a 2:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.23 (m, 2 H), 7.21–7.14 (m, 3 H), 5.88–5.78 (m, 1 H), 5.16–5.06 (m, 2 H), 4.56–4.43 (m, 1 H), 3.98–3.91 (m, 1 H), 3.90–3.83 (m, 1 H), 2.96 (dd, *J* = 4.4, 14.4 Hz, 1 H), 2.65–2.55 (m, 1 H), 2.38–2.24 (m, 2 H), 1.37–1.15 (m, 9 H), 0.92 (s, 9 H), 0.07 (s, 6 H).

(E)-(2*S*,3*R*,5*R*)-*tert*-Butyl 2-benzyl-3-(tert-butyldimethylsilyloxy)-5-(non-2-enyl)pyrrolidine-1-carboxylate (V-26). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **V-24** (128 mg, 0.32 mmol), $Pd_2(dba)_3$ (7.4 mg, 0.008 mmol, 2.5 mol %), Dpe-phos (9 mg, 0.016 mmol, 5 mol %), NaO*t*-Bu (37 mg, 0.384 mmol) and (*E*)-1-bromooct-1-ene (74 mg, 0.384 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring for 19 h, 50% of the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 2.5% ethyl/hexanes as the eluent to afford 45.4 mg (28%) of the title compound as a colorless

oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.09 (m, 5 H), 5.54– 5.40 (m, 1 H), 5.38–5.22 (m, 1 H), 4.06–3.75 (m, 2 H), 3.12–2.98 (m, 0.4 H), 2.97–2.81 (m, 0.6 H), 2.74–2.56 (m, 0.6 H), 2.50–2.28 (m, 1.4 H), 2.26–2.08 (m, 1 H), 2.07–1.92 (m, 2 H), 1.91–1.71 (m, 1 H), 1.55–1.41 (m, 9 H), 1.40–1.02 (m, 10 H), 0.96–0.79 (m, 3 H), 0.74 (s, 9 H), -0.12–-0.34 (m, 6 H).

(±)–(2*S*,3*R*,5*R*)–2-Benzyl-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-27). Protected pyrrolidine **V-26** (29.4 mg, 0.057 mmol) was converted to the title compound using a procedure analogous to that employed for the conversion of **V-22** to **V-23** to afford 25 mg (86%) as a colorless oil. The compound obtained gave ^{1}H and ^{13}C NMR spectrum identical to those reported above. This mixture was used in the following transformation without purification.

(±)–3-*epi*-Preussin (V-28).[6,9d] Protected pyrrolidine **V-27** (25 mg, 0.005 mmol) was converted to the title compound using a procedure analogous to that employed for the conversion of **V-23** to **V-1** to afford 17 mg (quantitative) of a colorless oil in ~70% purity. The compound obtained was identified as the title compound by comparison of ^{1}H NMR data to literature ^{1}H NMR data for known **V-1**.

(2*S*,3*S*)-*tert*-Butyl-1-phenyl-3-(trimethylsilyloxy)hex-5-en-2-ylcarbamate (V-

36). A flame-dried flask was cooled under a stream of nitrogen and charged with **V-19** (500 mg, 1.72 mmol), tetrahydrofuran (12 mL), and triethylamine (0.53 mL, 3.8 mmol). TMS-Cl (0.52 mL, 3.4 mmol) was then added dropwise. The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 24 h). The crude mixture was then concentrated *in vacuo*. The crude residue was diluted with methylene chloride (10 mL) and washed with saturated $NaHCO_3$ solution. The aqueous layer was then extracted with methylene chloride (2 x 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate/hexanes as the eluent to afford 494 mg (79%) of the title compound as a colorless oil. This compound was found to exist as a 4:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2 H), 7.25–7.14 (m, 3 H), 5.76–5.61 (m, 1 H), 5.07–4.98 (m, 2 H), 4.90–4.68 (m, 1 H), 3.94–3.83 (m, 0.8 H), 3.78–3.69 (m, 0.4 H), 3.68–3.62 (m, 0.8 H), 2.85–2.75 (m, 1 H), 2.74–2.64 (m, 1 H), 2.35–2.13 (m, 2 H), 1.43–1.19 (m, 9 H), 0.14 (s, 9 H).

(E)-(2*S*,3*S*,5*R*)-*tert*-Butyl-2-benzyl-5-(non-2-enyl)-3-(trimethylsilyloxy)pyrrolidine-1-carboxylate (V-37). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **V-36** (65 mg, 0.18 mmol), $Pd_2(dba)_3$ (3.3 mg, 0.0036 mmol, 2 mol %), dpe-phos (3.9 mg, 0.0072 mmol, 4 mol %), NaO*t*-Bu (21 mg, 0.22 mmol) and (*E*)-1-bromooct-1-ene (42 mg, 0.22 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring until the starting material had been

consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 2.5% → 5% ethyl/hexanes as the eluent to afford 25 mg (30%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.09 (m, 5 H), 5.55– 5.42 (m, 1 H), 5.39–5.27 (m, 1 H), 4.25–4.15 (m, 1 H), 4.14–3.95 (m, 1 H), 3.77–3.57 (m, 1 H), 3.02–2.91 (m, 1 H), 2.87–2.74 (m, 1 H), 2.72–2.53 (m, 1 H), 2.23–2.03 (m, 2 H), 2.02–1.94 (m, 2 H), 1.78–1.67 (m, 1 H), 1.54–1.10 (m, 17 H), 0.88 (t, J = 9.0 Hz, 3 H), 0.18–-0.09 (m, 9 H).

(2*S*,3*S*)-*tert*-Butyl-3-(methoxymethoxy)-1-phenylhex-5-en-2-ylcarbamate (V-38). A flame-dried flask was cooled under a stream of nitrogen and charged with **V-19** (500 mg, 1.72 mmol), CH_2Cl_2 (5 mL) and diisopropylamine (2.8 mL, 16.0 mmol). The resulting mixture was cooled to 0 ^{o}C and MOM-Cl (0.6 mL, 7.7 mmol) was added dropwise. The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 24 h). The reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1 M HCl, water, and brine, and then were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 343 mg (60%) of the title compound as a colorless oil. This compound was found to exist as a 4:1 mixture of rotamers as judged by ^{1}H NMR

analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.15 (m, 5 H), 5.76–5.60 (m, 1 H), 5.10–4.99 (m, 2 H), 4.95–4.83 (m, 1 H), 4.77–4.70 (m, 1 H), 4.67–4.60 (m, 1 H), 4.01–3.91 (m, 0.8 H), 3.85–3.75 (m, 0.2 H), 3.60–3.51 (m, 1 H), 3.43 (s, 3 H), 2.90–2.73 (m, 2 H),), 2.44–2.30 (m, 1 H), 2.29–2.20 (m, 1 H), 1.46–1.18 (m, 9 H).

(*E*)-(2*S*,3*S*,5*R*)-*tert*-Butyl-2-benzyl-3-(methoxymethoxy)-5-(non-2-enyl)pyrrolidine-1-carboxylate (V-39). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **V-38** (42 mg, 0.13 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol, 2 mol %), Dpe-phos (2.7 mg, 0.005 mmol, 4 mol %), NaO*t*-Bu (15 mg, 0.15 mmol) and (*E*)-1-bromooct-1-ene (29 mg, 0.15 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 5% → 10% ethyl/hexanes as the eluent to afford 32 mg (60%) of the title compound as a colorless oil in ~60% purity (36% yield of **V-39**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.10 (m, 5 H), 5.58– 5.44 (m, 1 H), 5.41–5.28 (m, 1 H), 4.55–4.17 (m, 2 H), 4.16–4.07 (m, 1 H), 3.80–3.62 (m, 1 H), 3.37–3.20 (m, 3 H), 3.00–2.89 (m, 1 H), 2.88–2.76 (m, 1 H), 2.32–2.19 (m, 1 H), 2.18–2.03 (m, 1 H), 2.02–1.93 (m, 2 H), 1.85–1.73 (m, 1 H), 1.53–1.06 (m, 19

H), 0.88 (t, J = 6.2 Hz, 3 H).

(2*S*,3*S*,5*R*)-*tert*-Butyl-2-benzyl-5-(4-*tert*-butylbenzyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-1-carboxylate (V-40). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **V-20** (37.1 mg, 0.09 mmol), $Pd_2(dba)_3$ (1.7 mg, 0.0018 mmol, 2 mol %), Dpe-phos (2.0 mg, 0.0037 mmol, 4 mol %), NaO*t*-Bu (11 mg, 0.11 mmol) and 4-bromo-*t*-butylbenzene (24 mg, 0.11 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 5% → 10% ethyl/hexanes as the eluent to afford 37 mg (68%) of the title compound as a colorless oil in ~90% purity. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–6.97 (m, 9 H), 4.32–4.14 (m, 1 H), 4.13–3.93 (m, 0.5 H), 3.92–3.69 (m, 1 H), 3.57–3.25 (m, 0.5 H), 3.06–2.83 (m, 1 H), 2.82–2.67 (m, 1 H), 2.58–2.29 (m, 1 H), 2.16–1.89 (m, 1 H), 1.77–1.62 (m, 1 H), 1.52–1.08 (m, 19 H), 1.01–0.67 (m, 9 H), 0.17–-0.13 (m, 6 H).

(2*S*,3*R*,5*R*)-*tert*-Butyl-2-benzyl-5-(4-*tert*-butylbenzyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-1-carboxylate (V-41). A flame-dried Schlenk tube

equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **V-24** (41 mg, 0.1 mmol), $Pd_2(dba)_3$ (1.9 mg, 0.002 mmol, 2 mol %), Dpe-phos (2.2 mg, 0.004 mmol, 4 mol %), NaO*t*-Bu (12 mg, 0.12 mmol) and 4-bromo-*t*-butylbenzene (26 mg, 0.11 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 5% → 10% ethyl/hexanes as the eluent to afford 33.2 mg (62%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^1H NMR analysis; data are for the mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.02 (m, 9 H), 4.30– 4.15 (m, 0.6 H), 4.14–4.05 (m, 0.6 H), 4.01–3.93 (m, 0.4 H), 3.92–3.85 (m, 1 H), 3.84–3.75 (m, 0.4 H), 3.29–3.18 (m, 0.6 H), 3.17–3.06 (m, 0.4 H), 2.97–2.87 (m, 0.4 H), 2.81–2.65 (m, 1 H), 2.57–2.43 (m, 0.6 H), 2.09–1.96 (m, 0.6 H), 1.92–1.80 (m, 1.4 H), 1.79–1.68 (m, 1 H), 1.64–1.42 (m, 9 H), 1.30 (s, 9 H), 0.72 (s, 9 H), -0.28 (d, J = 9.5 Hz, 6 H).

(*E*)-*tert*-Butyl 2-(non-2-enyl)pyrrolidine-1-carboxylate (V-42). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **II-5** (19 mg, 0.1 mmol), $Pd_2(dba)_3$ (1.0 mg, 0.001 mmol, 1 mol %), Dpe-phos (1.1 mg, 0.002 mmol, 2 mol %), NaO*t*-Bu (12 mg, 0.12 mmol) and (*E*)-1-bromooct-

1-ene (23 mg, 0.12 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 2.5% → 5% ethyl/hexanes as the eluent to afford 16.2 mg (55%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49–5.39 (m, 1 H), 5.38– 5.24 (m, 1 H), 3.87–3.63 (m, 1 H), 3.44–3.21 (m, 2 H), 2.53–2.41 (m, 0.5 H), 2.40–2.28 (m, 0.5 H), 2.09–2.01 (m, 0.5 H), 2.00–1.93 (m, 2.5 H), 1.91–1.66 (m, 4 H), 1.47 (s, 9 H), 1.39–1.14 (m, 8 H), 0.88 (d, J = 6.6 Hz, 3 H).

(*E*)-(2*S*,5*R*)-*tert*-Butyl 2-(non-2-enyl)-5-phenylpyrrolidine-1-carboxylate (V-43). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **II-21** (26 mg, 0.1 mmol), $Pd_2(dba)_3$ (1.0 mg, 0.001 mmol, 1 mol %), Dpe-phos (1.1 mg, 0.002 mmol, 2 mol %), NaO*t*-Bu (12 mg, 0.12 mmol) and (*E*)-1-bromooct-1-ene (23 mg, 0.12 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 110 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was

extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was observed through ^1H NMR analysis of the crude material, and was identified by comparison to ^1H NMR data previously reported for pyrrolidine **II-41**.

Aryl Bromide Route (B)

Synthesis of (±)-Preussin (Scheme 28)

3-Hydroxytetradec-1-en-5-one (V-48). A flame-dried flask was cooled under a stream of nitrogen and charged with diisopropylamine (7.4 mL, 52.5 mmol) and tetrahydrofuran (300 mL). The resulting solution was cooled to -78 °C and *n*-butyllithium (20.8 mL, 52 mmol, 2.5 M in hexanes) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min and then a solution of 2-undecanone (8.52g, 50 mmol) in tetrahydrofuran (30 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1h then a solution of acrolein (3.5 mL, 52.5 mmol) in tetrahydrofuran (30 mL) was then slowly added dropwise. The resulting mixture was stirred at -78 °C for 35 min and then warmed to rt. Saturated aqueous NH_4Cl (25 mL) and diethyl ether (200 mL) were added, the layers were separated and the aqueous layer was extracted with diethyl ether (3 x 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% → 10% ethyl acetate/hexanes as the eluent to afford 8.88 g (78%) of the title compound as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.89– 5.82

(m, 1 H), 5.32–5.27 (m, 1 H), 5.15–5.12 (m, 1 H), 4.60–4.55 (m, 1 H), 3.06 (s, br, 1 H), 2.68–2.59 (m, 2 H), 2.45– 2.40 (m, 2 H), 1.62–1.49 (m, 2 H), 1.33–1.20 (m, 12 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 139.0, 115.0, 68.6, 48.5, 43.7, 31.8, 29.39, 29.36, 29.2, 29.1, 23.6, 22.7, 14.1; IR (film) 3432, 1710 cm^{-1}. Anal calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.25; H, 11.47.

3-Hydroxytetradec-1-en-5-one-*O*-benzyl oxime (V-49). A flame-dried flask was cooled under a stream of nitrogen and charged with **V-48** (11.9 g, 52.6 mmol), methanol (190 mL), *O*-benzylhydroxylamine (10.1 g, 63.2 mmol) and pyridine (11 mL). The resulting mixture was refluxed until the starting material was consumed as judged by TLC analysis (ca. 1h). The mixture was cooled to rt and concentrated *in vacuo.* The resulting residue was diluted with water (100 mL) and dichloromethane (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography using 5% → 10% ethyl acetate/hexanes as the eluent to afford 16.9 g (98%) of the title compound as a colorless oil. This compound was judged to be a 1:1 mixture of oxime isomers as judged by ^{1}H NMR and ^{13}C NMR. Data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37– 7.27 (m, 5 H), 5.90–5.81 (m, 1 H), 5.28–5.20 (m, 1 H), 5.12–5.04 (m, 3 H), 4.46–4.38 (m, 1 H), 2.71–2.65 (m, 0.5 H), 2.50–2.45 (m, 0.5 H), 2.40–2.28 (m, 2 H), 2.24–2.20 (m, 1 H), 1.54–1.41 (m, 2 H), 1.33–1.19 (m, 13 H), 0.88 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 159.2, 140.3, 139.5, 138.0, 137.6, 128.38, 128.37, 128.14,

128.06, 127.82, 127.79, 114.8, 114.7, 75.7, 75.6, 70.7, 69.4, 41.0, 36.5, 35.3, 31.9, 29.6, 29.5, 29.48, 29.43, 29.36, 29.31, 29.27, 29.23, 26.3, 25.5, 22.7, 14.1 (4 sets of aliphatic carbons are incidentally equivalent); IR (film) 3414, 1631 cm^{-1}. Anal calcd for $C_{21}H_{33}NO_3$: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.92; H, 10.02; N, 4.30.

3-Hydroxy-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester. A flame-dried flask was cooled under a stream of nitrogen and charged with **V-49** (16.6 g, 50 mmol) and diethyl ether (100 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (200 mL, 200 mmol, 1 M in diethyl ether) was added dropwise via cannula. The resulting mixture was heated to reflux until the starting material was consumed as judged by TLC analysis (ca. 1h). The reaction mixture was cooled to 0 °C, slowly quenched with water (30 mL) and diluted with diethyl ether (100 mL). Aqueous NaOH (16 mL, 10 M) and water (16 mL) were added sequentially and an insoluble white precipitate formed. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered to afford a solution of 3-hydroxy-1-nonylpent-4-enylamine in diethyl ether (ca. 0.1 M). A portion of this solution was concentrated *in vacuo* and ^1H NMR analysis of this sample indicated that the product was obtained as a 54:46 mixture of syn:anti diastereomers.

A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of 3-hydroxy-1-nonylpent-4-enylamine in diethyl ether (500 mL, 50 mmol, 0.1 M). Di-tert-butyl dicarbonate (16.4 g, 75 mmol) was added to the solution and the

resulting mixture was stirred until the starting material was consumed as judged by TLC analysis (ca. 2h). Aqueous NaOH (200 mL, 1 M) was added and the resulting biphasic mixture was vigorously stirred for 8h. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% → 20% ethyl acetate/hexanes as the eluent to afford 6.31 g (40%) of **V-50** and 7.62 g (46%) of **V-51** as colorless oils.

(±)–(1*R*,3*S*)-3-Hydroxy-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (V-50): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89–5.81 (m, 1 H), 5.27–5.22 (m, 1 H), 5.06–5.02 (m, 1 H), 4.56–4.46 (m, 1 H), 4.18–4.08 (m, 2 H), 3.81–3.69 (m, 1 H), 1.61–1.53 (m, 1H), 1.50– 1.16 (m, 26 H), 0.88 (t, *J* = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 140.3, 113.6, 79.8, 68.4, 47.4, 44.2, 35.6, 31.8, 29.45, 29.43, 29.3, 29.2, 28.3, 26.1, 22.6, 14.0; IR (film) 3342, 1690 cm^{-1}. Anal calcd for $C_{19}H_{37}NO_3$: C, 69.68; H, 11.39; N, 4.28. Found: C, 69.84; H, 11.46; N, 4.34.

(±)–(1*R*,3*R*)-3-Hydroxy-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (51): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.81 (m, 1 H), 5.25–5.20 (m, 1 H), 5.08–5.05 (m, 1 H), 4.58–4.44 (m, 1 H), 4.23–4.14 (m, 1 H), 3.72–3.54 (m, 1 H), 3.06–2.90 (m, 1 H), 1.72–1.53 (m, 2 H), 1.52–1.14 (m, 25 H), 0.85 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 140.9, 114.3, 79.2, 70.9, 48.3, 43.1, 36.0, 31.8, 29.51, 29.46, 29.42, 29.2, 28.4, 25.7, 22.6, 14.0; IR (film) 3333, 1682 cm^{-1}. Anal calcd for $C_{19}H_{37}NO_3$:

C, 69.68; H, 11.39; N, 4.28. Found: C, 69.79; H, 11.54; N, 4.31.

(±)–(1*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (V-47). A flame-dried flask was cooled under a steam of nitrogen and charged with **V-51** (6.0 g, 18.3 mmol), dimethylformamide (36 mL), imidazole (2.50 g, 36.6 mmol) and TBS-Cl (4.42 g, 29.3 mmol). The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 24 h). The reaction mixture was diluted with water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 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 using 5% ethyl acetate/hexanes as the eluent to afford 7.6 g (94%) of the title compound as a white solid, m.p. 64–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84–5.75 (m, 1 H), 5.17–5.11 (m, 1 H), 5.05–5.01 (m, 1 H), 4.93 (s, br, 1 H), 4.30–4.22 (m, 1 H), 3.69–3.54 (m, 1 H), 1.74–1.62 (m, 1 H), 1.54–1.36 (m, 12 H), 1.34–1.15 (m, 14 H), 0.94–0.83 (m, 12 H), 0.10–0.01 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 141.4, 114.1, 78.4, 71.8, 48.1, 42.0, 35.5, 31.9, 29.58, 29.55, 29.50, 29.3, 28.4, 25.9, 25.8, 22.6, 18.0, 14.1, -4.1, -5.1; IR (film) 3339, 1677 cm^{-1}. Anal calcd for $C_{25}H_{51}NO_3Si$: C, 67.97; H, 11.64; N, 3.17. Found: C, 68.09; H, 11.76; N, 3.18.

(±)–(2*S*,3*S*,5*R*)–2-Benzyl-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-23).[38] A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with V-47 (111 mg,

0.25 mmol), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 2 mol %), Dpe-phos (5.4 mg, 0.01 mmol, 4 mol %), NaO*t*Bu (56 mg, 0.575 mmol) and bromobenzene (32 μL, 0.3 mmol). The tube was purged with nitrogen and toluene was added (1 mL). The resulting mixture was heated to 90 °C with stirring for 5 hours until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 2.5% ethyl acetate/hexanes as the eluent to afford 85.4 mg (66%) of the title compound as a colorless oil. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.13 (m, 5 H), 4.34– 4.22 (m, 1.25 H), 4.12–3.97 (m, 0.75 H), 3.74–3.50 (m, 1 H), 3.09–2.98 (m, 1 H), 2.88–2.73 (m, 0.25 H), 2.64–2.49 (m, 0.75 H), 2.36–2.13 (m, 1.75 H), 2.07–1.92 (m, 0.25 H), 1.74–1.58 (m, 1 H), 1.50–1.06 (m, 24 H), 1.00–0.84 (m, 12 H), 0.17– -0.08 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 140.0, 129.8, 128.0, 125.6, 78.9, 71.3, 62.3, 55.6, 37.9, 37.2, 35.9, 31.9, 29.6, 29.5, 29.3, 28.0, 26.5, 25.8, 22.7, 18.1, 14.1, -4.8, -5.0.

(±)–Preussin (V-1).[15] A flame-dried flask was cooled under a steam of nitrogen and charged with **V-23** (200 mg, 0.39 mmol) and tetrahydrofuran (5 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (2.4 mL, 2.4 mmol, 1 M in tetrahydrofuran) was added dropwise. The resulting mixture was heated to reflux with stirring until the starting material was consumed as judged by TLC analysis (ca. 13h). The reaction mixture was

cooled to 0 °C, slowly quenched with water (1 mL) and diluted with diethyl ether (5 mL). Aqueous NaOH (1 mL, 10 M) and water (1 mL) were added sequentially and an insoluble white precipitate formed. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil obtained was purified by flash chromatography using 10% methanol/dichloromethane as the eluent to afford 106.2 mg (85%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.21 (m, 4 H), 7.20–7.12 (m, 1 H), 3.80–3.69 (m, 1 H), 2.90–2.76 (m, 2 H), 2.29 (s, 3 H), 2.26–2.19 (m, 1 H), 2.18–2.11 (m, 1 H), 2.10–2.02 (m, 1 H), 1.74–1.62 (m, 1 H), 1.41–1.34 (m, 1 H), 1.33–1.13 (m, 16 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 129.3, 128.3, 126.0, 73.6, 70.3, 65.8, 39.4, 38.6, 34.9, 33.6, 31.9, 29.9, 29.6, 29.5, 29.3, 26.3, 22.7, 14.1

Synthesis of (±)-3-*epi*-Preussin (Scheme 29)

(±)–(1*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (V-53). Syn amino-alcohol derivative **V-50** (3.27 g, 10 mmol) was converted to the title compound (4.0 g, 91 % yield) using a procedure analogous to that employed for the conversion of **V-51** to **V-47**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.77 (m, 1 H), 5.18–5.14 (m, 1 H), 5.05–5.01 (m, 1 H), 4.51–4.41 (m, 1 H), 4.20–4.10 (m, 1 H), 3.60–3.46 (m, 1 H), 1.63–1.53 (m, 2 H), 1.40–1.32 (m, 11 H), 1.31–1.18 (m, 14 H), 0.95–0.79 (m, 12 H), 0.02 (d, J = 9.2 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 141.1, 114.4, 78.6, 72.1, 48.2, 44.0, 36.0, 31.9, 29.56, 29.51, 29.49, 29.3, 28.4, 25.9, 25.7,

22.6, 18.1, 14.1, -4.3, -4.9; IR (film) 3362, 1703 cm^{-1}. Anal calcd for $C_{25}H_{51}NO_3Si$: C, 67.97; H, 11.64; N, 3.17. Found: C, 68.07; H, 11.79; N, 3.20.

(±)–(2*S*,3*R*,5*R*)–2-Benzyl-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-27). Silyl ether **V-53** (111 mg, 0.25 mmol) was converted to the title compound using a procedure analogous to that employed for the conversion of **V-47** to **V-23** to afford 71.6 mg (55%) of the title compound as a colorless oil. This compound was found to exist as a ~2:1 mixture of rotamers as judged by ^1H NMR analysis; data are for the mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.12 (m, 5 H), 4.02–3.77 (m, 3 H), 3.09–3.01 (m, 0.3 H), 2.93–2.83 (m, 0.7 H), 2.44–2.36 (m, 1 H), 2.18–2.08 (m, 0.6 H), 2.03–1.91 (m, 1.4 H), 1.78–1.69 (m, 1 H), 1.51–1.38 (m, 9 H), 1.35–1.14 (m, 15 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.75 (s, 9 H), -0.20– -0.28 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 138.7, 129.3, 128.3, 126.2, 78.8, 73.2, 72.2, 69.7, 69.1, 57.2, 40.5, 39.7, 39.3, 38.9, 36.0, 31.9, 29.7, 29.5, 29.4, 29.3, 28.4, 26.1, 25.8, 25.6, 22.6, 17.7, 14.1, -5.18, -5.23. IR (film) 1697 cm^{-1}. Anal calcd for $C_{31}H_{55}NO_3Si$: C, 71.90; H, 10.70; N, 2.70. Found: C, 72.15; H, 10.75; N, 2.78.

(±)–3-*epi*-Preussin (V-28).[6,9d] Protected pyrrolidine **V-27** (200 mg, 0.39 mmol) was converted to the title compound using a procedure analogous to that employed for the conversion of **V-23** to **V-1** to afford 105 mg (86%) of a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.17 (m, 5 H), 4.02–3.95 (m, 1 H), 3.08–3.00 (m, 1 H), 2.59–2.50 (m, 1 H), 2.49–2.38 (m, 2 H), 2.35 (s, 3 H), 1.79–1.71 (m, 1 H), 1.70–1.59 (m, 2 H), 1.35–1.09 (m, 16 H), 0.87 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9,

129.3, 128.6, 126.4, 77.3, 74.7, 64.9, 39.4, 39.14, 39.05, 33.8, 31.9, 30.0, 29.6, 29.5, 29.3, 26.4, 22.7, 14.1.

Asymmetric Synthesis of (+)–Preussin (Scheme 30)

(–)-(*R*)-*N*-Decylidene-2-methylpropanesulfinamide (V-56). A flame-dried flask was cooled under a stream of nitrogen and charged with decanal (1.7 mL, 9.1 mmol), titanium ethoxide (3.5 mL, 16.5 mmol) and tetrahydrofuran (33 mL). Solid (*R*)-*tert*-butanesulfinamide (1.0 g, 8.25 mmol) was added in one portion and the mixture was stirred at rt for 3 h. The reaction mixture was poured into a vigorously stirred solution of saturated aqueous NaCl (33 mL), the mixture was filtered through celite, and the celite was washed with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 1.91g (90%) of the title compound as a colorless oil: $[\alpha]^{23}_D$ –212.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (t, *J* = 5.0 Hz, 1 H), 2.53–2.49 (m, 2 H), 1.62 (p, *J* = 8.0 Hz, 2 H), 1.39–1.20 (m, 12 H), 1.19 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 56.4, 36.1, 31.8, 29.4, 29.3, 29.20, 29.18, 25.5, 22.6, 22.3, 14.1; IR (neat, cm^{-1}) 1623. Anal calcd for $C_{14}H_{29}NOS$: C, 64.81; H, 11.27; N, 5.40. Found: C, 64.93; H, 11.33; N, 5.36.

(–)-(*R*$_S$,4*R*)-4-(2-Methylpropane-2-sulfinylamino)tridecene (V-57). A flame-dried flask was cooled under a stream of nitrogen and charged with (–)-(*R*)-N-decylidene-2-methylpropanesulfinamide (900 mg, 3.47 mmol) and dichloromethane (35 mL). The

flask was cooled to 0 °C and a solution of allylmagnesium bromide (5.2 mL, 5.2 mmol, 1.0 M in diethyl ether) was added slowly dropwise. The mixture was stirred at 0 °C for 30 min then a solution of saturated aqueous ammonium chloride (20 mL) was added. The mixture was warmed to rt, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Analysis of the crude product by ^{1}H NMR indicated that a 10:1 mixture of diastereomers had formed. The crude material was purified by flash chromatography on silica gel to afford 824 mg (79%) of the title compound (a colorless oil) as a single pure diastereomer: $[\alpha]^{23}_D$ –53.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83–5.73 (m, 1 H), 5.14 (d, *J* = 15.0 Hz, 2 H), 3.34–3.26 (m, 1 H), 3.19 (d, *J* = 7.5 Hz, 1 H), 2.44–2.39 (m, 1 H), 2.33–2.27 (m, 1 H), 1.51–1.45 (m, 2 H), 1.36–1.22 (m, 14 H), 1.20 (s, 9 H), 0.88 (t, *J* = 8.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 118.8, 55.7, 54.8, 40.4, 34.9, 31.8, 29.50, 29.48, 29.4, 29.2, 25.4, 22.6, 14.1; IR (neat, cm^{-1}) 3216, 1640. Anal calcd for $C_{17}H_{35}NOS$: C, 67.72; H, 11.70; N, 4.65. Found: C, 67.43; H, 11.82; N, 4.62.

(+)-(1*R*)-1-Nonylpent-4-enylcarbamic acid *tert*-butyl ester (V-58). A round-bottom flask was charged with (–)-(R_S,4*R*)-4-(2-methylpropane-2-sulfinylamino)tridecene (1.25 g, 4.15 mmol) and methanol (5 mL). A solution of anhydrous hydrochloric acid (5 mL, 10 mmol, 2 M in diethyl ether) was added and the mixture was stirred at rt for 30 min, at which time TLC analysis indicated that the starting material had been completely consumed. The mixture was concentrated *in vacuo*, and the resulting material was dissolved in a mixture of dioxane (15 mL), water (5 mL), and 1 M

aqueous NaOH (16 mL, 16 mmol). Solid di-*tert*-butyldicarbonate was added in one portion and the reaction mixture was stirred at rt for 2 h, at which time TLC analysis indicated the primary amine intermediate had been completely consumed. Tetrahydrofuran (7 mL) and additional 1 M NaOH (7 mL) were added and the resulting mixture was stirred at rt for 12 h. The reaction mixture was then extracted with ether (3 x 40 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the title compound (1.10 g, 89%) as a white solid, m.p. 41–42 °C: $[\alpha]^{23}_D$ +19.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.74 (m, 1 H), 5.09–5.05 (m, 2 H), 4.34–4.28 (m, br, 1 H), 3.62 (s, br, 1 H), 2.28–2.12 (m, 2 H), 1.43 (s, 9 H), 1.33–1.25 (m, 16 H), 0.88 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 134.6, 117.5, 78.9, 50.1, 39.5, 34.7, 31.9, 29.6, 29.5, 29.3, 28.4, 25.9, 22.7, 14.1; IR (neat, cm^{-1}) 3345, 1690. Anal calcd for $C_{17}H_{35}NO_2$: C, 72.68; H, 11.86; N, 4.71. Found: C, 72.91; H, 11.92; N, 4.75.

(+)-(1*R*)-1-(2-Oxoethyl)decylcarbamic acid *tert*-butyl ester (V-59). A round-bottom flask was charged with (+)-(1*R*)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (594 mg, 2.0 mmol) and dichloromethane (80 mL). The solution was cooled to –78 °C and ozone was bubbled through the mixture until a blue color persisted. Dry nitrogen was then bubbled through the solution until the blue color dissipated. Solid triphenylphosphine (1.05 g, 4.0 mmol) was added in one portion and the flask was warmed to rt and stirred for 2h. The reaction mixture was then concentrated *in vacuo* and the crude material was purified by flash chromatography on silica gel to afford the title

compound (381 mg, 63%) as a colorless oil: $[\alpha]^{23}_{D}$ +30.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (t, *J* = 2.5 Hz, 1 H), 4.71 (d, *J* = 9.0 Hz, 1 H), 4.00–3.93 (m, 1 H), 2.60–2.46 (m, 2 H), 1.48–1.43 (m, 2 H), 1.37 (s, 9 H), 1.26–1.20 (m, 14 H), 0.82 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 155.3, 79.3, 49.1, 46.4, 35.0, 31.8, 29.4, 29.20, 29.16, 28.4, 25.9, 22.5, 14.0; IR (neat, cm^{-1}) 3343, 1716; MS (ESI): 322.2352 (322.2358 calculated for $C_{17}H_{33}NO_3$, M + Na^+).

(+)–(1*R*,3*S*)-3-Hydroxy-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (V-51). A flame-dried flask was charged with $CuBr_2$•Me_2S (1.30g, 6.3 mmol) and ether (23 mL). The resulting suspension was cooled to –20 °C and vinyllithium[39] (12.6 mL, 12.6 mmol, 1.0 M in ether) was added dropwise. The resulting dark-colored solution was cooled to –78 °C and a solution of **V-59** (381 mg, 1.26 mmol) in ether (4 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 2 h then methanol (4 mL) was added and the mixture was warmed to rt. Saturated aqueous ammonium chloride (30 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Analysis of the crude material by ^{1}H NMR revealed that the product had been formed as a 3:1 mixture of diastereomers. The crude product was purified by flash chromatography on silica gel to afford 230 mg (56%) of the title compound as a white solid, m.p. 49–50 °C, $[\alpha]^{23}_{D}$ +6.1° (*c* 1.0, $CHCl_3$). Spectral data were identical to the racemic compound **V-51** described above. This material was judged to be of 97% ee using the method described below.

The enantiomeric purity of **V-51** was determined through HPLC analysis of the *O*-benzoyl derivative, which was prepared as follows: A flame-dried flask cooled under a stream of nitrogen was charged with (±)**V-51** (40 mg, 0.122 mmol), pyridine (2 mL) and cooled to 0 °C. Neat benzoyl chloride (90 μL, 0.78 mmol) was added dropwise. The resulting mixture was stirred at 0 °C until the starting material was consumed as judged by TLC analysis (ca. 1h). The reaction mixture was then diluted with water (3 mL) and ethyl acetate (5 mL). The layers were separated and the remaining aqueous phase was extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 47.5 mg (90 %) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.3 Hz, 2 H), 7.55 (t, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 5.96–5.85 (m, 1 H), 5.63–5.55 (m, 1 H), 5.33 (d, *J* = 17.1 Hz, 1 H), 5.20 (d, *J* = 10.5 Hz, 1 H), 4.45 (s, br, 1 H), 3.80–3.61 (m, br, 1 H), 2.04–1.91 (m, 1 H), 1.85–1.75 (m, 1 H), 1.57–1.15 (m, 25 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 165.6, 155.2, 136.3, 132.9, 130.4, 129.6, 128.3, 116.8, 78.9, 72.6, 48.5, 47.6, 40.8, 39.5, 36.5, 35.4, 31.9, 29.6, 29.5, 29.3, 28.4, 25.8, 22.6, 14.1.

Assay for determination of enantiomeric excess (ee): The *O*-benzoyl derivative of (±)**V-51** (10 mg) was dissolved in isopropanol (50 μL) and hexanes (1 mL) and injected in an HPLC apparatus equipped with chiral column (R,R) WHELK-O 1 (Regis Tech.). The system permitting separation of enantiomers (RT = 5.825 min and

6.733min) was found to be 5 % isopropanol/hexanes, flow rate = 1 mL/min at wavelength of 231 nm. The HPLC analysis indicated the material was of 97 % ee.

(–)–(1*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester (V-47). Treatment of **V-51** (180 mg, 0.55 mmol) with TBS-Cl (133 mg, 0.88 mmol) and imidazole (75 mg, 1.1 mmol) using a procedure analogous to that described above for the synthesis of racemic compound **V-47** afforded the nonracemic title compound (226 mg, 93%) as a colorless oil, $[\alpha]^{23}_{D}$ –1.3° (*c* 1.0, $CHCl_3$). Spectral data were identical to the racemic compound **V-47** described above.

(–)–(2*S*,3*S*,5*R*)–2-Benzyl-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-23).[38] Treatment of (–)–(1*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-1-nonylpent-4-enylcarbamic acid *tert*-butyl ester **V-47** (110 mg, 0.25 mmol) with bromobenzene (32 μL, 0.3 mmol) using a procedure analogous to that described above for the synthesis of racemic compound **V-23** afforded the nonracemic title compound (80.2 mg, 62 %) as a colorless oil, $[\alpha]^{23}_{D}$ –51.8° (*c* 1.1, $CHCl_3$) [lit.[38] $[\alpha]^{20}_{D}$ –48.6° (*c* 1.1, $CHCl_3$)]. Spectral data were identical to the racemic compound **V-23** described above. This material was judged to be of 96% ee using the method described below.

Assay for determination of enantiomeric excess (ee): Compound **V-23** (10 mg) was dissolved in isopropanol (50 μL) and hexanes (1 mL) and injected in an HPLC apparatus equipped with chiral column (R,R) WHELK-O 1 (Regis Tech.). The system

permitting separation of enantiomers (RT = 8.350 min and 9.433 min) was found to be 2.5 % isopropanol/hexanes, flow rate = 0.5 mL/min at wavelength of 254 nm. The HPLC analysis indicated the material was of 96% ee.

(+)–Preussin (V-1).[3] Treatment of (–)–(2*S*,3*S*,5*R*)–2-benzyl-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (27 mg, 0.05 mmol) with $LiAlH_4$ (313 μL, 0.313 mmol) using a procedure analogous to that described above for the synthesis of racemic compound **V-1** afforded the nonracemic title compound (16 mg, 95 %) as a colorless oil, $[\alpha]^{23}_D$ +21.2° (*c* 1.0, $CHCl_3$) [lit.[3] $[\alpha]^{25}_D$ +22.0° (*c* 1.0, $CHCl_3$)]. Spectral data were identical to the racemic compound **V-1** described above.

Synthesis of *N*-Boc-*O*-TBS Preussin and 3-*epi*-Preussin Analogs (Tables 13–14).

(±)–(2*S*,3*S*,5*R*)–2-(4-Benzoylbenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-60). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 4-bromobenzophenone (157 mg, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 208 mg (67%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.66 (m, 4 H), 7.59–7.52 (m, 1 H), 7.49–7.42 (m, 2 H), 7.40–7.29 (m, 2 H), 4.34–4.18 (m, 1.4 H), 4.15–4.00 (m, 0.6 H), 3.74–3.50 (m, 1 H), 3.15–3.03 (m, 1 H), 2.89–2.75 (m, 0.4 H), 2.72–2.56 (m, 0.6 H), 2.34–2.12 (m, 1.6 H), 2.08–1.93 (m, 0.4 H), 1.67–1.55 (m, 1 H),

1.43–1.11 (m, 24 H), 0.95–0.82 (m, 12 H), 0.13–0.07 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 154.7, 145.6, 138.0, 135.0, 132.0, 130.0, 129.8, 129.7, 128.1, 79.1, 71.3, 62.0, 61.5, 55.6, 38.7, 38.0, 37.1, 36.2, 31.8, 29.6, 29.5, 29.2, 28.1, 26.5, 25.8, 22.6, 18.1, 14.1, -4.7, -5.0. IR (film) 1693, 1661 cm^{-1}. Anal calcd for $C_{38}H_{59}NO_4Si$: C, 73.38; H, 9.56; N, 2.25. Found: C, 73.23; H, 9.67; N, 2.32.

(±)–(2*S*,3*R*,5*R*)–2-(4-Benzoylbenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-61). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-27** except 4-bromobenzophenone (157 mg, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 194.8 mg (63%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis and contained a small amount (ca 3–5%) of an inseparable aromatic impurity; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.67 (m, 4 H), 7.56–7.48 (m, 1 H), 7.45–7.38 (m, 2 H), 7.34–7.21 (m, 2 H), 4.02–3.74 (m, 3 H), 3.13–3.00 (m, 0.4 H), 2.96–2.81 (m, 0.6 H), 2.56–2.45 (m, 1 H), 2.18–2.03 (m, 0.4 H), 2.02–1.88 (m, 1.6 H), 1.85–1.66 (m, 1 H), 1.49–1.33 (m, 10 H), 1.31–1.10 (m, 14 H), 0.83 (t, *J* = 6.6 Hz, 3 H), 0.75–0.69 (m, 9 H), -0.17–-0.27 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 195.5, 159.9, 155.2, 143.7, 137.9, 137.6, 135.6, 132.1, 131.8, 131.6, 130.2, 129.8, 129.6, 129.2, 128.1, 128.0, 122.0, 79.4, 79.0, 73.3, 72.4, 69.3, 68.8, 57.2, 40.4, 39.6, 39.2, 38.8, 36.0, 38.0, 31.8, 29.6, 29.4, 29.2, 28.8, 28.3, 25.5, 22.5, 17.7, 14.0, -5.1, -5.2. IR (film) 1694, 1660 cm^{-1}. Anal calcd for $C_{38}H_{59}NO_4Si$: C, 73.38; H, 9.56; N, 2.25.

Found: C, 73.68; H, 9.48; N, 2.16.

(±)–(2*S*,3*S*,5*R*)–2-(4-Methoxybenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-62). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 4-bromoanisole (76 μL, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 149.7 mg (55%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.04 (m, 2 H), 6.84–6.75 (m, 2 H), 4.30–4.18 (m, 1 H), 4.17–4.08 (m, 0.4 H), 4.01–3.90 (m, 0.6 H), 3.77 (s, 3 H), 3.70–3.46 (m, 1 H), 2.99–2.89 (m, 1 H), 2.78–2.62 (m, 0.4 H), 2.56–2.41 (m, 0.6 H), 2.32–2.09 (m, 1.6 H), 2.01–1.86 (m, 0.4 H), 1.63–1.50 (m, 1 H), 1.48–1.02 (m, 24 H), 0.97–0.79 (m, 12 H), 0.13– -0.08 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.9, 132.1, 130.7, 113.5, 78.9, 71.4, 62.4, 61.7, 55.6, 55.3, 38.7, 38.0, 37.2, 34.9, 31.9, 29.7, 29.5, 29.3, 28.1, 26.5, 25.8, 22.7, 18.1, 14.1, -4.7, -5.0. IR (film) 1692 cm^{-1}. Anal calcd for $C_{32}H_{57}NO_4Si$: C, 70.15; H, 10.49; N, 2.56. Found: C, 70.08; H, 10.30; N, 2.52.

(±)–(2*S*,3*S*,5*R*)–2-(4-Methoxybenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-63). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-27** except 4-bromoanisole (76 μL, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 131.2 mg (48%) of the title compound as a

colorless oil. This compound was found to exist as a ~1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.03 (m, 2 H), 6.86–6.78 (m, 2 H), 4.00–3.96 (m, 1 H), 3.95–3.85 (m, 1 H), 3.84–3.73 (m, 4 H), 3.04–2.93 (m, 0.35 H), 2.86–2.76 (m, 0.65 H), 2.40–2.31 (m, 1 H), 2.17–2.05 (m, 0.65 H), 2.00–1.86 (m, 1 H), 1.85–1.77 (m, 0.35 H), 1.76–1.67 (m, 1 H), 1.53–1.37 (m, 10 H), 1.35–1.12 (m, 14 H), 0.88 (t, *J* = 6.3 Hz, 3 H), 0.75 (s, 9 H), -0.17– -0.26 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 155.4, 130.9, 130.2, 113.8, 78.8, 73.2, 72.3, 69.8, 69.2, 57.2, 55.3, 39.5, 38.9, 38.7, 36.0, 31.9, 29.7, 29.5, 29.3, 28.5, 26.1, 25.9, 25.6, 22.7, 17.8, 14.1, -5.08, -5.13. IR (film) 1694 cm^{-1}. Anal calcd for $C_{32}H_{57}NO_4Si$: C, 70.15; H, 10.49; N, 2.56. Found: C, 70.01; H, 10.64; N, 2.53.

(±)–(2*S*,3*S*,5*R*)–2-(4-Trifluoromethylbenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-64). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 4-bromobenzotrifluoride (85 μL, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 201.3 mg (69%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.43 (m, 2 H), 7.41–7.25 (m, 2 H), 4.32–4.15 (m, 1.4 H), 4.06–3.93 (m, 0.6 H), 3.72–3.45 (m, 1 H), 3.10–3.00 (m, 1 H), 2.86–2.72 (m, 0.4 H), 2.65–2.51 (m, 0.6 H), 2.36–2.11 (m, 1.6 H), 2.05–1.90 (m, 0.4 H), 1.65–1.54 (m, 1 H), 1.45–1.00 (m, 24 H), 0.99–0.78 (m, 12 H), 0.14– -0.11 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 144.4, 130.1, 128.1 (q, *J* =

25.0 Hz), 124.9, 124.4 (q, J = 271.8 Hz), 79.2, 71.3, 62.2, 61.3, 56.5, 55.7, 38.8, 38.0, 37.3, 36.0, 31.9, 29.6, 29.5, 29.3, 28.3, 28.0, 26.5, 25.8, 22.7, 18.1, 14.1, -4.7, -5.0; IR (film) 1695 cm^{-1}. Anal calcd for $C_{32}H_{54}F_3NO_3Si$: C, 65.60; H, 9.29; N, 2.39. Found: C, 65.57; H, 9.40; N, 2.37.

(±)–(2*S*,3*R*,5*R*)–2-(4-Trifluoromethylbenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-65). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-27** except 4-bromobenzotrifluoride (85 μL, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 152 mg (52%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.50 (m, 2 H), 7.38–7.24 (m, 2 H), 4.03–3.77 (m, 3 H), 3.13–3.04 (m, 0.4 H), 2.89–2.79 (m, 0.6 H), 2.58–2.51 (m, 1 H), 2.17–2.07 (m, 0.6 H), 2.09–1.90 (m, 1.4 H), 1.80–1.70 (m, 1 H), 1.55–1.11 (m, 24 H), 0.88 (t, J = 6.6 Hz, 3 H), 0.75 (s, 9 H), -0.13– -0.27 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 142.9, 129.7, 128.7 (q, J = 32.2 Hz), 125.2, 124.3 (q, J = 272.0 Hz), 79.1, 73.6, 72.4, 69.3, 68.7, 57.4, 57.1, 40.3, 39.3, 39.0, 36.3, 31.9, 29.7, 29.5, 29.3, 28.4, 26.2, 25.9, 25.5, 22.7, 17.8, 14.1, -5.0, -5.2; IR (film) 1694 cm^{-1}. Anal calcd for $C_{32}H_{54}F_3NO_3Si$: C, 65.60; H, 9.29; N, 2.39. Found: C, 65.78; H, 9.48; N, 2.48.

(±)–(2*S*,3*S*,5*R*)–2-(Naphthalen-2-ylmethyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-66). This compound was

prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 2-bromonaphthalene (125 mg, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 187.9 mg (66%) of the title compound as a pale orange oil. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.71 (m, 3 H), 7.69–7.59 (m, 1 H), 7.51–7.31 (m, 3 H), 4.36–4.23 (m, 1.25 H), 4.18–4.02 (m, 0.75 H), 3.76–3.50 (m, 1 H), 3.24–3.14 (m, 1 H), 3.06–2.88 (m, 0.25 H), 2.81–2.64 (m, 0.75 H), 2.38–2.11 (m, 1.75 H), 2.03–1.90 (m, 0.25 H), 1.71–1.58 (m, 1 H), 1.47–1.12 (m, 20 H), 1.05–0.79 (m, 16 H), 0.16– -0.14 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 137.6, 133.5, 132.0, 128.6, 128.0, 127.4, 127.3, 125.6, 124.9, 78.8, 71.4, 62.4, 61.6, 55.7, 38.7, 38.0, 37.2, 36.2, 31.9, 29.6, 29.5, 29.3, 28.3, 27.8, 26.5, 25.8, 22.7, 18.1, 14.1, -4.7, -5.0 (two aromatic carbons are incidentally equivalent); IR (film) 1693 cm^{-1}. Anal calcd for $C_{35}H_{57}NO_3Si$: C, 74.02; H, 10.12; N, 2.47. Found: C, 73.89; H, 10.28; N, 2.55.

(±)–(2*S*,3*S*,5*R*)–2-(2-Methylbenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-67). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 2-bromotoluene (66 μL, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 148.3 mg (56%) of the title compound as a pale yellow oil. This compound was found to exist as a 9:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.03 (m, 4 H), 4.31–4.20 (m, 1 H), 4.10–3.99 (m, 0.9 H), 3.88–3.78 (m, 0.1 H), 3.71–3.57 (m, 1

H), 3.29–3.12 (m, 1 H), 2.56–2.46 (m, 0.1 H), 2.40–2.19 (m, 5.8 H), 2.10–2.00 (m, 0.1 H), 1.72–1.61 (m, 1 H), 1.46–1.19 (m, 20 H), 1.09–0.82 (m, 16 H), 0.16– -0.04 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 138.1, 136.4, 130.7, 129.9, 125.8, 125.7, 78.7, 71.2, 60.0, 55.7, 38.0, 37.7, 33.3, 31.9, 29.8, 29.7, 29.5, 29.3, 27.7, 26.7, 25.8, 25.7, 22.7, 19.6, 18.0, 14.1, -4.8, -5.1; IR (film) 1693 cm^{-1}. Anal calcd for $C_{32}H_{57}NO_3Si$: C, 72.26; H, 10.80; N, 2.63. Found: C, 72.07; H, 10.65; N, 2.62.

(±)–(2*S*,3*S*,5*R*)–2-(4-Cyanobenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-68). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 4-bromobenzonitrile (110 mg, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 175 mg (65%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.48 (m, 2 H), 7.43–7.23 (m, 2 H), 4.34–4.21 (m, 1 H), 4.20–4.11 (m, 0.4 H), 4.05–3.92 (m, 0.6 H), 3.74–3.45 (m, 1 H), 3.05 (dd, *J* = 5.1, 13.7, 1 H), 2.81–2.67 (m, 0.4 H), 2.66–2.51 (m, 0.6 H), 2.36–2.10 (m, 1.6 H), 2.06–1.86 (m, 0.4 H), 1.75–1.50 (m, 1 H), 1.49–1.04 (m, 24 H), 0.96–0.76 (m, 12 H), 0.14– -0.11 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 146.1, 131.8, 130.6, 119.2, 109.4, 79.3, 71.3, 70.9, 62.0, 61.3, 55.6, 38.7, 37.9, 37.2, 36.5, 31.9, 29.7, 29.5, 29.3, 28.1, 26.5, 25.8, 22.6, 18.0, 14.1, -4.7, -5.0; IR (film) 1694 cm^{-1}. Anal calcd for $C_{32}H_{54}N_2O_3Si$: C, 70.80; H, 10.03; N, 5.16. Found: C, 70.99; H, 9.90; N, 5.34.

(±)–(2*S*,3*S*,5*R*)–2-(3-pyridyl-2-ylmethyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-69). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 3-bromopyridine (60 μL, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 150.8 mg (58%) of the title compound as a colorless oil. This compound was found to exist as a ~ 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47–8.34 (m, 2 H), 7.64–7.41 (m, 1 H), 7.20–7.10 (m, 1 H), 4.30–4.20 (m, 1 H), 4.19–4.11 (m, 0.35 H), 4.02–3.90 (m, 0.65 H), 3.69–3.44 (m, 1 H), 3.02–2.92 (m, 1 H), 2.77–2.64 (m, 0.35 H), 2.57–2.44 (m, 0.65 H), 2.34–2.08 (m, 1.65 H), 2.02–1.90 (m, 0.35 H), 1.60–1.47 (m, 1 H), 1.44–1.04 (m, 24 H), 0.94–0.77 (m, 12 H), 0.13– -0.13 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 151.1, 147.0, 137.1, 135.4, 122.9, 79.2, 71.2, 62.0, 61.1, 55.6, 38.8, 37.9, 37.2, 33.3, 31.8, 29.6, 29.5, 29.2, 28.0, 26.4, 25.8, 22.6, 18.0, 14.0, -4.8, -5.1; IR (film) 1694 cm^{-1}. Anal calcd for $C_{30}H_{54}N_2O_3Si$: C, 69.45; H, 10.49; N, 5.40. Found: C, 69.50; H, 10.45; N, 5.34.

(±)–(2*S*,3*S*,5*R*)–2-(*N*-benzyl-5-indolyl-2-ylmethyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-70). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except *N*-benzyl-5-bromoindole (172 mg, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 135.9 mg (42%) of the title compound as a colorless oil. This compound was found to exist as a 1.5:1 mixture of

rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.40 (m, 1 H), 7.30–7.20 (m, 3 H), 7.18–6.96 (m, 5 H), 6.48–6.43 (m, 1 H), 5.30 (s, 2 H), 4.31–4.21 (m, 1 H), 4.10–3.99 (m, 1 H), 3.79–3.50 (m, 1 H), 3.16–3.06 (m, 1 H), 2.95–2.77 (m, 0.4 H), 2.69–2.53 (m, 0.6 H), 2.34–2.12 (m, 1.6 H), 2.08–1.86 (m, 0.4 H), 1.70–1.58 (m, 1 H), 1.46–1.13 (m, 18 H), 1.03–0.81 (m, 18 H), 0.13– -0.14 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 137.9, 135.0, 130.8, 128.9, 128.6, 128.1, 127.4, 126.6, 124.0, 121.7, 109.1, 101.2, 78.6, 71.4, 62.8, 55.6, 50.0, 38.0, 37.3, 35.8, 35.2, 31.9, 29.73, 29.67, 29.5, 29.3, 28.5, 27.9, 26.6, 25.9, 25.7, 22.7, 18.1, 14.1, -4.7, -5.0; IR (film) 1689 cm^{-1}. Anal calcd for $C_{40}H_{62}N_2O_3Si$: C, 74.25; H, 9.66; N, 4.33. Found: C, 73.87; H, 9.90; N, 4.31.

(±)–(2*S*,3*S*,5*R*)–2-(4-Chlorobenzyl)-3-(*tert*-butyldimethylsilyloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-71). This compound was prepared on a 0.5 mmol scale using a procedure analogous to that employed for the synthesis of **V-23** except 4-bromochlorobenzene (115 mg, 0.6 mmol) was used in place of bromobenzene. This procedure afforded 195.4 mg (71%) of the title compound as a pale orange oil. This compound was found to exist as a ~ 1.5:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.09 (m, 4 H), 4.33–4.22 (m, 1 H), 4.21–4.11 (m, 0.35 H), 4.05–3.93 (m, 0.65 H), 3.73–3.51 (m, 1 H), 3.04–2.94 (m, 1 H), 2.79–2.65 (m, 0.35 H), 2.60–2.46 (m, 0.65 H), 2.36–2.13 (m, 1.65 H), 2.04–1.94 (m, 0.35 H), 1.66–1.49 (m, 1 H), 1.48–1.08 (m, 24 H), 0.99–0.81 (m, 12 H), 0.17– -0.08 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 138.5,

131.4, 131.2, 128.0, 79.1, 71.3, 62.2, 61.5, 55.6, 38.7, 38.0, 37.2, 35.4, 31.9, 29.6, 29.5, 29.3, 28.0, 26.5, 25.8, 25.7, 25.5, 22.6, 18.0, 14.1, -4.7, -5.0; IR (film) 1694 cm^{-1}. Anal calcd for $C_{31}H_{54}ClNO_3Si$: C, 67.41; H, 9.85; N, 6.42. Found: C, 67.25; H, 9.82; N, 2.54.

General Procedure for Pd-Catalyzed Carboamination Reactions of Aryl Bromides Using Cs_2CO_3. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (2 mol %), Dpe-phos (4 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (5 mL/mmol substrate) was then added via syringe. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

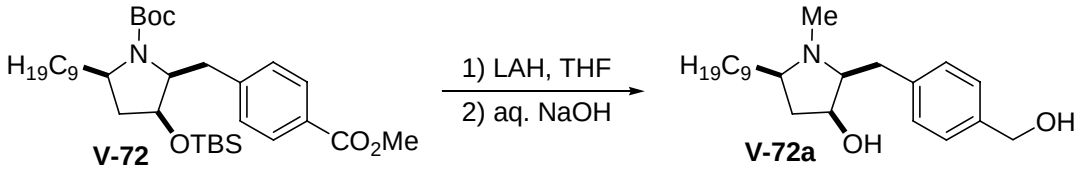
(±)–(2*S*,3*S*,5*R*)-2-Benzyl-3-(*tert*-butyldimethylsiloxy)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-71).[38] The general procedure was employed for the reaction of bromobenzene (26 μL, 0.24 mmol) with **V-47** (89 mg, 0.20 mmol). ^{1}H NMR analysis of the crude material obtained upon workup showed the formation of the desired product as a >20:1 mixture of diastereomers. This procedure afforded 74 mg (71%) of the title compound as a colorless oil with >20:1 dr. The stereochemistry was assigned by

comparison of the ^{1}H NMR spectrum to data previously reported in the literature. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.06 (m, 5 H), 4.32– 4.15 (m, 1.25 H), 4.08–3.95 (m, 0.75 H), 3.83–3.44 (m, 1 H), 3.06–2.96 (m, 1 H), 2.82–2.68 (m, 0.25 H), 2.61–2.47 (m, 0.75 H), 2.32–2.12 (m, 1.75 H), 2.05–1.93 (m, 0.25 H), 1.67–1.54 (m, 1 H), 1.51–1.03 (m, 24 H), 0.97–0.84 (m, 12 H), 0.13– -0.08 (m, 6 H).

(±)–(2*S*,3*S*,5*R*)-3-(*tert*-Butyldimethylsiloxy)-2-(4-methoxycarbonylbenzyl)-5-nonylpyrrolidine-1-carboxylic acid *tert*-butyl ester (V-72). The general procedure was employed for the reaction of methyl 4-bromobenzoate (52 mg, 0.24 mmol) with **V-47** (89 mg, 0.20 mmol). The diastereoselectivity of the transformation was assessed by LAH reduction of the crude product obtained in a duplicate reaction, and was found to be >20:1 dr as judged by ^{1}H NMR analysis. Chromatographic purification afforded 83 mg (72%) of the title compound as a colorless oil with >20:1 dr. This compound was found to exist as a 3:1 mixture of rotamers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.88 (m, 2 H), 7.39–7.22 (m, 2 H), 4.32–4.19 (m, 1.3 H), 4.07–3.98 (m, 0.7 H), 3.90 (s, 3 H), 3.72–3.51 (m, 1 H), 3.11–3.01 (m, 1 H), 2.87–2.75 (m, 0.3 H), 2.67–2.53 (m, 0.7 H), 2.33–2.12 (m, 1.7 H), 2.07–1.93 (m, 0.3 H), 1.65–1.55 (m, 1 H), 1.46–1.05 (m, 24 H), 0.96–0.81 (m, 12 H), 0.12– -0.12 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 154.8, 145.9, 129.9, 129.4, 127.6, 79.2, 71.4, 62.1, 55.7, 51.9, 38.0, 37.2, 36.3, 31.9, 29.7, 29.6, 29.3, 28.1, 26.5, 25.8, 22.7, 18.1, 14.1, -4.7, -5.0; IR (film) 1726, 1694 cm^{-1}. Anal calcd for $C_{33}H_{57}NO_5Si$: C, 68.82; H, 9.98; N, 2.43.

Found: C, 68.43; H, 9.98; N, 2.42.

The stereochemistry of the above compound was determined through LAH reduction of **V-72** to afford **V-72a** as shown below. The stereochemistry of **V-72a** was assigned by comparison of the ^{1}H NMR spectrum of **V-72a** to that previously obtained for preussin **(V-1).**[38]



(±)–(2*S*,3*S*,5*R*)-2-(4-Hydroxymethylbenzyl)-1-methyl-5-nonylpyrrolidin-3-ol (V-72a). A flame-dried flask was cooled under a steam of nitrogen and charged with **V-72** (70 mg, 0.12 mmol) and tetrahydrofuran (3 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (1.2 mL, 1.2 mmol, 1 M in tetrahydrofuran) was added dropwise via syringe. The resulting mixture was heated to reflux until the starting material was consumed as judged by TLC analysis (ca. 21 h). The reaction mixture was cooled to 0 °C, slowly quenched with water (0.3 mL) and diluted with diethyl ether (5 mL). Aqueous NaOH (0.3 mL, 10 M) and water (0.3 mL) were added sequentially and an insoluble white precipitate formed. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil obtained was purified by flash chromatography using 10% → 20% methanol/dichloromethane as the eluent to afford 38 mg (91%) of the title compound as a

colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 4 H), 4.66 (s, 2 H), 3.83–3.75 (m, 1 H), 2.94–2.80 (m, 2 H), 2.33 (s, 3 H), 2.30–2.03 (m, 5 H), 1.77–1.66 (m, 1 H), 1.46–1.38 (m, 1 H), 1.37–1.15 (m, 15 H), 0.88 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 129.5, 127.1, 73.7, 70.2, 65.9, 64.9, 39.5, 38.6, 34.7, 33.1, 31.9, 29.9, 29.6, 29.5, 29.3, 26.4, 22.6, 14.1 (two aromatic carbons are incidentally equivalent); IR (film) 3384 cm^{-1}; MS (ESI): 348.2900 (348.2903 calculated for $C_{22}H_{37}NO_2$, M + H^+).

Synthesis of Deprotected Preussin and 3-*epi*-Preussin Analogs (Table 15)

(±)–(2*S*,3*S*,5*R*)–2-(4-Benzoylbenzyl)-3-hydroxy-5-nonylpyrrolidine (V-73). A flame-dried flask cooled under a steam of nitrogen was charged with **V-60** (62.2 mg, 0.1 mmol) and tetrahydrofuran (1 mL). Formic acid (1 mL, 26.5 mmol) was added dropwise and the resulting mixture was stirred at 60 °C until the starting material was consumed as judged by TLC analysis (ca. 5h). The reaction mixture was then cooled to 0 °C, an aqueous solution of formaldehyde (100 μL, 1.2 mmol, 37 wt. %) was added dropwise, and the mixture was stirred at 0 °C for 1h. The reaction mixture was then heated to 60 °C with stirring for 12h. The crude mixture was cooled to rt and was concentrated *in vacuo*. The resulting residue was then dissolved in tetrahydrofuran (1 mL). Solid K_2CO_3 (150 mg, 1.1 mmol) was added and the resulting suspension was cooled to 0 °C. A solution of TBAF (1 mL, 1 mmol, 1 M in tetrahydrofuran) was then added dropwise and the reaction was stirred at rt until the silyl protecting group was completely removed as judged by crude ^{1}H NMR analysis of an aliquot from the reaction mixture (ca. 5h). The crude mixture was concentrated *in vacuo*. The crude material was purified by flash chromatography using 5% MeOH/CH_2Cl_2 as the eluent to afford 36 mg (85%) of the title

compound as a light brown solid, m.p. 50–52 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2 H), 7.74 (t, *J* = 8.1 Hz, 2 H), 7.60–7.56 (m, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 3.84–3.78 (m, 1 H), 3.02–2.95 (m, 1 H), 2.94–2.89 (m, 1 H), 2.39–2.30 (m, 4 H), 2.29–2.20 (m, 1 H), 2.19–2.13 (m, 1 H), 2.08–1.95 (s, br, 1 H), 1.77–1.68 (m, 1 H), 1.48–1.42 (m, 1 H), 1.38–1.17 (m, 15 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 144.6, 137.8, 135.5, 132.2, 130.3, 130.0, 129.3, 128.2, 73.2, 70.4, 65.7, 39.4, 38.6, 34.9, 33.8, 31.9, 29.9, 29.6, 29.5, 29.3, 26.2, 22.7, 14.1; IR (film) 3411, 1656 cm^{-1}; MS (ESI): 422.3058 (422.3059 calculated for $C_{28}H_{39}NO_2$, M + H^+).

(±)–(2*S*,3*R*,5*R*)–2-(4-Benzoylbenzyl)-3-hydroxy-5-nonylpyrrolidine (V-74). This compound was prepared on a 0.1 mmol scale using a procedure analogous to that employed for the synthesis of **V-73**. Substrate **V-61** (62.2 mg, 0.1 mmol) was transformed to the title compound to afford 36.2 mg (86%) of a light brown solid, m.p. 62–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.72 (m, 4 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.37 (d, *J* = 8.1 Hz, 2 H), 4.02–3.97 (m, 1 H), 3.05 (dd, *J* = 4.9, 13.7 Hz, 1 H), 2.74–2.67 (m, 1 H), 2.57–2.46 (m, 2 H), 2.34 (s, 3 H), 1.81–1.75 (m, 1 H), 1.72–1.57 (m, 2 H), 1.35–1.11 (m, 16 H), 0.87 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 144.3, 137.7, 135.5, 132.3, 130.3, 129.9, 129.3, 128.2, 76.8, 74.5, 64.8, 39.5, 39.4, 39.3, 33.8, 31.8, 29.9, 29.58, 29.53, 29.3, 26.3, 22.6, 14.1; IR (film) 3422, 1658 cm^{-1}; MS (ESI): 422.3057 (422.3059 calculated for $C_{28}H_{39}NO_2$, M + H^+).

(±)–(2*S*,3*S*,5*R*)–2-(4-Methoxybenzyl)-3-hydroxy-5-nonylpyrrolidine (V-75). A

flame-dried flask was cooled under a stream of nitrogen and charged with **V-62** (100 mg, 0.2 mmol) and tetrahydrofuran (1 mL). The resulting solution was cooled to 0 °C and $LiAlH_4$ (2 mL, 2 mmol, 1 M in tetrahydrofuran) was added dropwise via syringe. The resulting mixture was stirred at 60 °C until the starting material was consumed as judged by TLC analysis (ca. 16h). The reaction mixture was diluted with dry ether (2 mL), cooled to 0 °C and slowly quenched with an aqueous saturated solution of Na_2SO_4 (0.3 mL). The heterogeneous mixture was diluted with additional ether (2 mL) and was filtered through a small pad of celite. The filter was washed with additional ether and the combined organic filtrates were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil obtained was purified by flash chromatography using 5% MeOH/CH_2Cl_2 as the eluent to afford 62.8 mg (87%) of the title compound as a white solid, m.p. 47-49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.83–3.76 (m, 4 H), 2.83–2.76 (m, 2 H), 2.33 (s, 3 H), 2.26–2.06 (m, 3 H), 1.94–1.74 (m, 1 H), 1.76–1.55 (m, 2 H), 1.45–1.38 (m, 1 H), 1.37–1.16 (m, 14 H), 0.88 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 131.1, 130.2, 113.8, 73.9, 70.3, 66.0, 55.2, 39.2, 38.5, 34.6, 32.5, 31.9, 29.8, 29.6, 29.5, 29.3, 26.3, 22.7, 14.1; IR (film) 3412 cm^{-1}; MS (ESI): 348.2902 (348.2903 calculated for $C_{22}H_{37}NO_2$, M + H^+).

(±)–(2*S*,3*R*,5*R*)–2-(4-Methoxybenzyl)-3-hydroxy-5-nonylpyrrolidine (V-76). This compound was prepared on a 0.2 mmol scale using a procedure analogous to that employed for the synthesis of **V-75** except that removal of the silyl group required the use of TBAF after LAH reduction (see **V-73** for protocol, K_2CO_3 was not used). Substrate **V-63** (110 mg, 0.2 mmol) was transformed to the title compound to afford 63.2

mg (88%) of a white solid, m.p. 49-50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 4.03–3.96 (m, 1 H), 3.79 (s, 3 H), 3.05–2.97 (m, 1 H), 2.55–2.41 (m, 2 H), 2.40–2.32 (m, 4 H), 1.80–1.73 (m, 1 H), 1.72–1.59 (m, 2 H), 1.35–1.11 (m, 15 H), 0.96 (s, 1H), 0.88 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 130.7, 130.2, 114.0, 74.8, 64.9, 55.2, 39.1, 39.0, 38.3, 33.9, 31.9, 30.0, 29.59, 29.55, 29.3, 26.4, 22.7, 14.1 (two aliphatic carbons are incidentally equivalent); IR (film) 3392 cm^{-1}; MS (ESI): 348.2906 (348.2903 calculated for $C_{22}H_{37}NO_2$, M + H^+).

(±)–(2*S*,3*S*,5*R*)–2-(4-Trifluoromethylbenzyl)-3-hydroxy-5-nonylpyrrolidine (V-77). This compound was prepared on a 0.1 mmol scale using a procedure analogous to that employed for the synthesis of **V-73**. Substrate **V-64** (59 mg, 0.1 mmol) was transformed to the title compound to afford 31.5 mg (82%) of a white solid, m.p. 45–47 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2 H), 7.41 (d, *J* = 8.2 Hz, 2 H), 3.80–3.72 (m, 1 H), 3.00–2.92 (m, 1 H), 2.88 (dd, *J* = 4.4, 13.2 Hz, 1 H), 2.34 (s, 3 H), 2.30–2.11 (m, 3 H), 2.03–1.90 (m, 1 H), 1.78–1.67 (m, 1 H), 1.44 (dd, *J* = 5.6, 13.4 Hz, 1 H), 1.37–1.17 (m, 15 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 129.8, 128.4 (q, *J* = 32.2 Hz), 125.2, 124.3 (q, *J* = 272.0 Hz), 73.3, 70.3, 65.7, 39.3, 38.5, 34.9, 33.6, 31.9, 29.9, 29.61, 29.55, 29.3, 26.2, 22.7, 14.1; IR (film) 3401 cm^{-1}; MS (ESI): 386.2671 (386.2671 calculated for $C_{22}H_{34}F_3NO$, M + H^+).

(±)–(2*S*,3*R*,5*R*)–2-(4-Trifluoromethylbenzyl)-3-hydroxy-5-nonylpyrrolidine (V-78). This compound was prepared on a 0.1 mmol scale using a procedure analogous to that employed for the synthesis of **V-73**. Substrate **V-65** (59 mg, 0.1 mmol) was

transformed to the title compound to afford 30.8 mg (80%) of a white solid, m.p. 48–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 4.00–3.90 (m, 1 H), 3.00 (dd, *J* = 4.5, 13.5 Hz, 1 H), 2.75–2.62 (m, 1 H), 2.57–2.42 (m, 2 H), 2.32 (s, 3 H), 1.83–1.52 (m, 3 H), 1.48–1.06 (m, 16 H), 0.88 (t, *J* = 6.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 129.7, 128.5 (q, *J* = 32.4 Hz), 125.2, 124.3 (q, *J* = 272.0 Hz), 76.7, 74.5, 64.7, 39.6, 39.3, 39.1, 33.9, 31.9, 30.0, 29.6, 29.5, 29.3, 26.3, 22.7, 14.1; IR (film) 3369, 2927, 1326, 1126, 843 cm^{-1}; MS (ESI): 386.2673 (386.2671 calculated for $C_{22}H_{34}F_3NO$, M + H^+).

Asymmetric aldol reaction of 2-undecanone with acrolein. A flame-dried flask was cooled under a steam of nitrogen and charged with (-)-DIPCl (514 mg, 1.6 mmol), and CH_2Cl_2 (6 mL). A thermocouple was inserted to the solution through a rubber septum and the mixture was cooled to an internal temperature of –78 °C. Triethylamine (280 μL, 2 mmol) was added followed by a solution of 2-undecanone (207 μL, 1 mmol) in CH_2Cl_2 (1 mL). The resulting was mixture was stirred at -78 °C for 1.5h, then a solution of acrolein (100 μL, 1.5 mmol) in CH_2Cl_2 (3 mL) was added slowly dropwise and the reaction mixture was stirred at –78 °C for an additional 2.5h then warmed to 0 °C with stirring for 1h. The disappearance of starting material was verified by TLC analysis. The reaction mixture was diluted with Et_2O and quenched with a buffer solution (10 mL, pH = 7). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The organic extracts were combined and concentrated *in vacuo* in a flask equipped with a magnetic stir bar. The crude oil obtained was diluted with MeOH (7 mL), a buffer solution (1 mL, pH = 7) and the mixture was cooled to 0 °C. An aqueous solution of

H_2O_2 (2 mL, 30 wt. %) was slowly added and the mixture was stirred at rt for 3h. The reaction was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The extracts were washed with saturated aqueous $NaHCO_3$ solution and $FeSO_4$ saturated aqueous solution (3x, until the green color persisted). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified using 20 % Et_2O/Hexanes as the eluent to afford 169.5 mg (78 %) of nonracemic **V-48** as a colorless oil. This material was characterized by ^{1}H NMR analysis prior to derivatization to assay enantiopurity; NMR data were identical to those given above.

Benzoylation of nonracemic V-48. A flame-dried flask was cooled under a steam of nitrogen and charged with nonracemic **V-48** (165 mg, 0.73 mmol), and pyridine (7 mL). The mixture was cooled to 0 °C and benzoyl chloride (340 µL, 2.92 mmol) was added dropwise via syringe. The resulting mixture was stirred at 0 °C until the starting material was consumed as judged by TLC analysis (ca. 1h). The reaction mixture was then diluted with water (10 mL) and ethyl acetate (15 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash chromatography using 5% ethyl acetate/hexanes as the eluent to afford 174.8 mg (73 %) of *O*-benzoyl-**V-48** as a colorless oil. This optical purity of this material was judged to be 48% ee by HPLC analysis using the method described below. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.0 Hz, 2 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.43 (t, J = 7.8 Hz, 2 H), 6.00–5.90 (m, 2 H), 5.41–5.34 (m, 1 H), 5.26–5.20 (m, 1 H), 3.02–2.94 (m, 1 H), 2.82–2.74 (m, 1 H), 2.45 (t, J = 7.4 Hz, 2 H), 1.62–1.51 (m, 2 H), 1.33–1.18 (m,

12 H), 0.87 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 165.4, 135.4, 133.0, 130.1, 129.6, 128.4, 117.1, 71.1, 47.0, 43.5, 31.8, 29.38, 29.36, 29.2, 29.1, 23.6, 22.6, 14.1.

Assay for determination of enantiomeric excess of nonracemic V-48 prepared through asymmetric aldol reaction of undecanone with acrolein: The *O*-benzoyl derivative of V-48 (20 mg) was dissolved in hexanes (2 mL) and injected in an HPLC apparatus equipped with chiral column (*R*,*R*) WHELK-O 1 (Regis Tech.). The system permitting separation of enantiomers (RT = 8.200 min and 8.850 min) was found to be 5 % isopropanol/hexanes, flow rate = 1 mL/min at wavelengths 220 nm and 254 nm. The ee then measured was 48 %.

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[1] Reproduced in part with permission from Beaudoin Bertrand, M.; Wolfe, J. P. "A Concise Stereoselective Synthesis of Preussin, 3-*epi*-Preussin, and Analogues" *Org. Lett.* **2006**, *8*, 2353–2356. © 2006 American Chemical Society.

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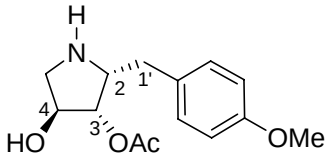
Chapter VI

Studies Towards the Synthesis of (–)-Anisomycin

Background

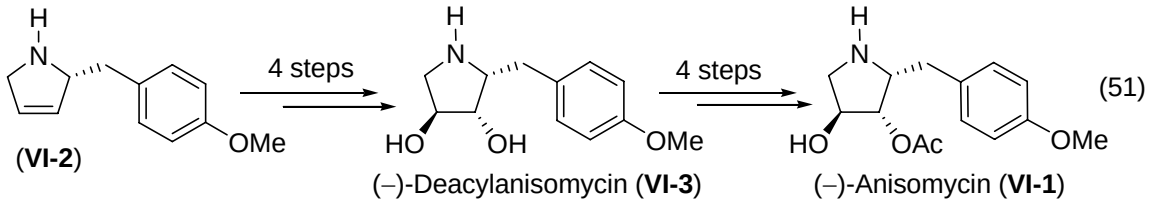
The pyrrolidine natural product (–)-anisomycin (**VI-1**) was first isolated in 1954 by Sobin and Tanner from the fermentation broths of *Streptomyces griseolous* and *Streptomyces roseochromogens*.[1] In 1968 its structure was elucidated[2] and its absolute configuration was determined as 2*R*,3*S*,4*S*.[3] Early studies revealed that anisomycin inhibits peptide synthesis in eukaryotic systems due to its ability to selectively bind to the 60S ribosomal unit, which has led to its widespread use as a control reference for protein synthesis inhibition in molecular biology.[4] The essential structural features anisomycin possesses that enable protein synthesis inhibition include a secondary amine group adjacent to an asymmetric carbon with the *R* configuration, linked through a methylene to a sterically unhindered six-membered aromatic ring.[4] Anisomycin also exhibits antiprotozoal and antifungal properties,[5] and is used in the clinical treatment of amoebic dysentery,[6] *Trichomona vaginitis*,[7] and for the eradication of bean mildew.[8] Anisomycin was also shown to have antitumor activity against human tumor cell lines,[9] and was found to be a potent activator of kinase cascades leading to apoptosis.[10] Finally, anisomycin was recently identified as a potential anti-psychotic drug.[11] Since protein

synthesis is required for memories to be saved in the brain,[12] anisomycin's ability to function as a protein synthesis inhibitor lends to its potential in the inhibition of "fear memory" in patients traumatized by memories of terror or tragedy.



(–)-Anisomycin (**VI-1**)

Owing to its interesting biological properties, (–)-anisomycin (**VI-1**) has been a popular target for total synthesis, and has been prepared via 21 different asymmetric routes[13] ranging from 8 to over 20 steps. However, these routes are not without limitations. The majority of these synthetic routes are lengthy, low yielding and/or suffer from inefficient protecting group chemistry in later stages of the syntheses due to problematic selective acylation of the hindered C3 hydroxyl group.[14,15] Most of these syntheses intercept one of two common intermediates, 2-arylmethyldihydropyrrole (**VI-2**)[16] or biologically active (–)-deacylanisomycin (**VI-3**),[9,17] which are further transformed to (–)-anisomycin (**VI-1**) in eight and four steps, respectively (eq 51).



(**VI-2**) (–)-Deacylanisomycin (**VI-3**) (–)-Anisomycin (**VI-1**) (51)

In all previously described (–)-anisomycin (**VI-1**) syntheses, the C2 *p*-methoxybenzyl group is introduced at the beginning of the sequence, starting with the chiral amino acid tyrosine, or via the reaction of an organometallic species (aryllithium or Grignard reagent) on a sugar-derived electrophile. Thus, the previously described syntheses of (–)-anisomycin (**VI-1**) are generally not well suited for the rapid generation of analogues that differ in the nature of the aryl substituent. A concise approach to this molecule that involves the installation of the aryl group near the end of the synthetic route would be of great value, particularly if the arene could be incorporated in a manner that would permit synthesis of functionalized and/or heteroaryl analogs from readily available precursors.

Due to the limitations of existing synthetic routes, few studies on the effect of arene substitution on the biological activity of anisomycin (**VI-1**) analogs have been performed. The aryl analogs prepared and tested for their antiprotozoal, antifungal and antibacterial activities are limited to racemic *p*-Me, *p*-H, *o*-OMe, *m*-OMe and C1'-Me substituted anisomycin derivatives.[18] These investigations demonstrated that the nature of the C1' aryl group has a profound effect on biological activity; only the *p*-Me and *p*-H analogs showed activity. The activity dropped dramatically as the methoxy substituent was moved to the *meta* and *ortho* position, or when an additional substituent was attached to the C1' benzylic carbon. Later, a study on an enantiopure anisomycin analog bearing a phenyl group in place of the *p*-methoxyphenyl moiety showed 40-fold less cytotoxic potency than **VI-1** against a human KB cell line.[17b] A number of other anisomycin analogs that differ on the oxygen substituent at C3[9,10,19] and C4[10] have been prepared and evaluated for their biological activities. However, they were not found to be as active as

VI-1. From this information, in combination with the anisomycin aryl analog results, a general structure that includes requirements for the molecule's bioactivity can be suggested (Figure 7).[17b,18] It would be highly desirable to evaluate the biological effect of the presence of other substituents on the arene portion of the natural product, such as electron-withdrawing groups. For this reason, we felt that a short synthetic route to anisomycin that would allow facile modification of the arene moiety would be of significant biological interest.

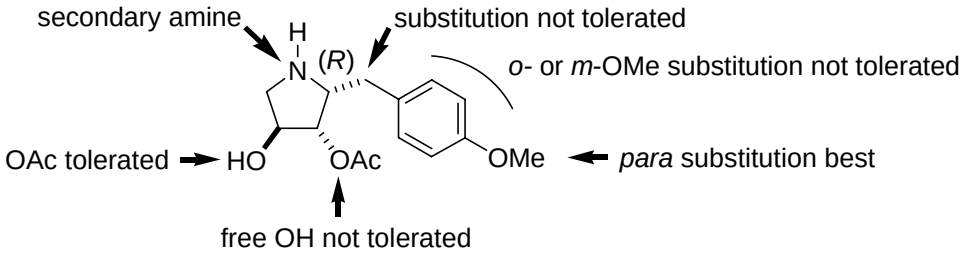


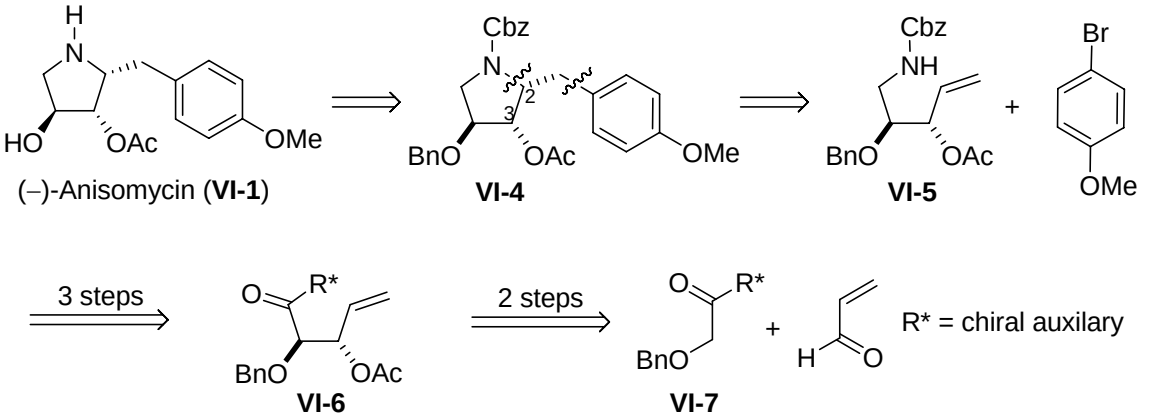
Figure 7. Anisomycin General Structural Requirements for Biological Activity

Synthetic Studies

We envisioned that anisomycin (**VI-1**) could be potentially attainable using our developed carboamination chemistry (Scheme 31), through coupling of substrate **VI-5** with 4-bromoanisole in a stereoselective fashion. This reaction could provide pyrrolidine intermediate **VI-4**, which could be further transformed in one step to the natural product via tandem deprotection of the N-Cbz and O-Bn protecting groups. Substrate **VI-5** could be accessed in three steps from protected diol **VI-6**, which could be prepared in two steps from a diastereoselective aldol reaction between **VI-7** and acrolein. This synthetic approach differs greatly from previous syntheses of anisomycin, and has many potential

advantages. First, it would circumvent the protecting group chemistry issues experienced previously, since both N-Cbz and O-Bn could potentially be removed in the final step in one operation (possibly via hydrogenation).[20] Additionally, this strategy would incorporate the aryl portion of the molecule towards the end of the sequence, which would allow for preparation of analogs by simply changing the aryl halide coupling partner in the key Pd-catalyzed carboamination step. The mild reaction conditions required for the N-Cbz and O-Bn deprotection of intermediate **VI-4** would tolerate sensitive arene functional groups, and thus would allow for preparation of various functionalized anisomycin analogs otherwise not accessible via previous routes. If successful, this route would become the shortest synthesis of (–)-anisomycin (**VI-1**) to date with a total of seven steps.[15]

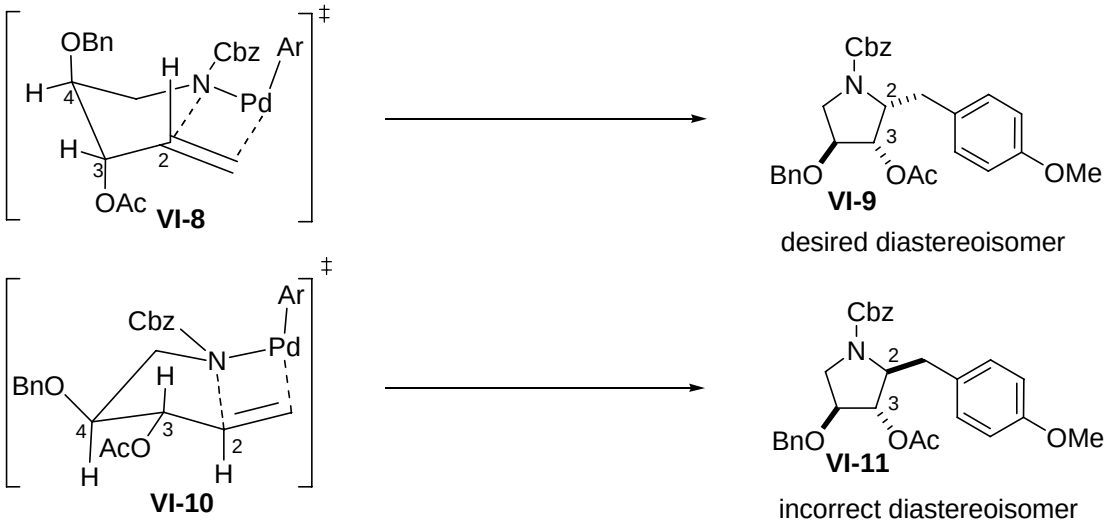
Scheme 31. Anisomycin Synthetic Strategy



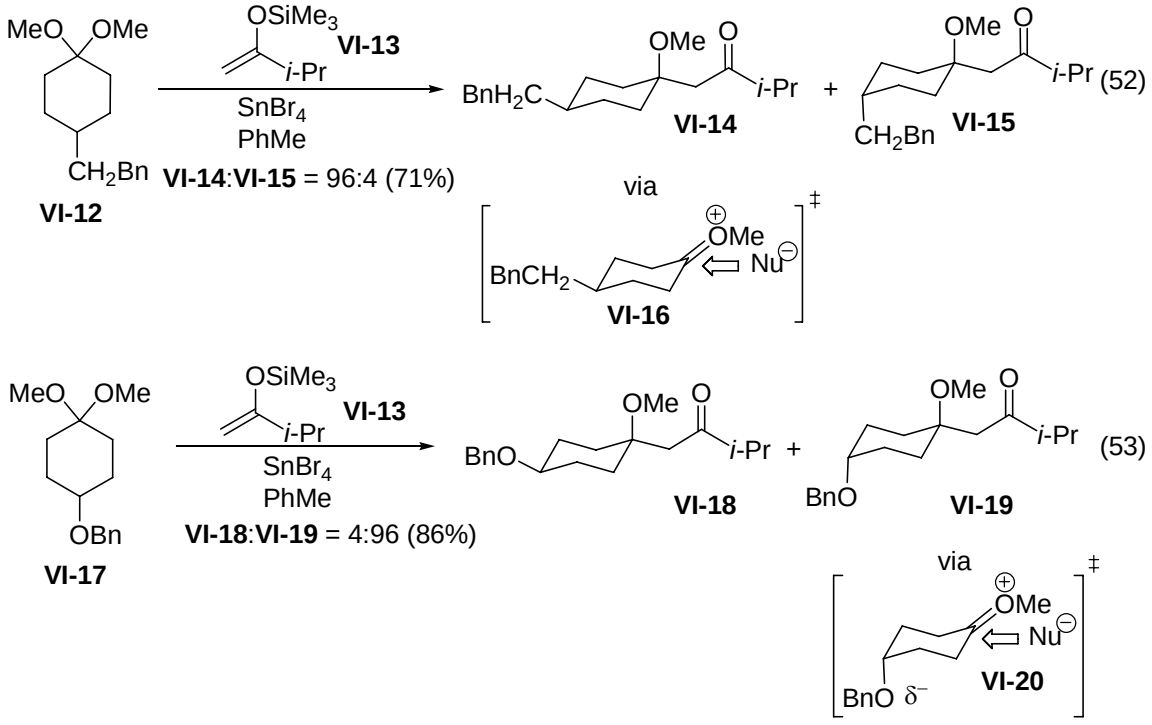
The key cyclization step proposed for the synthesis of trisubstituted pyrrolidine **VI-4** would challenge our previously developed methodology, as well as our proposed stereochemical model. One foreseen complication is related to the necessity of an O-Ac

moiety to be present in the allylic position of the substrate (**VI-5**). We anticipated that competing oxidative addition of the allylic acetate to generate a π-allyl palladium complex[21] may occur under the cyclization reaction conditions. A potential solution would then involve the use of a different oxygen protecting group and/or use of an aryl iodide to increase the relative rate of Ar–X vs allyl–X oxidative addition. An additional challenge with our proposed strategy lies in the requirement for the formation of a pyrrolidine product with a *cis* relationship between the C2 and C3 substituents. Indeed, the carboamination chemistry developed so far has only permitted access to 2,3-*trans* pyrrolidines (Chapters II-III). In order to obtain the desired 2,3-*cis* pyrrolidine isomer **VI-9**, transition state **VI-8**, in which both protected oxygen substituents lie in pseudo-axial positions, would have to be accessed (Scheme 32). In contrast, cyclization via transition state **VI-10**, in which both OR groups are pseudoequatorial, would produce the incorrect diastereoisomer (**VI-11**).

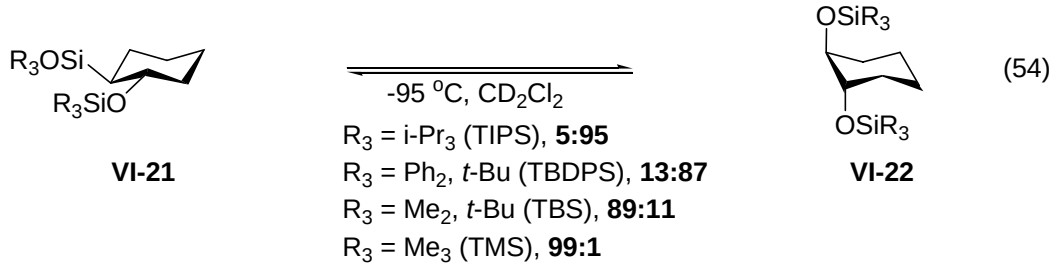
Scheme 32. Stereochemical Analysis



We imagined that electronic factors could play a critical role in the stereoselectivity of the carboamination, as it is possible that the C3-OAc and C4-OBn substituents would lie in the pseudoaxial positions (**VI-8**) to minimize dipole-dipole interactions. [22] Recent work from Woerpel and coworkers demonstrated that stereoelectronic effects have a large impact on diastereoselectivity in the reactions of alkoxy-substituted cyclohexanone oxocarbenium ions with enolsilanes. [23] When C4-alkylsubstituted cyclohexane substrate **VI-12** was treated with nucleophile **VI-13** and Lewis acid $SnBr_4$, a majority (96:4) of the expected 1,4-*trans* product **VI-14** was formed (eq 52). Conversely, when C4 O-Bn substituted cyclohexane substrate **VI-17** was subjected to the same reaction conditions, complete reversal of selectivity (4:96) was observed favoring the 1,4-*cis* product **VI-19** (eq 53). It was proposed that products **VI-14** and **VI-19** were formed via transition states **VI-16** and **VI-20**, respectively. The authors postulated that the alkoxy OBn group (**VI-17**) prefers an axial conformation in order to bring the opposing charges in closer proximity, thus leading to the observed 1,4-*cis* selectivity. Although this work was not directly related to our current proposal, it provided some indications that the axial C3-OAc and C4-OBn substituents in transition state **VI-8** may be favored for electronic reasons.

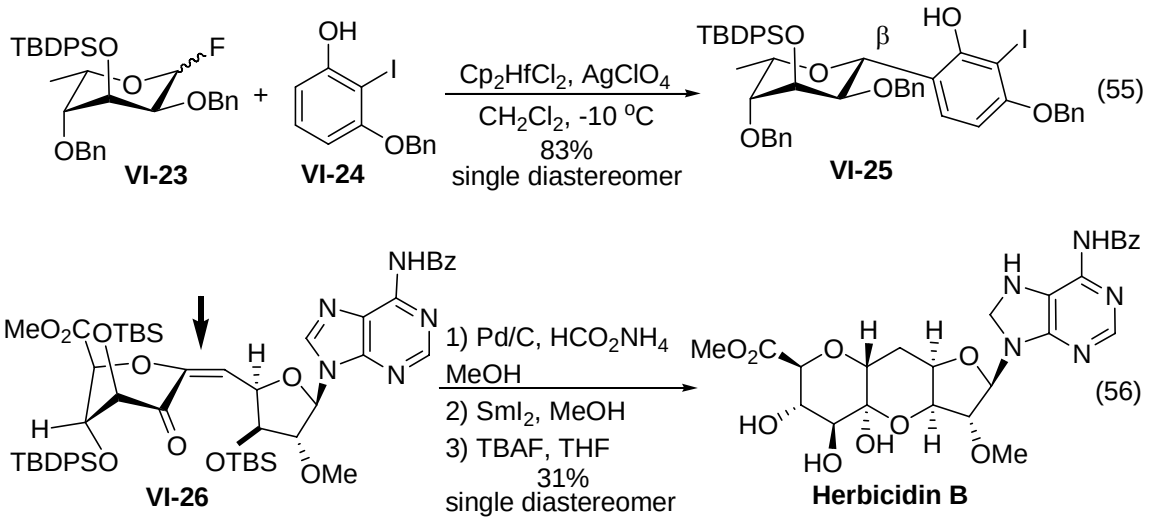


We also believed that transition state **VI-8** may be preferred on the basis of sterics. Marzabadi and co-workers demonstrated that at low temperature, the preferred conformation for 1,2-*trans*-cyclohexane diols protected with very bulky silyl groups was the 1,2-di-axial arrangement **VI-22** (eq 54).[24] Very recently, crystal structures of the 1,2-di-axial TIPS and TBDPS derivatives **VI-22** were obtained, showing that these di-axial conformations are preferred and stable at room temperature in the solid state as well as in solution.[25] This phenomenon is more commonly observed in pyranose systems where introduction of bulky protecting groups at vicinal hydroxyl groups causes the substituents to lie in axial orientations due to steric repulsions between the bulky protecting groups.[26]



(54)

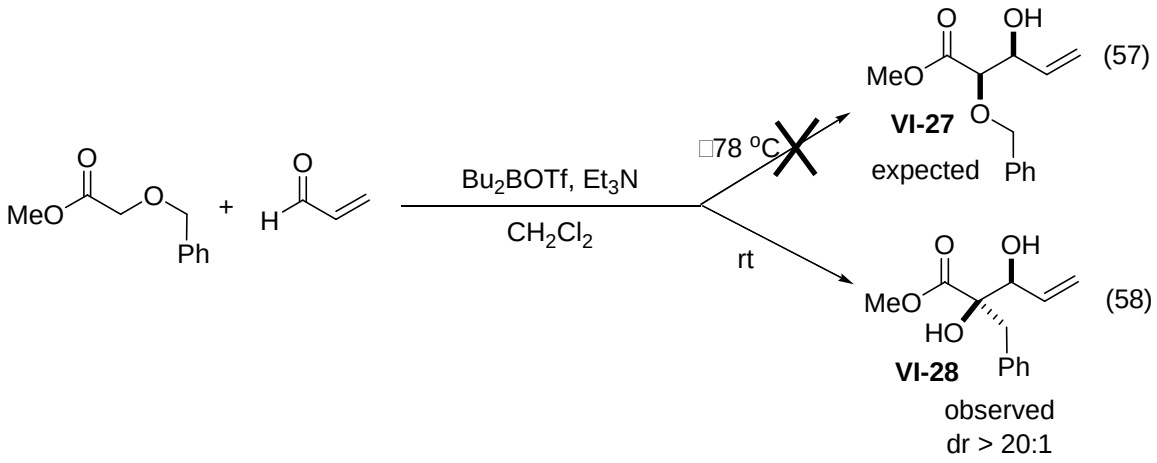
This substrate-control strategy has previously been applied to the stereoselective synthesis of sugar derivatives. As part of the synthesis of ravidomycin, the substrate's conformation was used to promote exclusive β-attack of the nucleophile **VI-24** on the activated sugar **VI-23** (eq 55).[27] The bulky O-TBDPS group was believed to force the O-Bn/O-TBDPS in the *trans*-diaxial conformation (**VI-23**) and consequently blocked the α-face for nucleophilic attack. Another elegant example of this strategy was demonstrated in the total synthesis of herbicidin B.[28] As shown in eq 56, the *trans*-diaxial conformation of **VI-26** blocked the bottom face of the molecule and promoted alkene reduction from the top face. This method permitted the authors to generate the final target in three steps from **VI-26** in 31% yield and as a single diastereoisomer. Other groups have used this strategy in the stereoselective formation of other sugar derivatives,[29] and crystal structures of stable axial-rich chair conformers of *myo*-inositol derivatives have also been obtained.[30]



These studies provided guidance in the choice of the oxygen protecting groups that could be used for the stereoselective cyclization of **VI-5** to afford 2,3-*cis* pyrrolidine **VI-4** via di-axial transition state **VI-8** (Scheme 32). We hypothesized that it would be likely that at least one bulky silyl protecting group would be necessary to favor transition state **VI-8**, however changing the C3 oxygen protecting group in **VI-5**, for example, would add two additional steps to our synthesis (O-silyl deprotection and O-Ac protection). For this reason, we initially studied O-Bn/O-Ac substrate **VI-5**, which would permit access to anisomycin in the most efficient manner.

Since our primary goal was to investigate the stereoselectivity of the key Pd-catalyzed carboamination, we opted for a racemic synthesis of substrate **VI-5** via intermediate **VI-6**. We believed this intermediate could be readily prepared via a *syn* selective boron-mediated aldol reaction between benzyl glycolate and acrolein.[31] However, attempts at preparing intermediate **VI-27** using Bu_2BOTf at low temperature (–

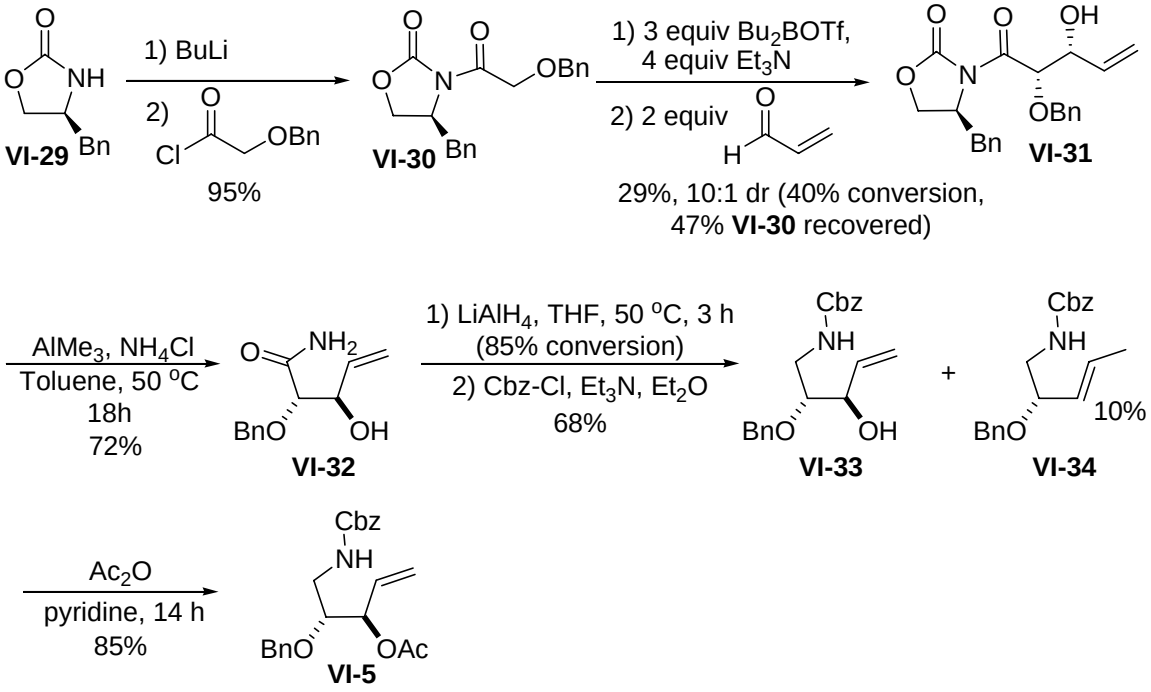
78 °C) were unsuccessful: unreacted starting material was recovered (eq 57). The reaction mixture was then warmed to rt and a new product **VI-28** was obtained in high selectivity (dr >20:1) (eq 58). NMR analysis suggested that the benzyl group had migrated from the oxygen to the carbon atom of the benzyl glycolate, and that the acrolein moiety had been incorporated. This indicated that the combination of both a Wittig rearrangement and an aldol reaction had occurred under the reaction conditions. This new tandem reaction was further investigated, and the results of these studies are presented in Chapters VII and VIII. Upon obtaining these results, we decided to rely on a different synthetic plan in order to access **VI-27**.



Our new synthetic plan for the synthesis of **VI-1** involved the use of the Evans chiral auxiliary **VI-29**, which would permit access to substrate **VI-5** in an enantiopure fashion (Scheme 33). Boron-mediated aldol reaction between **VI-30** and acrolein lead to 29% yield of **VI-31** as a 10:1 mixture of *syn*:*anti* diastereoisomers.[32] Transamination[33] of **VI-31** with $AlMe_3/NH_4Cl$ afforded amide **VI-32** in 72% yield. Amide **VI-32** was then partially reduced and protected with Cbz-Cl to afford **VI-33** in 68% yield along with 10%

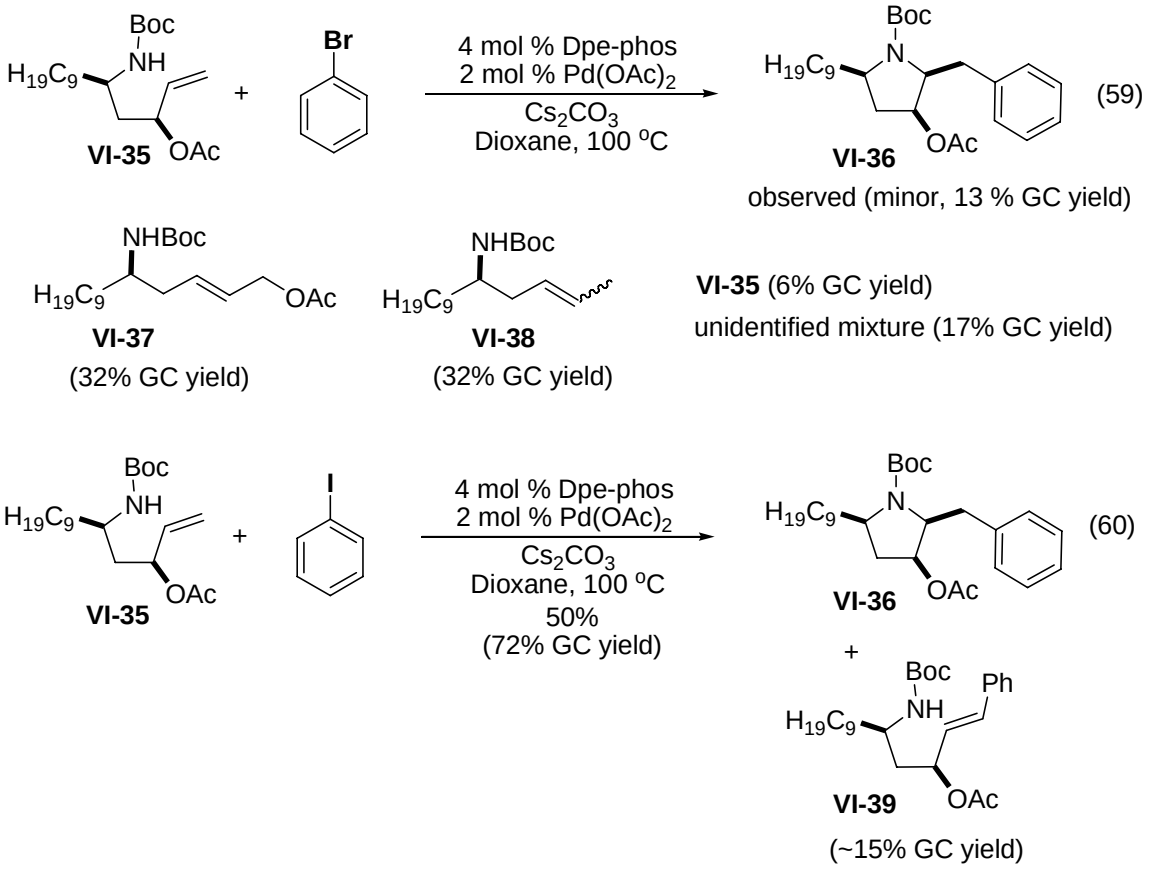
of elimination product **VI-34**.[34] Finally, substrate **VI-5** was accessed via acetate protection of **VI-33**.

Scheme 33. Synthetic Studies Towards Anisomycin I



Before attempting the key cyclization with chiral substrate **VI-5**, we tested the reactivity of model compound **VI-35** containing an allylic O-Ac group with bromobenzene under the optimized reactions (eq 59). As anticipated, competing oxidative addition of the allylic acetate to generate π-allyl palladium complex led to the formation of primarily **VI-37** and **VI-38**, and only a small amount of desired pyrrolidine **VI-36** was observed by crude ^{1}H NMR. We found that the use of iodobenzene improved the yield of the desired pyrrolidine **VI-36** to 50% (isolated), and the side-product (**VI-39**)

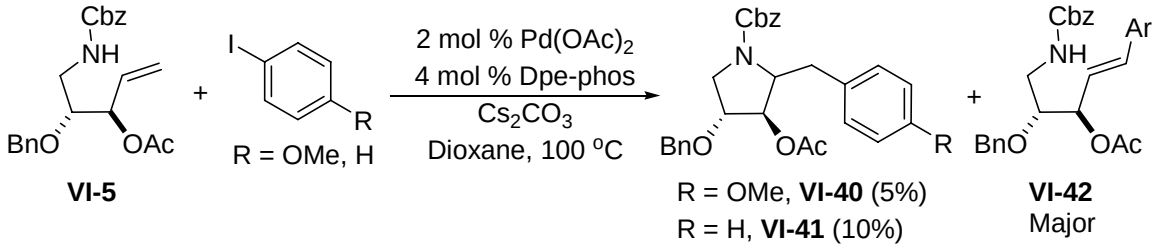
observed in this case resulted from competing Heck arylation of the substrate (eq 60).



The previous experiment provided the key information that an aryl iodide coupling partner would be preferable in the cyclization of anisomycin substrate **VI-5**. Thus, substrate **VI-5** was treated with iodoanisole or iodobenzene under the optimized carboamination reactions. Unfortunately, very small amounts of products **VI-40** or **VI-41** were generated, which was insufficient to elucidate the product stereochemistry. Most of the starting material (**VI-5**) was instead converted to Heck-type side-product **VI-42**. Since our initial efforts were towards evaluating the cyclization stereoselectivity, we opted to modify the C3 OAc protecting group (**VI-5**) to an O-silyl group. This

modification would allow testing of the key cyclization reaction selectivity with an aryl bromide and, according to the above discussion, would possibly favor *trans* di-axial transition state **VI-8** leading to the desired 2,3-*cis* pyrrolidine **VI-9** (Scheme 32).

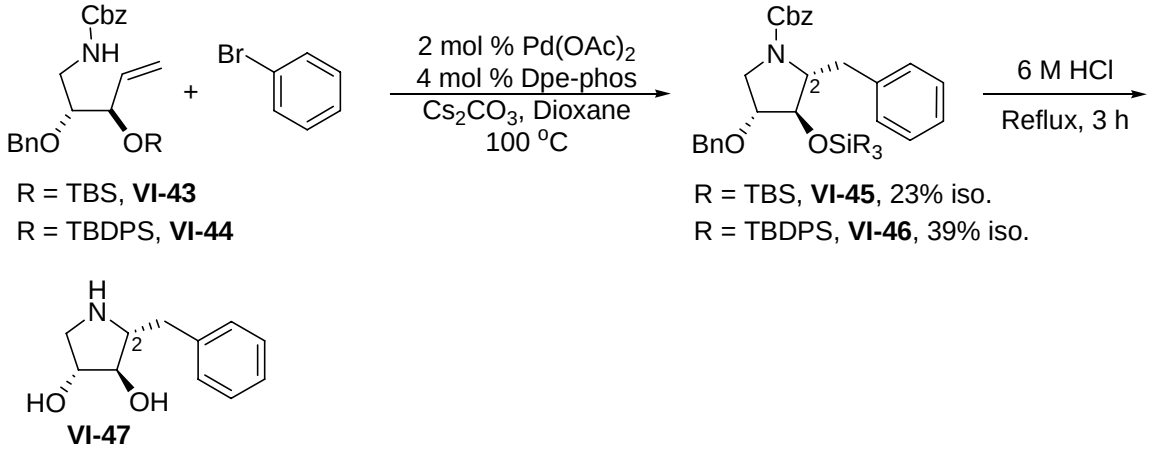
Scheme 34. Key Cyclization



Substrates **VI-43** and **VI-44** were then prepared in one step from **VI-33** and tested in the key cyclization (Scheme 35). Low yields of the pyrrolidines **VI-45** and **VI-46** were obtained, although in good diastereoselectivity (>15:1). The relative stereochemistry between C2-C3 was determined by comparison of NMR spectra of **VI-47** to literature data.[35] The stereochemistry of pyrrolidine isomers **VI-45** and **VI-46** was then assigned as the undesired 2,3-*trans* pyrrolidine isomer. We reasoned that a single bulky silyl group was not sufficient to favor the protected diol *trans*-diaxial arrangement at transition state **VI-8**, and that both oxygen silyl protecting groups needed to be bulkier. We were aware that the use of such a substrate would require many additional steps to prepare anisomycin and would most likely intercept (-)-deacylanisomycin (**VI-3**) (eq 51), leading to a formal synthesis of the natural product. At this point, however, our main goal was to determine if the change in protecting group would reverse or at least affect the relative

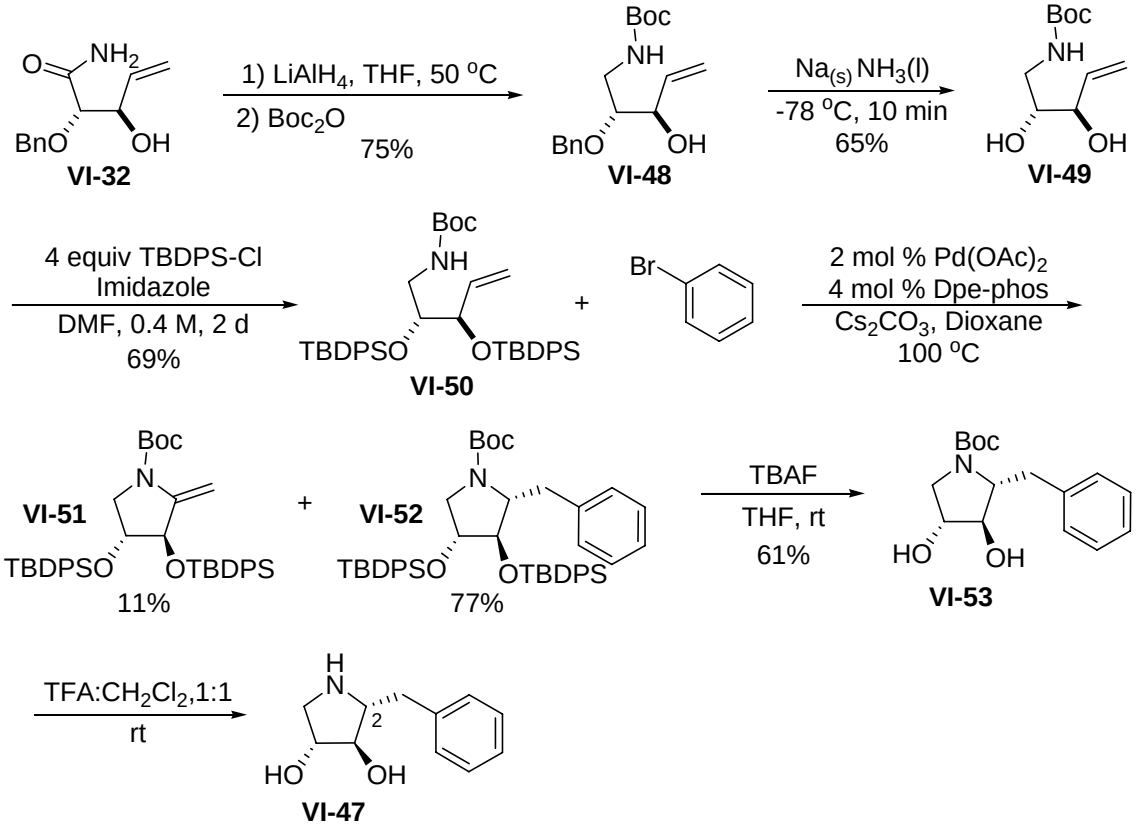
stereochemistry at C2 and C3.

Scheme 35. Synthetic Studies Towards Anisomycin II



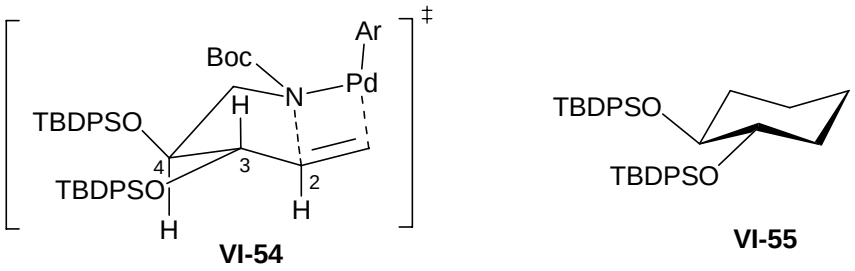
Di-TBDPS protected substrate **VI-50** was then prepared in three steps from **VI-32** and was subjected to the reaction conditions shown in Scheme 36. Pyrrolidine product **VI-52** was isolated in 77% yield and with good diastereoselectivity (>15:1), along with oxidative cyclization side-product **VI-51**. Derivative **VI-47** was then prepared in two steps from **VI-52** to compare to literature data as in the previous study. Unfortunately, the pyrrolidine isomer contained 2,3-*trans* stereochemistry.

Scheme 36. Synthetic Studies Towards Anisomycin III



These results indicate that the carboamination reaction is highly selective for the formation of 2,3-*trans* disubstituted products in this series, which are possibly obtained via transition state **VI-54** (Figure 8). It is surprising that the use of two bulky silyl protecting groups (TBDPS) did not affect the selectivity of the key cyclization and that the yield was dramatically increased (39% yield for **VI-46** vs 77% yield for **VI-52**). Indeed, it would be expected that the vicinal di-equatorial O-TBDPS substituents would suffer from severe gauche interactions in **VI-54**. A possible explanation is that **VI-54** compares to an open five-membered ring structure where the protected diols are in pseudoequatorial positions. The gauche interactions would then be less important than in

the related equatorial *trans* 1,2-cyclohexane diol **VI-55**.[25] In this transition state (**VI-54**), the O-TBDPS at C3 and olefin at C2 are in a *trans* relationship, leading to the observed 2,3-*trans* pyrrolidine product **VI-52** in high selectivity. The reasons for the higher yield of pyrrolidine product **VI-52** obtained in this particular example are unclear at this point.



VI-54 **VI-55**

Figure 8. Transition State Analysis

Conclusion

In conclusion, application of the carboamination methodology to the synthesis of (–)-anisomycin was investigated. The proposed synthetic route was designed to avoid protecting group issues, permit analog synthesis and limit the overall number of steps necessary to reach the natural product. A major challenge was the stereoselective formation of a product with 2,3-*cis* pyrrolidine stereochemistry, since our previous methodology only provided access to 2,3-*trans* pyrrolidines. Based on electronic and steric arguments, it was proposed that the desired pyrrolidine product should be obtained in high 2,3-*cis* selectivity. Unfortunately, performing the key reaction proposed initially did not afford synthetically useful amounts of the anisomycin precursor **VI-40**, and other substrate modifications led to the exclusive formation of a pyrrolidine with 2,3-*trans* stereochemistry. Although the proposed synthetic route did not allow for the synthesis of

anisomycin, it allowed the formation of **VI-47**, a biologically active stereoisomer of the natural product.[35] Further studies on the synthesis of aryl analogs of **VI-47** could be performed in order to evaluate their bioactivities.

Experimental section

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts and reagents were obtained from commercial sources and were used without further purification except (*S*)-4-benzyloxazolidin-2-one (**VI-29**)[36] and *tert*-butyl (3*S*,5*R*)-3-hydroxytetradec-1-en-5-ylcarbamate (**V-51**)[37] were prepared according to published procedures. Ratios of regioisomers and/or diastereomers were determined by ^{1}H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and/or combustion analysis, unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment.

(*S*)-4-Benzyl-3-(2-benzyloxyethanoyl)oxazolidin-2-one (VI-30).[38] A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with (*S*)-4-benzyloxazolidin-2-one **VI-29** (2.5 g, 14.1 mmol), and THF (43 mL) and cooled to -78 ^{o}C. A 1.59 M solution of BuLi in hexanes (9 mL, 14.2 mmol) was then added dropwise over 10 min followed by neat benzyloxyacetylchloride (2.4 mL, 15.5

mmol). The resulting mixture was stirred at -78 °C for 30 min then warmed to rt for 30 min. The reaction was quenched with a saturated solution of NH_4Cl (9 mL) and the solvent was removed under reduced pressure. The crude mixture was extracted with CH_2Cl_2 (100 mL), and the organic layer was washed with 1 M NaOH (50 mL) and brine (50 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using 20% ethyl acetate/hexanes as the eluent to afford 4.32 g (94%) of the title compound as a white solid, m.p. 68-70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.23 (m, 8 H), 7.22–7.15 (m, 2 H), 4.75–4.63 (m, 5 H), 4.28–4.15 (m, 2 H), 3.30 (dd, *J* = 3.1, 13.5 Hz, 1 H), 2.86–2.75 (m, 1 H).

(2*S*,3*R*)-4-Benzyl-3-2-(benzyloxy)-3-hydroxypent-4-enoyl)oxazolidin-2-one (VI-31).[39] A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and was charged with **VI-30** (6 g, 18.4 mmol), and CH_2Cl_2 (43 mL) and was cooled to 0 °C. A 1.0 M solution of Bu_2BOTf in CH_2Cl_2 (55 mL, 55 mmol) was then added followed by Et_3N (9.8 mL, 73.8 mmol). The resulting mixture was stirred at 0 °C for 1h. Neat acrolein (2.5 mL, 36.9 mmol) was then added and the mixture was stirred at 0 °C for 1h and at rt for 15 min. The reaction mixture was cooled to 0 °C and quenched by addition of pH 7 buffer (2 mL/mmol substrate). The heterogeneous mixture was diluted with MeOH (ca. 5-8 mL/mmol substrate) to afford a clear and homogeneous solution, then 30% aqueous H_2O_2 (3 mL/mmol substrate) was added slowly. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then diluted with

CH_2Cl_2 (~15 mL/mmol substrate), water (~8 mL/mmol substrate) and transferred to a separatory funnel. The layers were separated and the organic layer was washed with a saturated aqueous solution of $FeSO_4$ until the green color persisted in order to quench any peroxide remaining. *Caution! This procedure is highly exothermic. The $FeSO_4$ solution should be first added SLOWLY DROPWISE with a glass pipette.* The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated that the reaction went to 40% conversion. The crude product was purified by flash chromatography using 20% ethyl acetate/hexanes as the eluent to afford 2.84 g (47%) of recovered starting material and 2.1 g (29%) of the title compound as a colorless oil and as a 10:1 mixture of *syn*:*anti* diol diastereomers. The data is for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.22 (m, 8 H), 7.21–7.11 (m, 2 H), 6.03–5.88 (m, 1 H), 5.41–5.30 (m, 1 H), 5.27–5.18 (m, 2 H), 4.75–4.54 (m, 3 H), 4.46–4.37 (m, 1 H), 4.22–4.11 (m, 2 H), 3.25–3.16 (m, 1 H), 2.75–2.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 153.4, 136.9, 136.5, 135.0, 129.3, 128.9, 128.43, 128.35, 128.2, 127.4, 117.0, 79.6, 73.5, 73.3, 66.9, 55.5, 37.6.

(2*S*,3*R*)-2-(Benzyloxy)-3-hydroxypent-4-enamide (VI-32). A flame-dried flask was cooled under a stream of nitrogen and charged with ammonium chloride (864 mg, 16.2 mmol), and toluene (20 mL) and was cooled to 0 ^{o}C. A solution of trimethylaluminum in toluene (8 mL, 16 mmol, 2.0 M) was then added slowly. The mixture was allowed to warm to rt and was stirred for 30 min (bubbling was observed). To another flame-dried flask cooled with a stream of nitrogen was added **VI-31** (2.0 g,

5.3 mmol), and toluene (40 mL), and the solution was cooled to 0 °C. The $NH_4Cl/AlMe_3$ solution was then added slowly dropwise to this mixture. The resulting mixture was heated at 50 °C until the starting material was consumed as judged by TLC analysis (ca. 14 h). The mixture was cooled to 0 °C and a 1 M solution of HCl was added slowly dropwise (60 mL). Ethyl acetate was added and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl MeOH/CH_2Cl_2 as the eluent to afford 606 mg (52%) of the title compound as a colorless oil and as a 20:1 mixture of *syn*:*anti* diastereomers. The data is for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5 H), 6.65 (s, 1 H), 6.16 (s, 1 H), 5.98–5.88 (m, 1 H), 5.43–5.41 (m, 1 H), 5.39–5.36 (m, 1 H), 4.65 (s, 2 H), 4.48–4.42 (m, 1 H), 3.97 (d, J = 3.9 Hz, 1 H), 3.45 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 136.5, 136.1, 128.7, 128.4, 128.2, 116.8, 80.8, 73.5, 72.0; IR (film) 1668 cm^{-1}.

(2*R*,3*R*)-Benzyl-2-(benzyloxy)-3-hydroxypent-4-enylcarbamate (VI-33). A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with **VI-32** (140 mg, 0.63 mmol). The flask was purged with nitrogen, THF (5 mL) was added, and the resulting solution was cooled to 0 °C. A solution of $LiAlH_4$ in THF (3.2 mL, 3.2 mmol, 1.0 M) was added dropwise. The reaction mixture was warmed to 50 °C, and stirred for 3 h, then was cooled to 0 °C, quenched with H_2O (0.5 mL), and diluted with ether (5 mL). An aqueous solution of NaOH (2 mL, 10 M) was added followed by H_2O

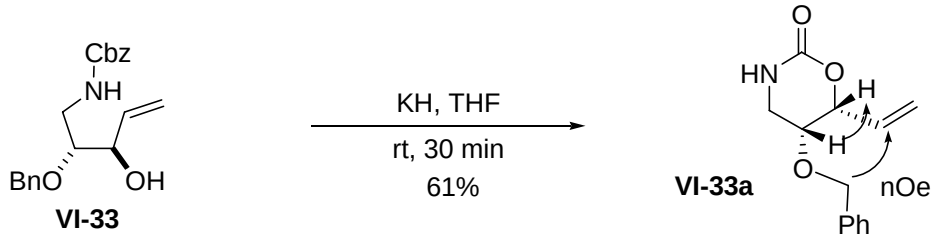
(0.5 mL), and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (15 mL). The combined extracts were dried over anhydrous sodium sulfate and filtered to afford a solution of (3*R*,4*R*)-5-amino-4-(benzyloxy)pent-1-en-3-ol in diethyl ether, which was used without purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of (3*R*,4*R*)-5-amino-4-(benzyloxy)pent-1-en-3-ol (6.3 mL, 0.63 mmol, 0.1 M) in diethyl ether and was cooled to 0 °C. Triethylamine (0.3 mL, 1.89 mmol) and benzyl chloroformate (0.2 mL, 1.26 mmol) were added, and the resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 24 h). A solution of 1.0 M HCl (10 mL) was added, the mixture was transferred to a separatory funnel, and was extracted with diethyl ether (3 X 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 2.5% MeOH/CH_2Cl_2 as the eluent to afford 146 mg (68%) of the title compound as a colorless oil. Elimination side-product **VI-34** was also isolated during purification and data for this product are provided below. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.22 (m, 10 H), 5.96–5.86 (m, 1 H), 5.39–5.31 (m, 1 H), 5.24–5.19 (m, 1 H), 5.18–5.12 (m, 1 H), 5.08 (s, 2 H), 4.68–4.49 (m, 2 H), 4.17–4.09 (m, 1 H), 3.54–3.38 (m, 2 H), 3.36–3.26 (m, 1 H), 2.67 (d, J = 5.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 137.7, 137.0, 136.4,

128.48, 128.46, 128.10, 128.05, 128.0, 126.9, 116.8, 80.0, 73.0, 72.9, 66.7, 40.9.

(*E*)-(2*S*)-Benzyl 2-(benzyloxy)pent-3-enylcarbamate (VI-34). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.23 (m, 10 H), 5.82–5.70 (m, 1 H), 5.40–5.30 (m, 1 H), 5.10 (s, 2 H), 4.58 (d, *J* =11.7 Hz, 1 H), 4.31 (d, *J* = 11.7 Hz, 1 H), 3.88–3.80 (m, 1 H), 3.47–3.39 (m, 1 H), 3.26–3.15 (m, 2 H), 1.74 (dd, *J* = 1.5, 6.6 Hz, 3 H).

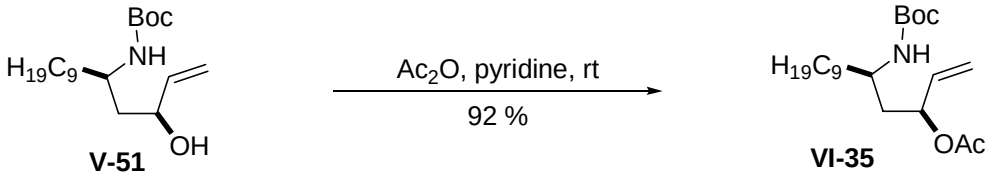
The stereochemistry of **VI-33** was determined by ^{1}H NMR nOe analysis of the product obtained through treatment of **VI-33** with KH to afford **VI-33a** as shown below.



(5*R*,6*R*)-5-(Benzyloxy)-6-vinyl-1,3-oxazinan-2-one (VI-33a). A flame-dried flask was cooled under a stream of nitrogen and charged with **VI-33** (52.2 mg, 0.153 mmol), KH (6.0 mg, 0.153 mmol) and THF (3 mL). The mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 0.5h). The reaction mixture was then diluted with diethyl ether (10 mL), and water (1 mL) was added slowly followed by a solution of 1.0 M HCl (1 mL). The layers were separated and the aqueous layer was washed with diethyl ether (3 x 5 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% MeOH/CH_2Cl_2 as the eluent to afford 22 mg (61%) of the title compound as a colorless oil and as a 10:1 mixture of *syn*:*anti*

diastereomers. The data is for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 6.43 (s, br, 1 H), 6.08–6.00 (m, 1 H), 5.48–5.42 (m, 1 H), 5.39–5.34 (m, 1 H), 4.81–4.77 (m, 1 H), 4.68–4.64 (m, 1 H), 4.59–4.55 (m, 1 H), 3.84–3.79 (m, 1 H), 3.45–3.34 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 137.2, 132.2, 128.5, 128.0, 127.7, 118.8, 78.5, 71.6, 69.2, 42.2.

(3*R*,4*R*)-4-Benzyloxy-5-(benzyloxycarbonylamino)pent-1-en-3-yl acetate (VI-5). A flame-dried flask was cooled under a stream of nitrogen and charged with **VI-33** (100 mg, 0.29 mmol), pyridine (5 mL) and acetic anhydride (6 mL). The mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 14h). The reaction mixture was diluted with water (5 mL) and 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 crude product was purified by flash chromatography using 20% EtOAc/hexanes as the eluent to afford 90 mg (81%) of the title compound as a colorless oil and as a 10:1 mixture of *syn*:*anti* diastereomers. The data is for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.21 (m, 10 H), 5.91–5.80 (m, 1 H), 5.50–5.43 (m, 1 H), 5.37–5.22 (m, 2 H), 5.13–4.99 (m, 3 H), 4.73–4.65 (m, 1 H), 4.64–4.55 (m, 1 H), 3.68–3.59 (m, 1 H), 3.44–3.34 (m, 1 H), 3.28–3.14 (m, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 156.2, 137.6, 136.4, 132.2, 128.4, 128.1, 128.0, 127.9, 118.4, 78.2, 73.6, 73.0, 66.7, 40.9, 21.0.



(3*S*,5*R*)-5-(*tert*-Butoxycarbonylamino)tetradec-1-en-3-yl acetate (VI-35). A flame-dried flask was cooled under a stream of nitrogen and charged with **V-51**[37] (400 mg, 1.2 mmol), pyridine (4 mL) and acetic anhydride (8 mL). The mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 6h). The reaction mixture was diluted with water (5 mL) and 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 crude product was purified by flash chromatography using 10% EtOAc/hexanes as the eluent to afford 413 mg (92%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.74 (m, 1 H), 5.33–5.27 (m, 1 H), 5.26–5.21 (m, 1 H), 5.18–5.13 (m, 1 H), 4.29–4.21 (m, 1 H), 3.75–3.66 (m, 1 H), 2.08 (s, 3 H), 1.86–1.76 (m, 1 H), 1.62–1.54 (m, 2 H), 1.50–1.20 (m, 25 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 155.3, 136.5, 116.3, 78.9, 71.4, 47.1, 39.7, 35.8, 31.8, 29.9, 29.52, 29.46, 29.2, 28.3, 25.8, 22.6, 21.1, 14.0; IR (film) 1745, 1691 cm^{-1}. Anal calcd for $C_{21}H_{39}NO_4$: C, 68.25; H, 10.64; N, 3.79. Found: C, 68.12; H, 10.70; N, 3.89.

(*E*)-(5*R*)-(*tert*-Butoxycarbonylamino)tetradec-2-enyl acetate (VI-37). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79–5.69 (m, 1 H), 5.66–5.55 (m, 1 H), 4.52 (d, *J* = 6.3 Hz, 2 H), 4.33–4.25 (m, 1 H), 3.67–3.56 (m, 1 H), 2.32–2.21 (m, 1 H), 2.20–2.10 (m, 1 H), 2.06 (s,

3 H), 1.52–1.19 (m, 25 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 156.0, 131.9, 126.8, 65.0, 50.0, 38.1, 34.8, 31.9, 29.6, 29.52, 29.47, 29.3, 28.4, 25.9, 22.7, 21.0, 14.1 (two aliphatic carbons are incidentally equivalent).

(2*S*,3*S*,5*R*)-*tert*-Butyl-3-acetoxy-2-benzyl-5-nonylpyrrolidine-1-carboxylate (VI-36). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with **VI-35** (74 mg, 0.2 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol, 2 mol %), Dpe-phos (4.3 mg, 0.008 mmol, 4 mol %), Cs_2CO_3 (150 mg, 0.46 mmol) and iodobenzene (27 μL, 0.24 mmol). The tube was purged with nitrogen and dioxane (1 mL) was added. The resulting mixture was heated to 100 °C with stirring for 17 hours until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography using 2.5% ethyl acetate/hexanes as the eluent to afford 45 mg (50%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.14 (m, 5 H), 5.12–5.04 (m, 1 H), 4.37 (q, J = 7.0 Hz, 1 H), 3.78–3.69 (m, 1 H), 2.85–2.76 (m, 2 H), 2.43–2.30 (m, 1 H), 2.19–2.02 (m, 1 H), 1.91 (s, 3 H), 1.83–1.73 (m, 1 H), 1.52–1.21 (m, 24 H), 0.89 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 154.7, 138.7, 129.4, 128.2, 126.0, 79.5, 72.5, 59.9, 55.8, 36.7, 34.5, 31.9, 29.63, 29.56, 29.51, 29.3, 28.3, 26.3, 22.7, 20.8, 14.1 (two aliphatic carbon is incidentally equivalent);

IR (film) 1745, 1694 cm^{-1}.

(*E*)-(3*S*,5*R*)-5-(*tert*-Butoxycarbonylamino)-1-phenyltetradec-1-en-3-yl acetate (VI-39). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.20 (m, 5 H), 6.60 (d, *J* = 16 Hz, 2 H), 6.19–6.09 (m, 1 H), 5.53–5.43 (m, 1 H), 4.32–4.23 (m, 1 H), 3.83–3.69 (m, 1 H), 2.10 (s, 3 H), 1.97–1.90 (m, 1 H), 1.69–1.60 (m, 1 H), 1.49–1.19 (m, 25 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

(2*R*,3*R*)-Benzyl-2-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)pent-4-enylcarbamate (VI-43). A flame-dried flask was cooled under a stream of nitrogen and charged with **VI-33** (345 mg, 1.0 mmol), imidazole (136 mg, 2.0 mmol), TBS-Cl (242 mg, 1.6 mmol) and DMF (2 mL). The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 20 h). The reaction mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 330 mg (72%) of the title compound as a colorless oil and as a 10:1 mixture of *syn*:*anti* diastereomers. The data is for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 10 H), 5.97–5.88 (m, 1 H), 5.32–5.24 (m, 1 H), 5.21–5.14 (m, 1 H), 5.13–5.00 (m, 3 H), 4.67–4.48 (m, 2 H), 4.30–4.25 (m, 1 H), 3.49–3.38 (m, 2 H), 3.24–3.16 (m, 1 H), 0.87 (s, 9 H), -0.06–-0.07 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 156.1, 138.1, 136.5, 128.35, 128.31, 128.26, 127.9, 127.73, 127.70, 127.67, 116.0, 80.0, 73.6, 72.6, 66.4, 40.6, 25.7, 18.0, -4.9, -5.1.

(2*R*,3*R*)-Benzyl-2-(benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)pent-4-enylcarbamate (VI-44). A flame-dried flask was cooled under a stream of nitrogen and charged with **VI-33** (396 mg, 1.2 mmol), imidazole (157 mg, 2.3 mmol), TBDPS-Cl (523 mg, 1.9 mmol) and DMF (4 mL). The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 20 h). The reaction mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 289 mg (67%) of the title compound as a colorless oil and as a ~15:1 mixture of *syn*:*anti* diastereomers. The data is for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.59 (m, 5 H), 7.44–7.37 (m, 2 H), 7.38–7.26 (m, 8 H), 7.27–7.16 (m, 3 H), 7.08–7.01 (m, 2 H), 5.99–5.87 (m, 1 H), 5.35–5.27 (m, 1 H), 5.19–5.13 (m, 1 H), 5.12–5.02 (m, 2 H), 4.94 (s, 1 H), 4.46–4.39 (m, 1 H), 4.25–4.19 (m, 1 H), 4.10–4.05 (m, 1 H), 3.61–3.53 (m, 1 H), 3.30–3.23 (m, 1 H), 3.20–3.11 (m, 1 H), 1.14–1.00 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 137.9, 136.7, 135.9, 135.8, 135.6, 134.8, 133.5, 133.1, 129.9, 129.7, 129.4, 128.4, 128.3, 127.91, 127.89, 127.7, 127.58, 127.55, 127.52, 116.3, 80.0, 72.9, 72.1, 66.4, 40.4, 27.0, 19.2.

General Procedure for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with the aryl bromide (1.2 equiv), $Pd(OAc)_2$ (2 mol %), dpe-phos (4 mol %) and Cs_2CO_3 (2.3 equiv). The tube was purged with nitrogen and a solution of the *N*-protected amine substrate (1.0 equiv) in dioxane (5 mL/mmol substrate) was then added via syringe. The resulting mixture was heated to 100 °C with stirring until the starting material had been consumed as determined by GC analysis. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

(2*R*,3*R*,4*R*)-Benzyl-2-benzyl-4-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-1-carboxylate (VI-45). The general procedure was employed for the reaction of bromobenzene (41 mg, 0.26 mmol) with **VI-43** (100 mg, 0.22 mmol). This procedure afforded 27 mg (23%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis and as a single diastereoisomer; data are for the mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.29 (m, 13 H), 7.23–7.07 (m, 2 H), 5.27–5.15 (m, 2 H), 4.65–4.56 (m, 2 H), 4.10 (d, *J* = 3.7 Hz, 1 H), 3.90 (dd, *J* = 3.9, 11.7 Hz, 0.5 H), 3.84–3.76 (m, 2 H), 3.75–3.65 (m, 1.5 H), 3.38 (d, *J* = 4.1, 12.9 Hz, 0.5 H), 3.16 (d, *J* = 4.2, 12.9 Hz, 1 H), 2.94–2.81 (m, 1 H), 0.69 (s, 9 H), -0.30 (d, *J* = 7.8 Hz, 3 H), -0.35 (d, *J* = 3.4 Hz, 1

H).

(2*R*,3*R*,4*R*)-Benzyl-2-benzyl-4-(benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)pyrrolidine-1-carboxylate (VI-46). The general procedure was employed for the reaction of bromobenzene (49 mg, 0.31 mmol) with **VI-44** (151 mg, 0.26 mmol). This procedure afforded 66 mg (39%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis and as a single diastereoisomer; data are for the mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.03 (m, 24 H), 6.90–6.84 (m, 1 H), 5.25–5.14 (m, 2 H), 4.27–4.22 (m, 0.5 H), 4.19–4.15 (m, 1 H), 4.13–4.07 (m, 0.5 H), 3.99–3.93 (m, 1.5 H), 3.90–3.83 (m, 1 H), 3.81–3.76 (m, 0.5 H), 3.71–3.68 (m, 0.5 H), 3.67–3.58 (m, 1.5 H), 3.37–3.31 (m, 0.5 H), 3.10–3.04 (m, 0.5 H), 2.76–2.67 (m, 1 H), 0.89 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 155.1, 138.6, 138.5, 137.7, 136.9, 136.8, 136.0, 135.7, 135.6, 133.6, 133.4, 132.7, 132.5, 129.9, 129.69, 129.67, 129.6, 129.3, 128.5, 128.43, 128.41, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 127.09, 127.07, 126.1, 83.5, 82.9, 76.5, 75.2, 70.9, 70.8, 68.3, 67.8, 67.0, 66.7, 51.6, 51.4, 37.7, 36.9, 26.73, 26.70, 18.9.

(2*R*,3*R*,4*R*)-2-Benzylpyrrolidine-3,4-diol (VI-47).[35] A flame-dried flask was charged with **VI-45** (27 mg, 0.05 mmol) and 6 M HCl solution (~5 mL). The mixture was heated to reflux with stirring 3 h. The reaction mixture was diluted with water (5 mL) and extracted with Et_2O (5 mL). The aqueous phase was basified with a 10 M NaOH solution to pH ~12. The aqueous layer was then extracted with CH_2Cl_2 (5 x 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in*

vacuo to afford 5 mg (35%) of the title compound. This compound was found to be water-soluble. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5 H), 4.13–4.07 (m, 1 H), 3.84–3.78 (m, 1 H), 3.19–3.13 (m, 1 H), 3.12–3.07 (m, 1 H), 3.00–2.93 (m, 1 H), 2.92–2.87 (m, 1 H), 2.86–2.78 (m, 1 H).

(2*R*,3*R*)-*tert*-Butyl-2-(benzyloxy)-3-hydroxypent-4-enylcarbamate (VI-48). A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with **VI-32** (157 mg, 0.71 mmol). The flask was purged with nitrogen, THF (6 mL) was added, and the resulting solution was cooled to 0 °C. A solution of $LiAlH_4$ in THF (3.5 mL, 3.5 mmol, 1.0 M) was added dropwise. The reaction mixture was warmed to 50 °C with stirring for 3 h, and then was cooled to 0 °C, quenched with H_2O (0.5 mL), and diluted with ether (5 mL). An aqueous solution of NaOH (2 mL, 10 M) was added followed by H_2O (0.5 mL) and an insoluble white material precipitated. The organic supernatant was decanted to a clean Erlenmeyer flask and the precipitate was washed with ether (15 mL). The combined extracts were dried over anhydrous sodium sulfate and filtered to afford a solution of (3*R*,4*R*)-5-amino-4-(benzyloxy)pent-1-en-3-ol in diethyl ether, which was used without purification.

A flame-dried round-bottom flask was cooled under a stream of nitrogen and charged with a solution of (3*R*,4*R*)-5-amino-4-(benzyloxy)pent-1-en-3-ol (0.71 mmol) in diethyl ether (10 mL) and di-*tert*-butyl dicarbonate (232 mg, 1.07 mmol). The resulting

mixture was stirred for 4 h and then aqueous NaOH (20 mL, 1.0 M) was added. The biphasic mixture was vigorously stirred for 12 h and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified using 5% MeOH/CH_2Cl_2 as the eluent to afford 185 mg (85%) of the title compound as a colorless oil and as a ~15:1 mixture of *syn*:*anti* diastereomers. The data is for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5 H), 5.97–5.88 (m, 1 H), 5.40–5.34 (m, 1 H), 5.26–5.20 (m, 1 H), 4.94–4.87 (m, 1 H), 4.68–4.57 (m, 2 H), 4.18–4.11 (m, 1 H), 3.52–3.46 (m, 1 H), 3.44–3.35 (m, 1 H), 3.30–3.21 (m, 1 H), 2.82–2.77 (m, 1 H), 1.43 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 137.8, 137.0, 128.4, 127.94, 127.92, 116.7, 80.4, 72.9, 72.3, 40.3, 28.3.

(2*R*,3*R*)-*tert*-Butyl-2,3-dihydroxypent-4-enylcarbamate (VI-49). Following a published procedure,[40] treatment of **VI-48** (65 mg, 0.21 mmol) with Li/NH_3 at –78 ^{o}C followed by column chromatography (5% → 10% MeOH/CH_2Cl_2) provided 43 mg (66%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94–5.85 (m, 1 H), 5.41–5.34 (m, 1 H), 5.29–5.23 (m, 1 H), 5.17–5.10 (m, 1 H), 4.09–4.00 (m, 1 H), 3.64–3.55 (m, 1 H), 3.50–3.43 (m, 1 H), 3.41–3.33 (m, 1 H), 3.32–3.24 (m, 1 H), 3.20–3.09 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 136.9, 117.4, 80.0, 73.5, 73.4, 43.0, 28.3.

(2*R*,3*R*)-*tert*-Butyl-2,3-bis(*tert*-butyldiphenylsilyloxy)pent-4-enylcarbamate (VI-50). A flame-dried flask was cooled under a stream of nitrogen and charged with **VI-49** (97 mg, 0.45 mmol), imidazole (137 mg, 2.0 mmol), TBDPS-Cl (492 mg, 1.8 mmol) and DMF (1 mL). The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 2 days). The reaction mixture was diluted with water (5 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 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 using 2.5% → 5% ethyl acetate/hexanes as the eluent to afford 214 mg (69%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.47 (m, 4 H), 7.46–7.41 (m, 4 H), 7.40–7.31 (m, 4 H), 7.30–7.25 (m, 4 H), 7.24–7.16 (m, 4 H), 6.08–5.98 (m, 1 H), 5.32–5.23 (m, 1 H), 5.19–5.12 (m, 1 H), 4.64–4.57 (m, 1 H), 4.30–4.23 (m, 1 H), 3.75–3.69 (m, 1 H), 3.38–3.31 (m, 1 H), 3.30–3.22 (m, 1 H), 1.37 (s, 9 H), 1.06–0.89 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 135.8, 135.71, 135. 68, 135.5, 133.4, 133.2, 133.0, 129.65, 129.57, 127.6, 127.53, 127.50, 127.4, 116.3, 78.5, 75.2, 73.4, 42.1, 28.4, 27.0, 26.8, 19.22, 19.19.

(2*R*,3*R*,4*R*)-*tert*-Butyl 2-benzyl-3,4-bis(*tert*-butyldiphenylsilyloxy)pyrrolidine-1-carboxylate (VI-52). The general procedure was employed for the reaction of bromobenzene (49 mg, 0.31 mmol) with **VI-50** (105 mg, 0.15 mmol). This procedure afforded 90 mg (77%) of the title compound as a colorless oil. This compound was found to exist as a 1:1 mixture of rotamers as judged by ^{1}H NMR analysis and as a ~15:1

mixture of diastereoisomer; data is for the major isomer (mixture of rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–6.98 (m, 24 H), 6.90–6.84 (m, 1 H), 4.20–4.17 (m, 1.5 H), 4.15–4.09 (m, 1.5 H), 3.97–3.90 (m, 1.5 H), 3.70–3.63 (m, 1 H), 3.45–3.37 (m, 2 H), 3.17–3.10 (m, 1 H), 2.92–2.84 (m, 1.5 H), 1.53–1.38 (m, 9 H), 1.07–0.94 (m, 9 H), 0.86–0.76 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 155.0, 139.12, 139.07, 136.2, 136.1, 136.0, 135.8, 135.70, 135.65, 135.6, 135.5, 135.4, 133.5, 133.2, 133.01, 133.00, 132.9, 132.7, 130.1, 129.9, 129.71, 129.66, 129.62, 129.5, 129.40, 129.36, 128.4, 128.3, 127.9, 127.80, 127.76, 127.7, 127.60, 127.58, 127.5, 126.0, 125.9, 125.7, 79.7, 79.3, 79.1, 78.9, 78.4, 77.8, 77.4, 74.8, 68.4, 68.1, 59.1, 54.0, 53.7, 49.5, 37.8, 37.1, 33.9, 31.6, 28.6, 28.4, 27.9, 27.4, 27.1, 27.0, 26.9, 26.8, 26.6, 22.6, 19.0, 18.9, 14.1.

(2*R*,3*R*,4*R*)-*tert*-Butyl 2-benzyl-3,4-dihydroxypyrrolidine-1-carboxylate (VI-53). A flame-dried flask was cooled under a stream of nitrogen and charged with **VI-52** (45 mg, 0.06 mmol), THF (1 mL) and TBAF (0.5 mL, 1.0 M in THF). The resulting mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 12 h). The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography using 5% → 10% MeOH/CH_2Cl_2 as the eluent to afford 10 mg (61%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5 H), 4.17–4.11 (m, 1 H), 4.03–3.93 (m, 1 H), 3.92–3.74 (m, 2 H), 3.40–3.19 (m, 2 H), 2.94–2.86 (m, 1 H), 2.25 (s br, 1 H), 1.81 (s br, 1 H), 1.58–1.44 (m, 9 H).

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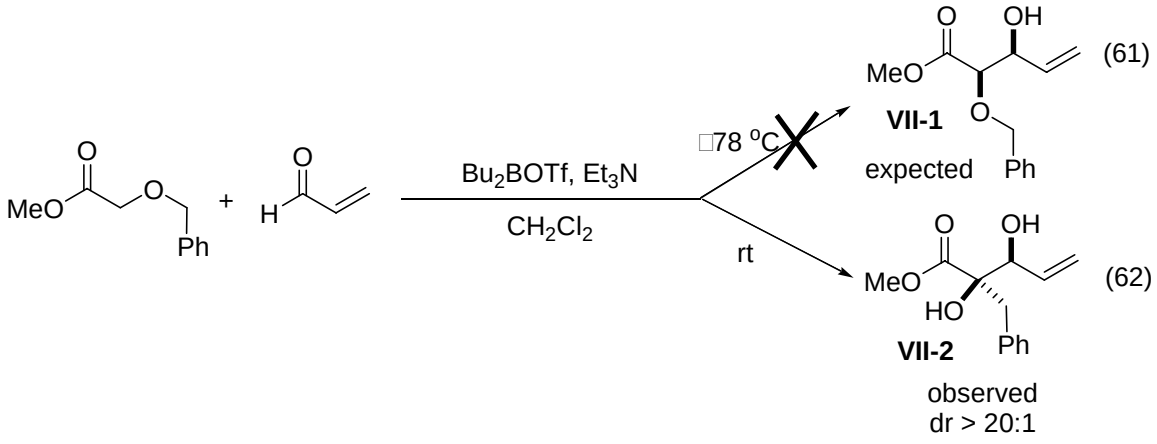
Part Two

Tandem Wittig Rearrangement-Aldol Reaction of Glycolate Esters with Aldehydes

Chapter VII

Introduction

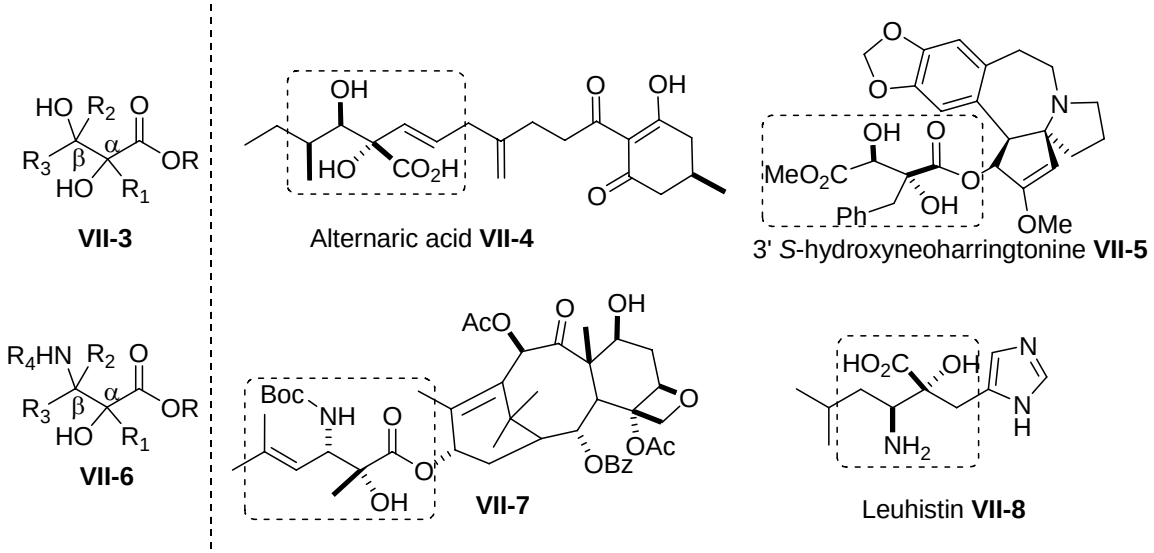
During our studies towards the synthesis of Anisomycin (Chapter VI), we discovered a tandem Wittig rearrangement-aldol reaction (eqs 61 and 62). The studies of this transformation in terms of scope, limitations and mechanism are presented in Chapter VIII. This chapter describes the significance of this new reaction as well as relevant background information on boron mediated aldol reactions and enolate [1,2]- and [2,3]-Wittig rearrangements.



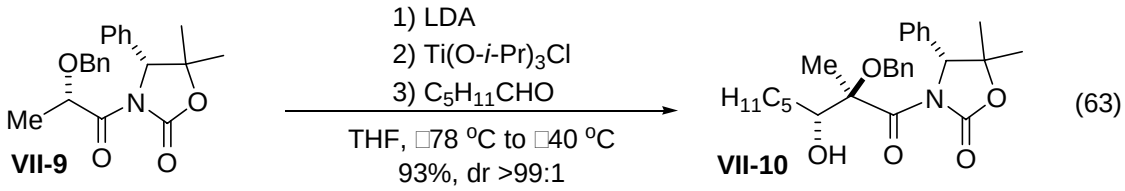
Significance and Synthesis of α-Alkyl-α-β-Dihydroxy Carbonyl Derivatives

Substituted α-alkyl-α-β-dihydroxy carbonyl-containing molecules (**VII-3**) bearing a tertiary alcohol moiety are important building blocks for organic synthesis and are found in various biologically active natural products (Figure 9). For example, alternaric acid (**VII-4**) inhibits germination of certain fungal strains at low concentrations (100 nM),[1] and displays selective phytotoxic activities.[2] Additionally, the natural product 3'*S*-hydroxyneoharringtonine (**VII-5**) exhibits antileukemia properties.[3] Substituted α-alkyl-α-β-amino ester derivatives (**VII-6**) are also of importance since they are used in the construction of unnatural β-peptides,[4] and in the preparation of active taxol derivatives (**VII-7**).[5] Substituted α-alkyl-α-β-amino esters (**VII-6**) are also found in biologically active natural products such as leuhistin (**VII-8**), which was identified as a potent aminopeptidase inhibitor.[6]

Figure 9. Biologically Active α-Alkyl-α-β-Dihydroxy and α-Alkyl-α-β-Amino Ester Derivatives

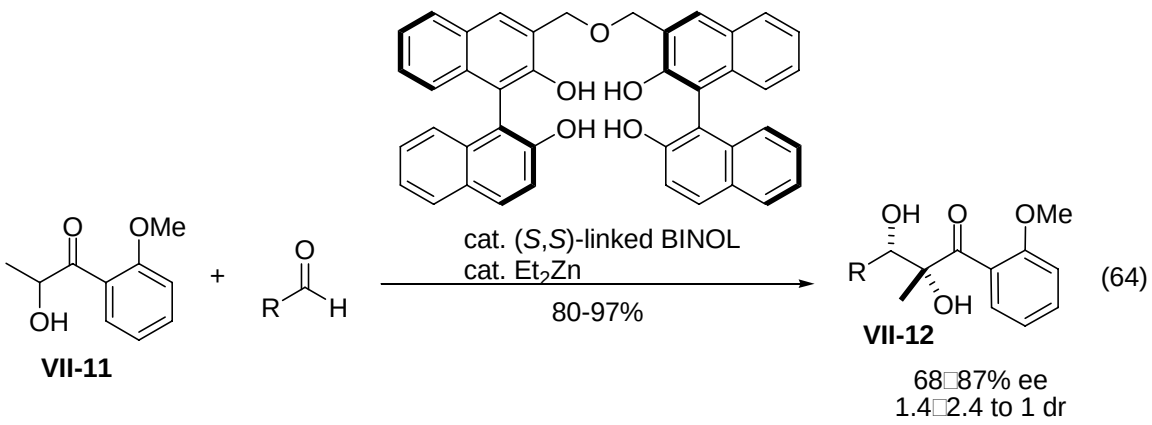


Many approaches have been developed for the construction of substituted α-alkyl-α,β-dihydroxy ester derivatives **VII-3**. However, most of these methods involve multiple synthetic steps, proceed with low selectivity, or are limited in scope. For example, aldol reactions of *O*-protected glycolate esters that form α-quaternary centers typically proceed with low diastereoselectivity (~3:1) unless BHT esters or chiral auxiliaries are employed.[7] A shown in eq 63, Kobayashi has demonstrated that the use of a chiral auxiliary allows for the synthesis of **VII-10** in high yield with excellent selectivity.[8]

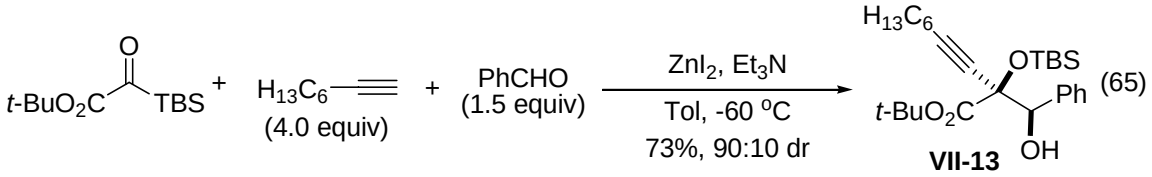


(63)

More recently, Shibasaki demonstrated that unprotected alcohols such as **VII-11** can react with various aldehydes in catalytic asymmetric aldol reactions that afford highly substituted products **VII-12**, albeit with modest ee and low diastereoselectivity (eq 64).[9] A drawback of this study is that additional chemical steps are required to effect oxidative cleavage of the aryl–acyl C–C bond to obtain an ester moiety from the ketone product **VII-12**.



Finally, a recent report from Johnson and coworkers described a three component coupling reaction between silyl glyoxylates, alkynes and aldehydes to afford products such as **VII-13** in good yields and good diastereoselectivity (eq 65).[10] The scope of this transformation has not been fully established, but it appears to be complementary to the Wittig rearrangement-aldol reaction described in Chapter VIII.

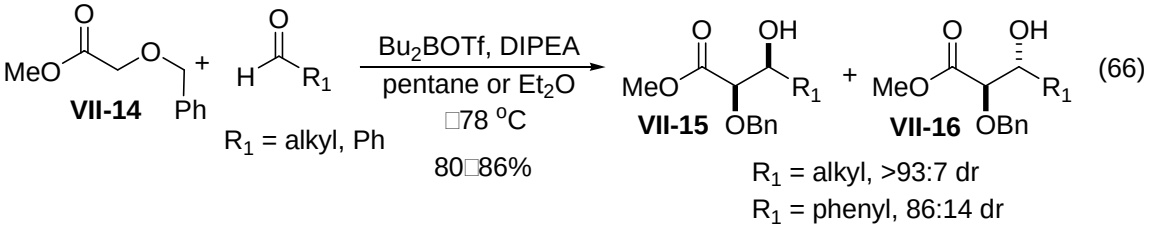


The tandem Wittig rearrangement-aldol reactions described in the following chapter have many potential advantages compared to the methodologies discussed above. The tandem reaction allows formation of two C–C bonds and creation of two stereocenters with high diastereoselectivity without the need for an auxiliary. Additionally, it permits the 'one-pot' synthesis of α-alkyl-α-β-dihydroxy esters from

readily available starting materials.

Boron-Mediated Glycolate Aldol Reactions

Despite the large amount of literature on boron-mediated aldol reactions,[11] only a single study on boron-mediated aldol reactions of methyl-*O*-benzyl glycolate **VII-14** has been reported (eq 66).[12] These reactions afforded good yields of the *syn* diol products **VII-15** with high diastereoselectivity using both benzaldehyde and aliphatic aldehydes. The authors did not observe the [1,2]-Wittig rearrangement of **VII-14** at low temperature (–78 °C).



(66)

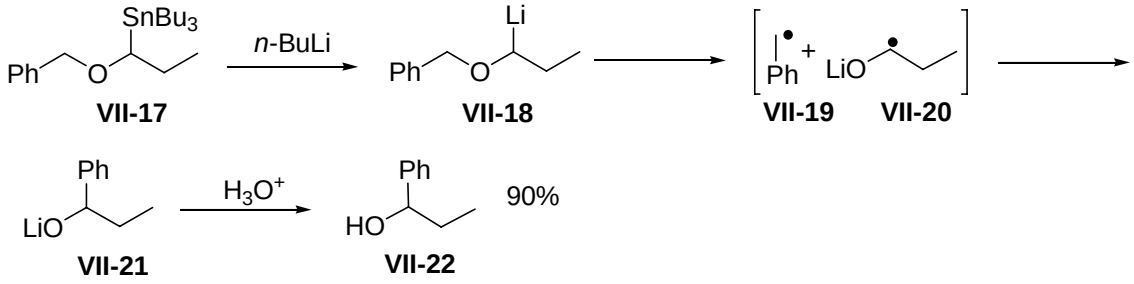
Our discovery occurred when we attempted to conduct the aldol reaction of **VII-14** with acrolein at low temperature (–78 °C). We observed incomplete conversion (60%) to aldol product **VII-15** by crude ^{1}H NMR. We opted to change DIPEA to a less hindered base such as Et_3N, but this modification lead to even lower conversion to product **VII-15** (<5 %) at –78 °C.[13] The reaction mixture was then warmed up to 0 °C and a new product (**VII-2**) was isolated. As described in Chapter VIII, we subsequently determined that

product **VII-2** originated from an unprecedented combination of an aldol reaction and a [1,2]-Wittig rearrangement.[14]

The Enolate [1,2]-Wittig Rearrangement

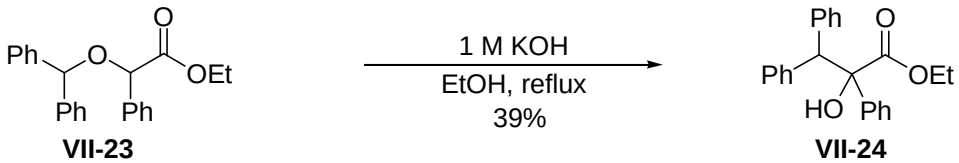
The classic [1,2]-Wittig rearrangement refers to the carbanion rearrangement of α-lithioethers, and involves a 1,2-alkyl shift onto the α-alkoxy carbanion terminus.[15] In a representative example, the benzyl ether carbanion **VII-18** is generated via transmetallation of **VII-17** with *n*-BuLi. This intermediate then undergoes a 1,2-benzyl migration to produce alkoxide **VII-21**, which yields **VII-22** upon aqueous workup (Scheme 37).[16] This reaction is believed to proceed via homolysis of the C–O bond to generate a radical (**VII-19**) and a radical anion (**VII-20**). As a result, the yields of the [1,2]-Wittig reactions depend highly on the migrating group radical stability. Additionally, since these transformations require strongly basic conditions, the yields are often low and the scope is frequently limited.

Scheme 37. [1,2]-Wittig Rearrangement

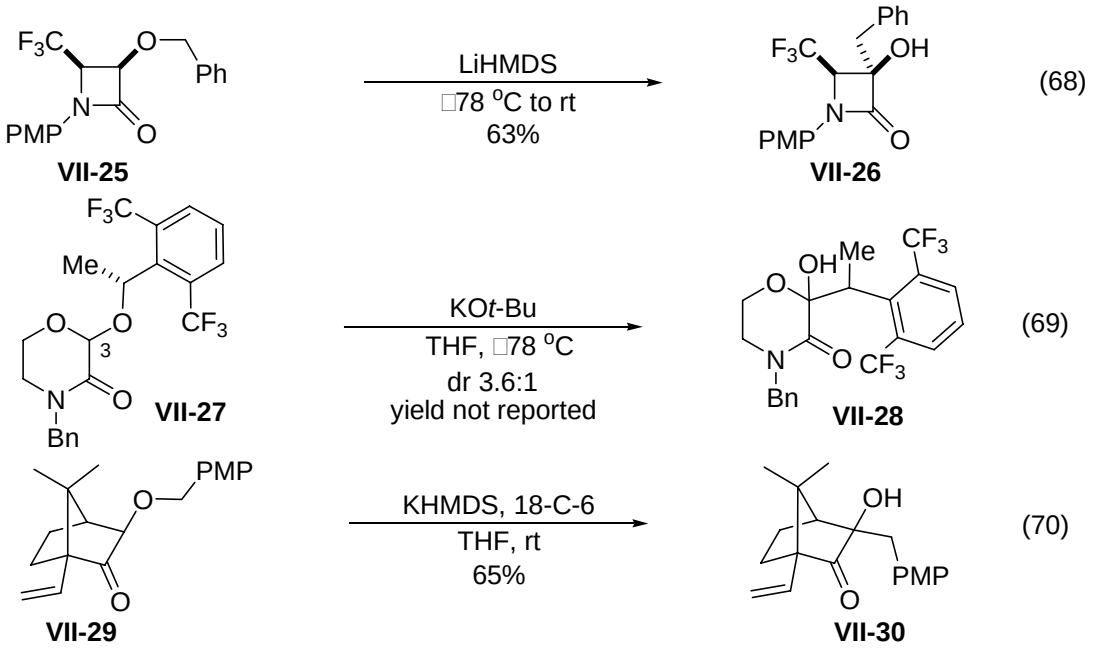


Although many reports of [1,2]-Wittig rearrangement reactions of organolithium species exist,[15] only six individual examples of 1,2-Wittig rearrangement of enolates have been described so far.[17] None of these examples involved the [1,2]-Wittig rearrangement from a boron enolate.

Early work described by Curtin dealt with the rearrangement of substrate **VII-23** under basic conditions at high temperature to afford product **VII-24** in low yield (eq 67).[17a,b] Later, the [1,2]-Wittig rearrangement of α-alkoxy lactam **VII-25** was observed using LiHMDS at rt to produce **VII-26** in 63% yield as a single diastereomer (eq 68).[17c] More recently, scientists at Merck subjected a 1:1 mixture of six-membered lactam diastereomers **VII-27** to basic conditions (KO*t*-Bu in THF at -78 ^{o}C) in order to improve the stereochemical purity of **VII-27** via C-3 enolization (eq 69). However, during the equilibration process they observed α-methyl benzyl migration of **VII-27** to afford **VII-28** as a mixture of diastereomers (~3.6:1 dr); no yield was reported for this transformation.[17d,18] Finally, Paquette demonstrated that the [1,2]-Wittig rearrangement could also occur from a ketone substrate (**VII-29**) to afford product **VII-30** in 65% yield as a single diastereomer (eq 70).[17e,f]

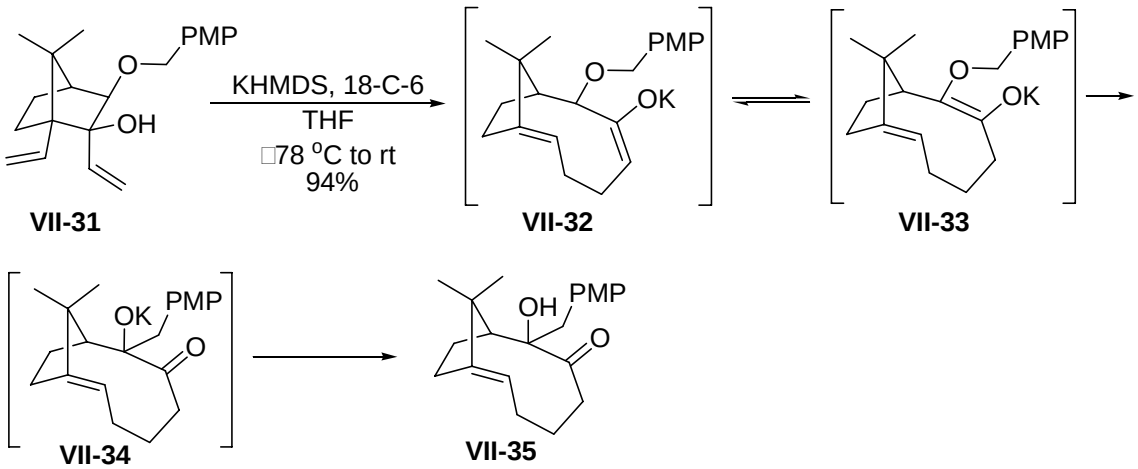


VII-23 **VII-24** (67)



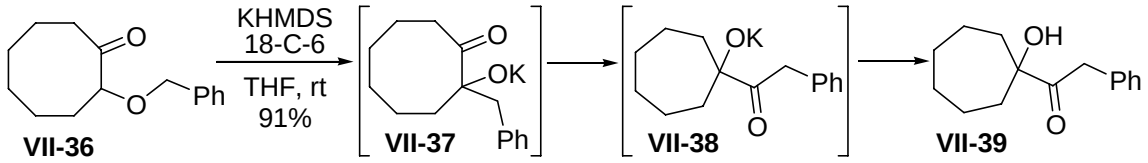
The use of the [1,2]-Wittig rearrangement in tandem processes is rare;[19] to date only two reports involving enolate 1,2-rearrangement have been described.[17e,f] In a first example, Paquette demonstrated the tandem oxy-Cope/[1,2]-Wittig rearrangement of **VII-31** to afford 94% yield of product **VII-35**.

Scheme 38. Tandem Oxy-Cope/[1,2]-Wittig Rearrangement



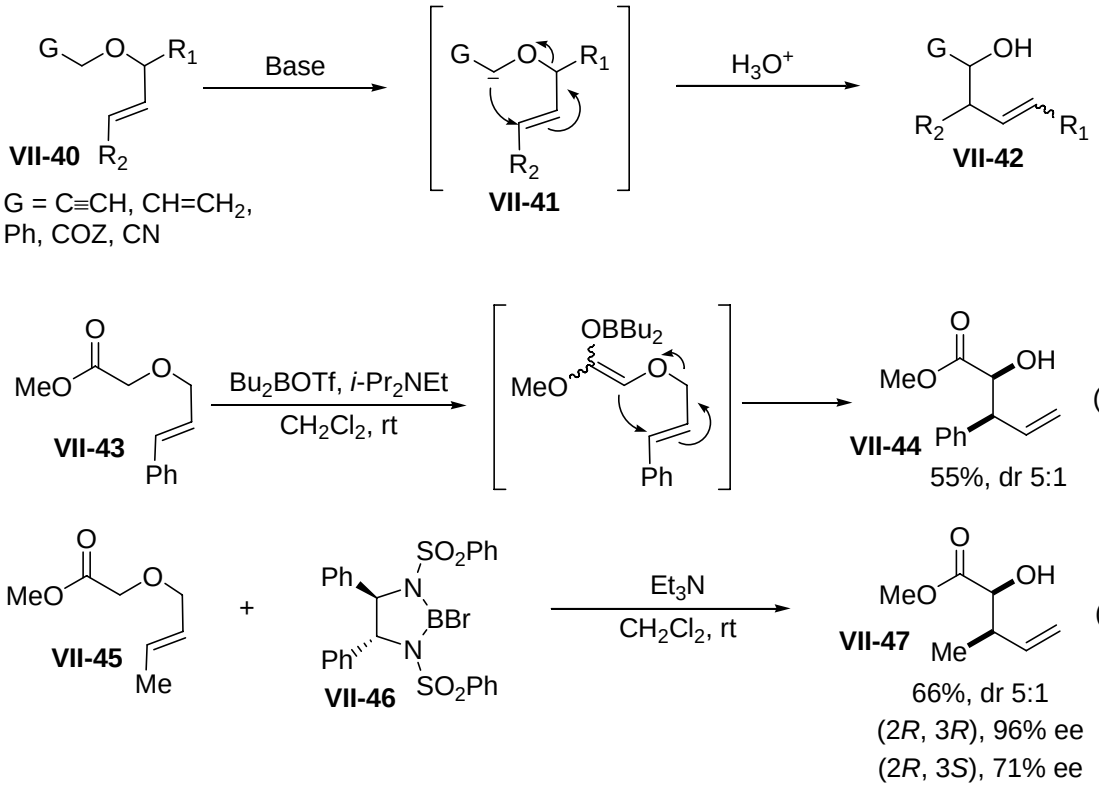
The second example, also reported by Paquette and coworkers, involved the [1,2]-Wittig rearrangement/α-ketol rearrangement of substrate **VII-36** to afford product **VII-39** in 91% yield.[17f]

Scheme 39. Tandem [1,2]-Wittig/α-Ketol Rearrangement



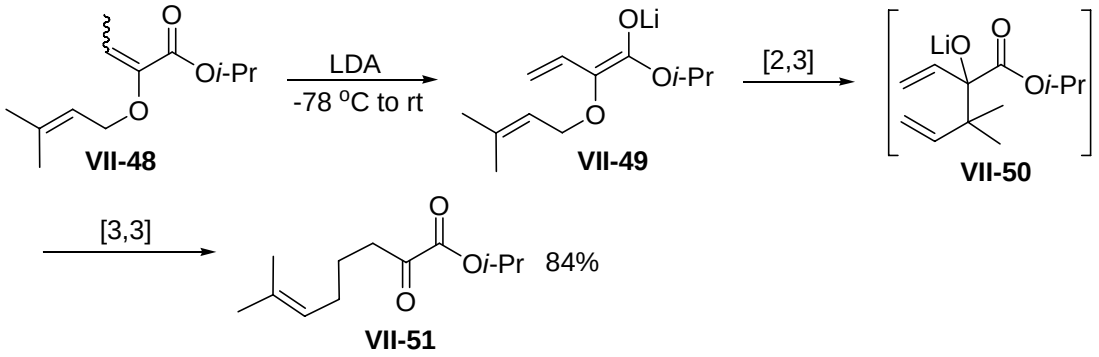
The related [2,3]-Wittig rearrangement of alkyl allyl ethers (**VII-40**) is a useful transformation often used in organic synthesis (Scheme 40).[15d,e,20] It is believed to occur via a symmetry-allowed concerted process (**VII-41**). Contrary to the [1,2]-Wittig rearrangement counterpart, the [2,3]-Wittig rearrangement of enolates is a well-known process.[21] More specifically, the boron-mediated enolate [2,3]-Wittig rearrangement was reported in two detailed studies.[22] In the first study, use of Bu_2BOTf and DIPEA reagents promoted the [2,3]-Wittig rearrangement of substrate **VII-43** to afford 55% yield of **VII-44** with modest diastereoselectivity (dr 5:1, eq 71).[22a] The second study involved the asymmetric [2,3]-Wittig rearrangement of substrate **VII-45** mediated by chiral boron reagent **VII-46** and Et_3N (eq 72).[22b] Under these reaction conditions, product **VII-47** was isolated in 66% yield in moderate diastereoselectivity and good enantioselectivity.

Scheme 40. [2,3]-Wittig Rearrangement



To date, only two reports of tandem reactions using enolate Wittig rearrangements have been described.[23] Both of these studies involved a [2,3]-Wittig reaction followed by a [3,3]-sigmatropic rearrangement of a dienolate species. For example, deprotonation of substrate **VII-48** with LDA afforded dienolate **VII-49** which underwent a [2,3]-Wittig rearrangement. The intermediate (**VII-50**) formed then underwent a [3,3] rearrangement to afford product **VII-51** in 84% yield.

Scheme 41. Tandem [2,3]-Wittig/[3,3]-Sigmatropic Rearrangement



These transformations illustrate the potential utility of the Wittig rearrangement in the context of tandem reactions, and provide the background relevant to our investigation of the tandem Wittig rearrangement-aldol reaction. The following chapter describes the scope, limitations and possible mechanism of this new transformation.

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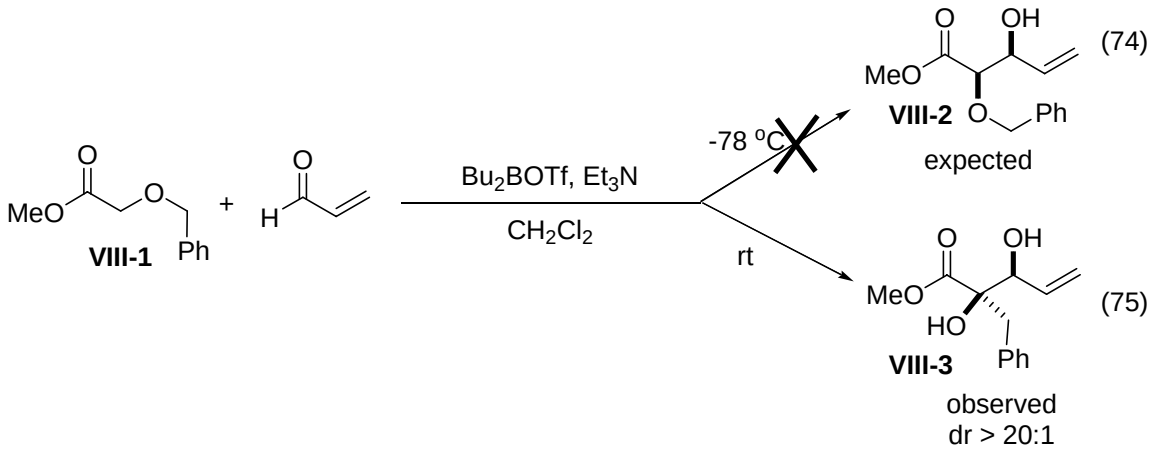
Chapter VIII

Investigation of the Tandem Wittig Rearrangement-Aldol Reaction of Glycolate Esters with Aldehydes[1]

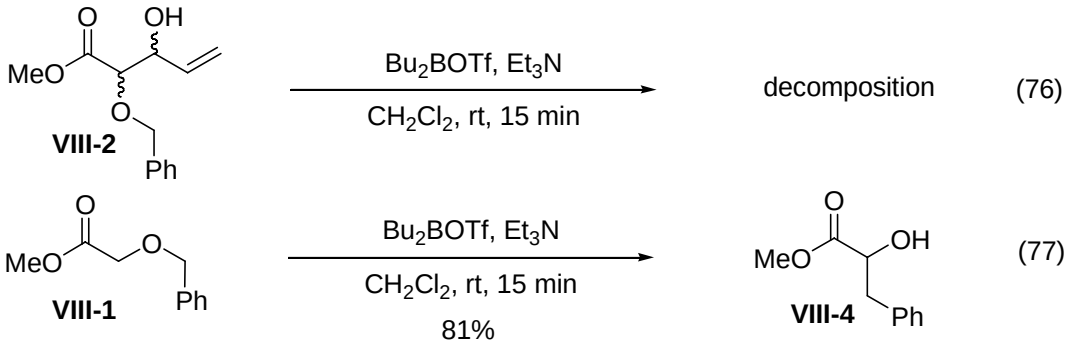
During our studies towards the synthesis of anisomycin (Chapter VI), we sought to effect a stereoselective boron-mediated aldol reaction between methyl *O*-benzylglycolate (**VIII-1**) and acrolein (eqs 74 and 75). This reaction failed to proceed at –78 °C, but when the transformation was attempted at 0 °C an interesting result was obtained. The expected aldol product **VIII-2** was not generated in significant amounts, but instead α-alkyl-α-β-dihydroxy ester **VIII-3** resulting from benzyl migration was observed with >20:1 diastereoselectivity. The conversion of **VIII-1** to **VIII-3** appears to involve the unprecedented combination of a [1,2]-Wittig rearrangement and an aldol reaction. This chapter describes our studies on the scope, limitations and mechanism of this new transformation.



Optimization studies and mechanism

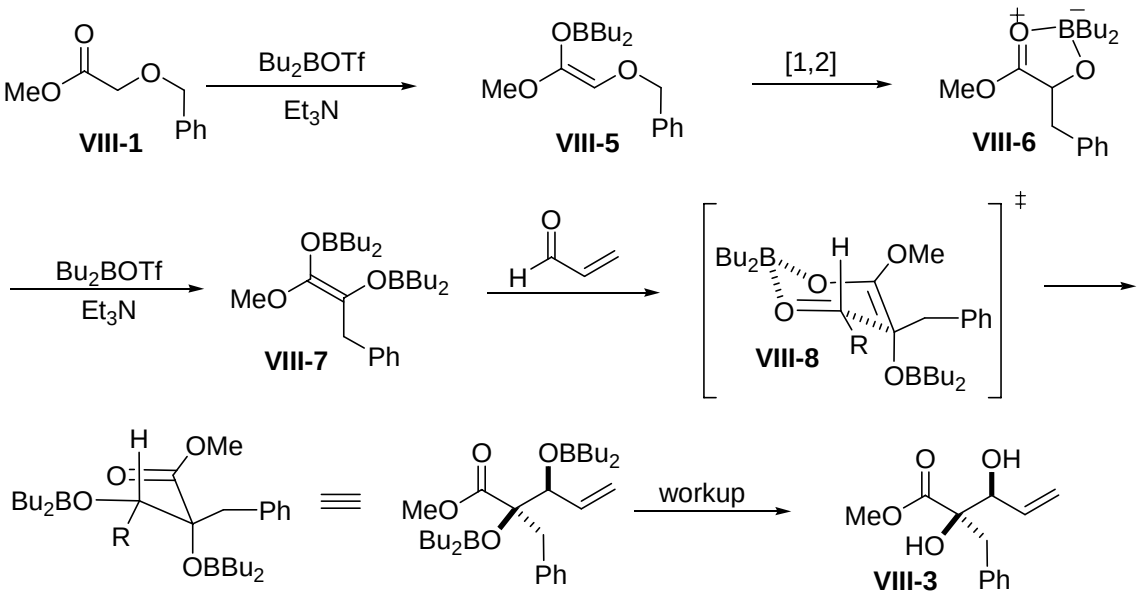
In our preliminary experiments we sought to determine which of the two reactions that led to the conversion of **VIII-1** to **VIII-3** occurred first, as this knowledge could aid in the development of optimal conditions for this transformation. The possibility that the sequence is initiated by an initial aldol reaction of **VIII-1** was rapidly discounted. The expected product of the boron-mediated aldol reaction, β–hydroxy ester **VIII-2**, was prepared as a 2:1 mixture of diastereomers[2] and treated with a mixture of Bu_2BOTf and Et_3N in CH_2Cl_2 at rt for 15 minutes. As shown in eq 76, these conditions resulted predominantly in decomposition of the starting material, and provided only trace amounts (< 5%) of **VIII-3**. The failure of **VIII-2** to undergo clean conversion to **VIII-3** suggested that the transformation of **VIII-1** to **VIII-3** likely proceeded via an initial [1,2]-Wittig rearrangement of boron ester enolate **VIII-5** to generate **VIII-6**. This hypothesis was supported by the fact that treatment of methyl *O*-benzyl glycolate ester (**VIII-1**) with Bu_2BOTf/Et_3N for 15 min at rt followed by aqueous workup afforded rearranged product

VIII-4 in 81% yield (eq 77).



A proposed mechanism for this new tandem [1,2]-Wittig rearrangement-aldol reaction is shown in Scheme 42. First, enolization of glycolate ester **VIII-1** would afford enolate **VIII-5**. A 1,2-Wittig rearrangement would then occur to afford intermediate **VIII-6**.[3] Following the initial Wittig rearrangement, conversion of **VIII-6** to boron enolate **VIII-7** presumably would occur with high selectivity for E(*O*)-enolate generation due to chelation between the ester carbonyl and the adjacent boron alkoxide. Enolate **VIII-7** would then undergo an aldol reaction via a closed, Zimmerman-Traxler[4] type transition state **VIII-8** to provide the observed *syn*-diol product **VIII-3** with excellent stereoselectivity. Evidence for the intermediacy of doubly borylated ester enolate **VIII-7** was obtained through HRMS analysis of a reaction mixture resulting from treatment of **VIII-1** with Bu_2BOTf/Et_3N for 15 min at rt. A signal was observed for m/z 428.3650 (calculated mass = 428.3633) with an isotopic distribution in accordance with the calculated pattern for **VIII-7**.

Scheme 42. Proposed Mechanism for the [1,2]-Wittig Rearrangement-Aldol Reaction



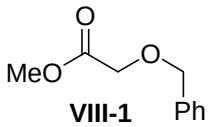
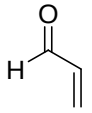
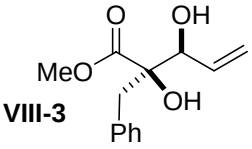
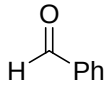
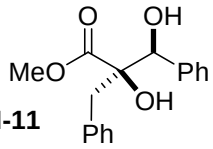
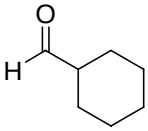
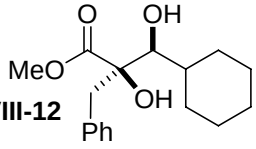
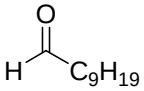
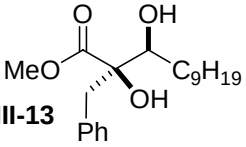
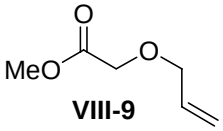
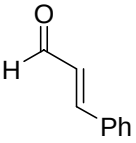
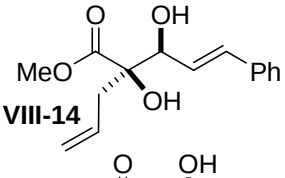
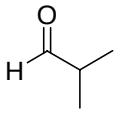
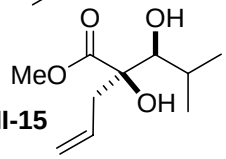
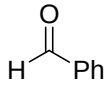
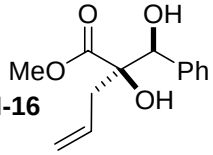
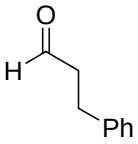
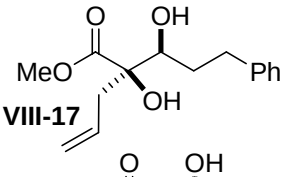
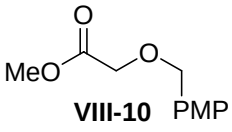
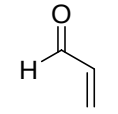
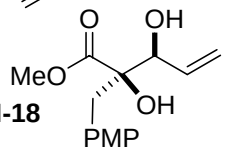
With knowledge of the reaction mechanism in hand, improved conditions were developed in which **VIII-1** was treated with excess Bu_2BOTf/Et_3N and allowed to undergo rearrangement before introduction of the aldehyde. In a representative experiment, **VIII-1** was added to a solution of Et_3N (4 equiv) and Bu_2BOTf (3.2 equiv) in CH_2Cl_2 at 0 °C and then warmed to rt for 15 min. The mixture was then cooled to 0 °C, acrolein (1.5 equiv) was added, and the reaction mixture was allowed to warm to rt and stir for 1h. Upon workup, the diol product **VIII-3** was obtained in 67% yield with >20:1 diastereoselectivity (eq 75).

Scope and Limitations

Having the reaction conditions for the Wittig rearrangement optimized, we next examined the use of several different aldehydes and glycolate esters in the reaction. As

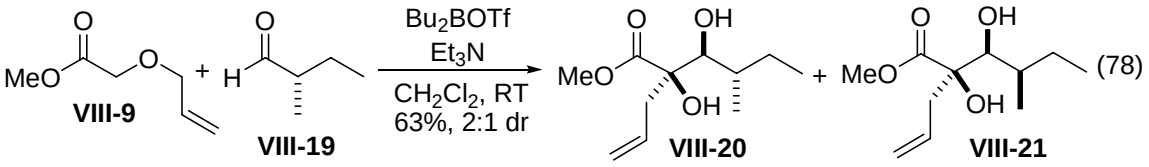
shown in Table 16, the diol products were obtained in good yields and excellent diastereoselectivities.[5] The transformation was effective when coupling **VIII-1** with α,β–unsaturated aldehydes (entry 1), aromatic aldehydes (entry 2), and both branched and linear aliphatic aldehydes (entries 3–4). A range of aliphatic and aromatic aldehydes were also coupled with methyl *O*-allyl glycolate ester (**VIII-9**) to afford the desired products with similarly high yields and diastereoselectivities. However, methyl *O*-(*p*-methoxybenzyl) glycolate ester **VIII-10** was found to rearrange and to undergo the aldol reaction in low yield (17%), possibly due to deprotection of the alcohol under the optimized reaction conditions.[6]

Table 16. Scope of the Tandem Wittig Rearrangement/Aldol Reaction[a]

Entry	Ester	Aldehyde	Product	dr[b]	Yield (%)[c]
1	 **VIII-1**		 **VIII-3**	>20:1	67
2			 **VIII-11**	>20:1	72
3			 **VIII-12**	>20:1[d]	75
4			 **VIII-13**	>20:1	78
5	 **VIII-9**		 **VIII-14**	>20:1[e]	61
6			 **VIII-15**	>20:1[f]	66
7			 **VIII-16**	>20:1	75
8			 **VIII-17**	>20:1	71
9	 **VIII-10** PMP		 **VIII-18**	>20:1	17[g]

[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]Diastereomeric ratio obtained upon purification. In most cases the crude product was obtained in >20:1 dr prior to purification. [c]Yields represent average isolated yields of two or more experiments. [d]The crude product was obtained in 14:1 dr. [e]The crude product was obtained in 17:1 dr. [f]The crude product was obtained in 20:1 dr. [f]A product resulting from 1,2-Wittig rearrangement of **VIII-10** was isolated in 26% yield (**VIII-10a**).

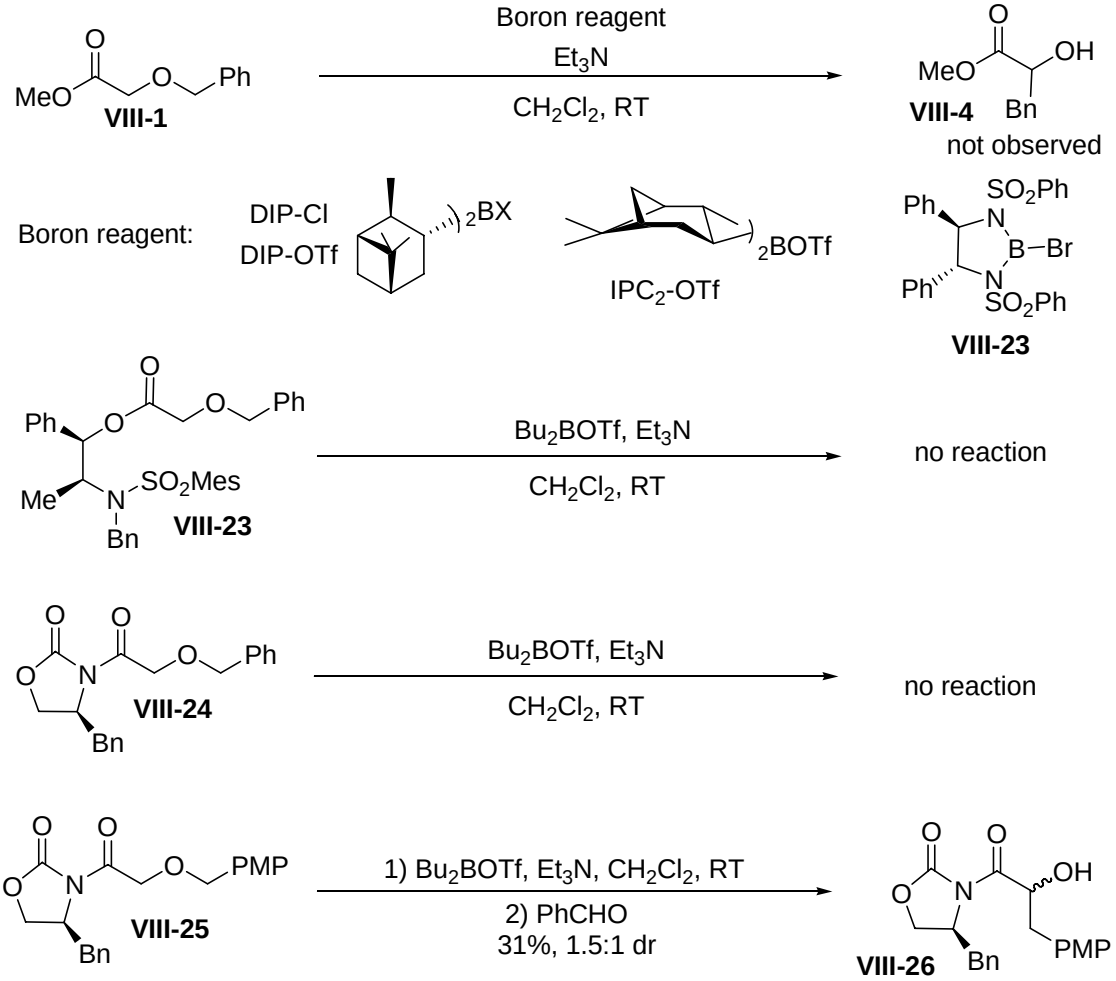
Preliminary studies towards the application of the methodology to natural product synthesis were performed. The chosen target was compound **VIII-20**, a key intermediate in Trost's synthesis of alternaric acid **VII-4** that was previously synthesized in eight steps (eq 78).[7] The new tandem Wittig rearrangement-aldol reaction would allow the synthesis of **VIII-20** in two steps (oxidation to aldehyde **VIII-19** and tandem Wittig-aldol reaction of **VIII-9**). Encouraging results were obtained when **VIII-9** was treated with **VIII-19** under the optimized reaction conditions: product **VIII-20** was isolated in 63% yield with high *syn* selectivity. The diastereoselectivity observed with chiral aldehyde **VIII-19** was low (~2:1 dr) but this result could potentially be improved upon the use of a chiral boron reagent ('reagent control') or a chiral auxiliary ('substrate control').



Preliminary studies towards an asymmetric version of the tandem reaction were also performed (Scheme 43). Different strategies were investigated, including the use of chiral boron reagents such as DIP-Cl, DIP-OTf, IPC_2-OTf, **VIII-22**[8] and the use of chiral auxiliaries[9] such as Masamune auxiliary **VIII-23**[10] Evans auxiliaries **VIII-24** and **VIII-25**.[11] Unfortunately, none of the chiral boron reagents promoted the [1,2]-Wittig rearrangement, and substrates **VIII-23** and **VIII-24** bearing chiral auxilaries did not rearrange under the optimal reaction conditions.[12,13] PMP substrate **VIII-25** was found to

rearrange, but did not undergo the subsequent aldol reaction. The rearranged product **VIII-26** was then observed as a 1.5:1 mixture of diastereomers and 31% yield. It is likely that the steric bulk of the auxiliary impedes the aldol reaction with these substrates.

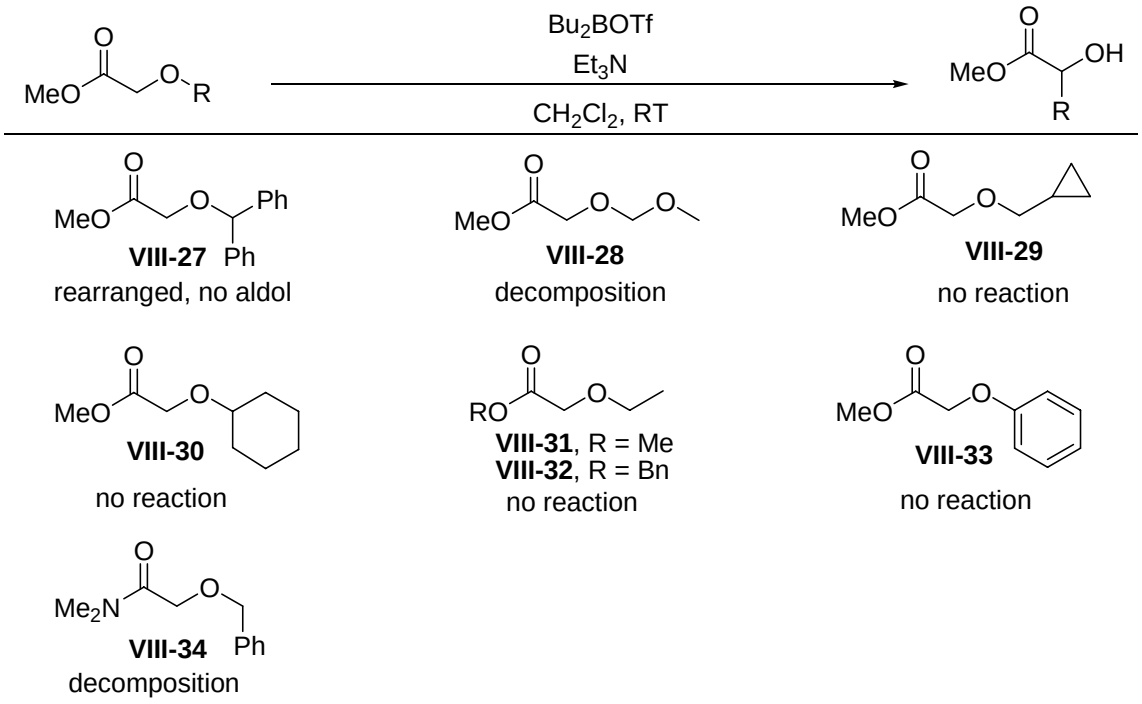
Scheme 43. Preliminary Studies Towards a Tandem Asymmetric Wittig-Aldol Reaction



At the present time, the scope of the tandem [1,2]-Wittig rearrangement-aldol reaction is limited to methyl *O*-benzyl (**VIII-1**), methyl *O*-allyl (**VIII-9**) glycolate esters and methyl *O*-(*p*-methoxybenzyl) glycolate ester (**VIII-10**). Methyl *O*-diphenylmethyl

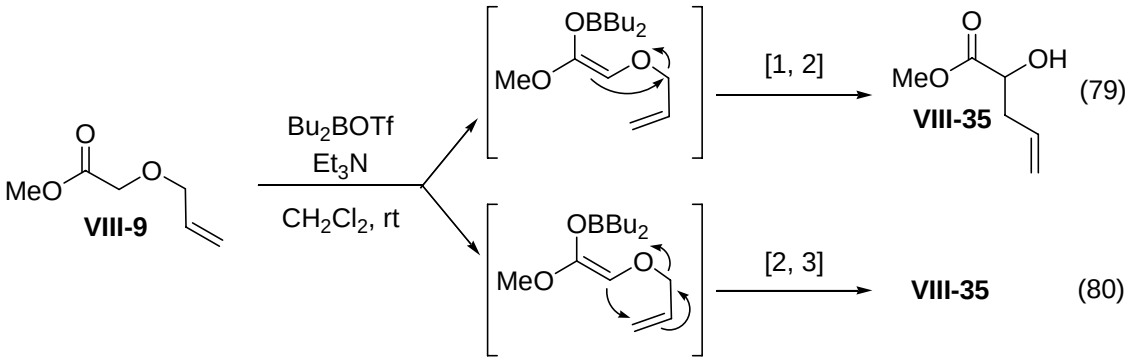
glycolate ester **VIII-27** was found to rearrange under the optimized reaction conditions, but did not undergo the subsequent aldol reaction, possibly due to increased steric bulk (Scheme 44). The other substrates tested did not react (**VIII-29**–**VIII-32** and **VIII-34**) or decomposed under the Lewis acidic conditions (**VIII-28** and **VIII-34**).

Scheme 44. Migrating Group Study

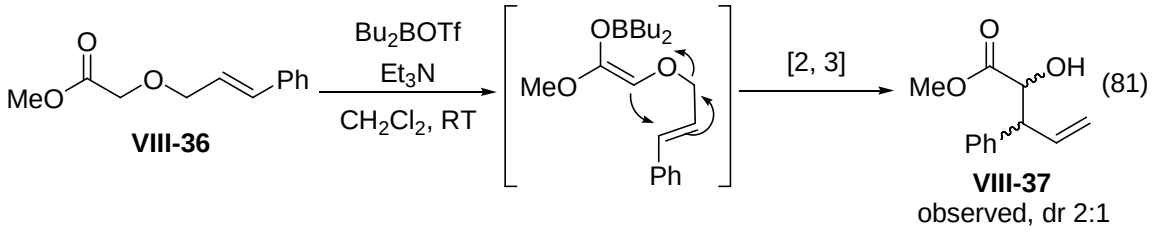


[1,2]- vs [2,3]-Wittig rearrangement

The rearrangement of methyl *O*-allyl glycolate **VIII-9** to product **VIII-35** could occur via either a [1,2]- or a [2,3]-Wittig rearrangement. However, these pathways cannot be distinguished with a terminal alkene substrate (eqs 79 and 80).

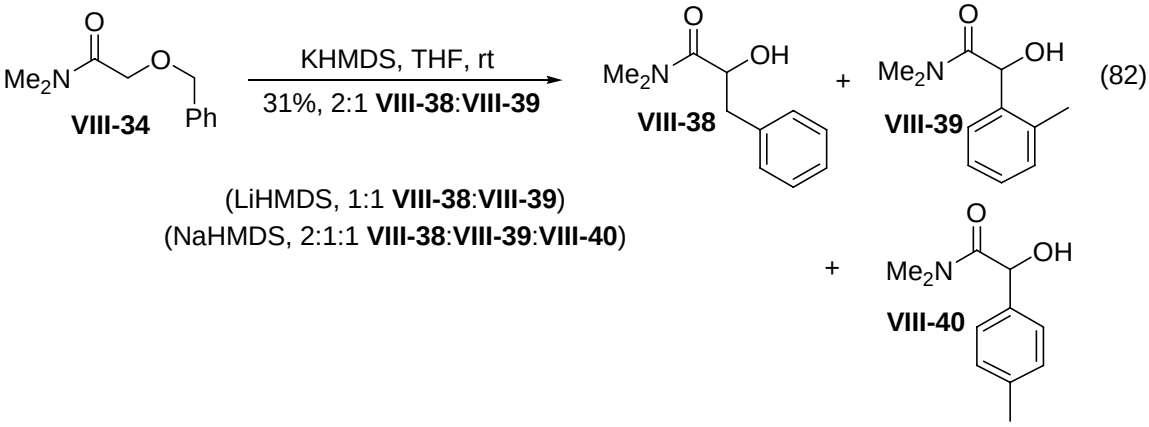


We reasoned that by using a substrate containing a substituted olefin such as **VIII-36**, it would be possible to determine which pathway is operative (eq 81). When **VIII-36** was treated with Bu_2BOTf, Et_3N for 15 min at rt, the [2,3]-Wittig rearrangement product **VIII-37** was observed exclusively as a 2:1 mixture of diastereomers.[14] Thus, it is likely that methyl *O*-allyl glycolate ester **VIII-9** also rearranges via a [2,3]-Wittig rearrangement (eq 80).

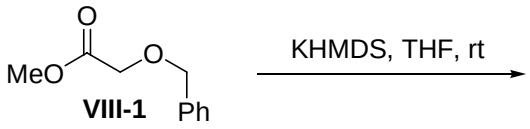


The use of basic conditions to promote the enolate [1,2]-Wittig rearrangement was briefly examined. When amide substrate **VIII-34** was treated with excess KHMDS in THF for 15 minutes at rt, a 2:1 mixture of [1,2]- and [2,3]-Wittig rearrangement products **VIII-38** and **VIII-39** was isolated in 31% yield (eq 82).[15] Interestingly, use of

LiHMDS afforded a 1:1 mixture of **VIII-38**:**VIII-39** and NaHMDS afforded a 2:1:1 mixture of **VIII-38**:**VIII-39**:**VIII-40**. Unfortunately, efforts to effect the tandem Wittig-aldol reaction were not successful with this substrate. Methyl *O*-benzyl glycolate ester (**VIII-1**) substrate decomposed under the KHMDS/THF reaction conditions (eq 83).



(82)



(83)

Conclusion

In conclusion, we have developed a new tandem Wittig rearrangement-aldol reaction for the synthesis of glycolate aldol products bearing tertiary alcohols. A migrating group study revealed that benzyl and allyl glycolate esters **VIII-1** and **VIII-9** underwent the Wittig rearrangement followed by an aldol reaction. Under optimized reaction conditions, a wide array of aldehyde electrophiles were used with these substrates to afford *syn*-diol products with excellent levels of diastereoselectivity.

Preliminary studies towards an asymmetric version of this new transformation included the use of various chiral boron reagents and auxiliaries, but few promoted the initial [1,2]-Wittig rearrangement and none the subsequent aldol reaction. Additionally, application of the methodology to the preparation of synthetic intermediate **VIII-20** provided encouraging results. Future work regarding the tandem Wittig rearrangement-aldol reaction could include expansion of the scope to other electrophiles such as Michael acceptors and imines.[16] In particular, reaction with imines would permit access to α-hydroxy-β-amino derivatives, which could be applied to the synthesis of natural products such as leuhistin (**VII-8**). Finally, studies towards the modifications of the reaction conditions to afford 1,2-*trans* diol products would be of interest, as well as mechanistic studies related to the 1,2-Wittig rearrangement.[17]

Experimental Section

General Considerations. All reactions were carried out under a nitrogen atmosphere in oven or flame dried glassware. Dibutylboron triflate (1.0 M solution in methylene chloride) was purchased from Aldrich Chemical Co. and used without further purification. All aldehydes were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were purified by distillation from Ca_2SO_4 except acrolein, which was obtained from Fluka Chemical Co. and used without further purification. Triethylamine was obtained from Aldrich Chemical Co. and was purified by distillation from CaH. Phosphate buffer solution (pH 7) was obtained from Aldrich Chemical Co. Methylene chloride was purified using a GlassContour solvent purification

system. Allyloxyacetic acid methyl ester (**VIII-9**)[18] was prepared from methyl 2-hydroxyacetate using a procedure analogous to that employed for the conversion of ethyl 2-hydroxyacetate to allyloxyacetic acid ethyl ester.[19] 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, whereas the yields reported in Table 16 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 16.

Methyl *O*-benzylglycolate (VIII-1).[20] A flame-dried flask was cooled under a stream of nitrogen and charged with benzyloxyacetyl chloride (3.67 g, 19.9 mmol), methylene chloride (60 mL) and methanol (1.6 mL, 39.8 mmol). The resulting solution was cooled to 0 $^\circ$C, pyridine (3.4 mL, 41.7 mmol) was added slowly, and the mixture was warmed to rt and stirred for 15 h. The reaction mixture was then concentrated *in vacuo* and the crude material was partitioned between water (50 mL) and diethyl ether (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 15% ethyl acetate/hexanes as the eluent to afford 3.23 g (90%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5 H), 4.64 (s, 2 H), 4.11 (s, 2 H), 3.77 (s, 3 H).

General procedure for tandem Wittig rearrangement/aldol reactions (Table 16). An oven or flame-dried flask was cooled under a stream of nitrogen and charged with a 1 M solution of dibutylboron triflate in methylene chloride (4.0 equiv). The pale yellow solution was cooled to 0 °C and triethylamine (3.2 equiv) was added dropwise to afford a colorless solution. The ester substrate (1.0 equiv) was added dropwise and the mixture was warmed to rt and stirred for 15 min then cooled to 0 °C. The aldehyde was added dropwise (1.5 equiv) and the reaction mixture was warmed to rt and allowed to stir for 1-6 h. The reaction was then quenched by addition of pH 7 buffer (2 mL/mmol substrate). The heterogeneous mixture was transferred to a larger flask and diluted with MeOH (ca. 5–8 mL/mmol substrate) to afford a clear and homogeneous solution. The solution was cooled to 0 °C, 30% aqueous H_2O_2 (6 mL/mmol substrate) was added slowly, and the resulting mixture was warmed to rt and stirred for 1 h. The reaction mixture was then diluted with Et_2O (~15 mL/mmol substrate), water (~8 mL/mmol substrate) and transferred to a separatory funnel. The layers were separated and the organic layer was washed with a saturated aqueous solution of $FeSO_4$ until the green color persisted in order to quench any peroxide remaining. *Caution! This procedure is highly exothermic. The $FeSO_4$ solution should be first added SLOWLY DROPWISE with a glass pipette.* 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 using 15–30% ethyl acetate/hexanes as the eluent.

(±)-(2*R,3*S**)-Methyl-2-benzyl-2,3-dihydroxypent-4-enoate (VIII-3).** The

reaction of **VIII-1** (181 mg, 1.0 mmol) and acrolein (100 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 163 mg (69%) of the title compound as a white solid, m.p. 65–67 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3 H), 7.19–7.15 (m, 2 H), 6.10–6.02 (m, 1 H), 5.47–5.37 (m, 2 H), 4.38–4.33 (m, 1 H), 3.74 (s, 3 H), 3.32 (s, 1 H), 3.00–2.95 (m, 1 H), 2.91–2.86 (m, 1 H), 2.40 (d, *J* = 9.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 135.2, 135.1, 129.9, 128.2, 127.0, 119.1, 80.8, 77.1, 52.8, 41.6; IR (film) 3497, 1740 cm^{-1}. Anal calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.07; H, 6.97.

(±)-(2*R,3*S**)-Methyl-2-benzyl-2,3-dihydroxy-3-phenylpropanoate (VIII-11).** The reaction of **VIII-1** (181 mg, 1.0 mmol) and benzaldehyde (153 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 216 mg (75%) of the title compound as a white solid, m.p. 134–135 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2 H), 7.40–7.31 (m, 3 H), 7.24–7.15 (m, 3 H), 7.11–7.04 (m, 2 H), 4.93 (d, *J* = 7.6 Hz, 1 H), 3.70 (s, 3 H), 3.43 (s, 1 H), 3.03–2.92 (m, 2 H), 2.46 (d, *J* = 13.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 138.9, 135.2, 129.8, 128.3, 128.2, 128.1, 128.0, 126.8, 81.3, 77.8, 52.8, 41.9; IR (film) 3476, 1734 cm^{-1}. Anal calcd for $C_{17}H_{18}O_4$:

C, 71.31; H, 6.34. Found: C, 71.10; H, 6.38.

(±)-(2*R,3*S**)-Methyl-2-benzyl-3-cyclohexyl-2,3-dihydroxypropanoate (VIII-12).** The reaction of **VIII-1** (181 mg, 1.0 mmol) and cyclohexane carboxaldehyde (182 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with 14:1 dr. Chromatographic purification afforded 227 mg (78%) of the title compound as a white solid, m.p. 115–116 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.20 (m, 3 H), 7.19–7.15 (m, 2 H), 3.76–3.71 (m, 1 H), 3.69 (s, 3 H), 3.34 (s, 1 H), 3.05–2.94 (m, 2 H), 2.27 (d, *J* = 11.2 Hz, 1 H), 1.95–1.89 (m, 1 H), 1.84–1.73 (m, 3 H), 1.71–1.58 (m, 2 H), 1.54–1.44 (m, 1 H), 1.38–1.22 (m, 2 H), 1.20–1.09 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 135.4, 129.9, 128.2, 127.0, 81.5, 78.6, 52.8, 42.0, 38.9, 31.6, 26.7, 26.2, 25.8 (two aliphatic carbon signals are incidentally equivalent); IR (film) 3512, 1728 cm^{-1}. Anal calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.75; H, 8.39.

(±)-(2*R,3*S**)-Methyl-2-benzyl-2,3-dihydroxydodecanoate (VIII-13).** The reaction of **VIII-1** (181 mg, 1.0 mmol) and decanal (282 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 259 mg (77%) of the title compound as a white solid, m.p. 76–77 °C. This material was

judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.22 (m, 3 H), 7.20–7.16 (m, 2 H), 3.88–3.79 (m, 1 H), 3.73 (s, 3 H), 3.27 (s, 1 H), 3.02–2.92 (m, 2 H), 1.97–1.86 (m, 1 H), 1.78–1.70 (m, 1 H), 1.68–1.54 (m, 1 H), 1.52–1.22 (m, 14 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 135.5, 129.9, 128.3, 127.0, 81.4, 75.4, 52.7, 41.3, 31.9, 31.0, 29.60, 29.57, 29.3, 25.9, 22.7, 14.1 (two pairs of aliphatic carbon signals are incidentally equivalent); IR (film) 3501, 1731 cm^{-1}. Anal calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.60.

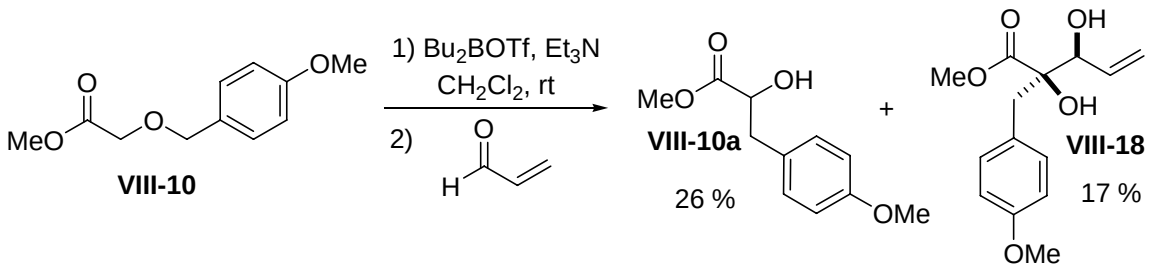
(±)-(*E*)-(2*R,3*S**)-Methyl-2-allyl-2,3-dihydroxy-5-phenylpent-4-enoate (VIII-14).** The reaction of **VIII-9** (130 mg, 1.0 mmol) and cinnamaldehyde (189 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with 17:1 dr. Chromatographic purification afforded 173 mg (66%) of the title compound as a white solid, m.p. 97–99 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H), 7.34–7.29 (m, 2 H), 7.28–7.23 (m, 1 H), 6.68–6.62 (m, 1 H), 6.34–6.27 (m, 1 H), 5.77–5.67 (m, 1 H), 5.13–5.06 (m, 2 H), 4.41 (t, *J* = 8.1 Hz, 1 H), 3.82 (s, 3 H), 3.60 (s, 1 H), 2.60–2.55 (m, 1 H), 2.45–2.34 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 136.1, 134.5, 131.5, 128.5, 128.1, 126.7, 125.8, 119.2, 80.4, 76.7, 53.0, 40.0; IR (film) 3482, 1738 cm^{-1}. Anal calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.90; H, 7.00.

(±)-(1'*S,2*R**)-Methyl-2-hydroxy-2-(1'-hydroxy-2'-methylpropyl)pent-4-enoate (VIII-15).** The reaction of **VIII-9** (130 mg, 1.0 mmol) and isobutyraldehyde (137 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with 20:1 dr. Chromatographic purification afforded 131 mg (64%) of the title compound as a colorless oil. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.67 (m, 1 H), 5.15–5.08 (m, 2 H), 3.79 (s, 3 H), 3.69 (dd, *J* = 2.4, 10.7 Hz, 1 H), 3.49 (s, 1 H), 2.45 (d, *J* = 7.3 Hz, 2 H), 2.22 (d, *J* = 10.7 Hz, 1 H), 2.07–1.97 (m, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 131.8, 119.2, 80.7, 78.0, 53.0, 40.4, 28.5, 21.7, 15.4; IR (film) 3502, 2960 cm^{-1}. Anal calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.60; H, 9.22.

(±)-(1'*S,2*R**)-Methyl-2-hydroxy-2-(1'-hydroxybenzyl)pent-4-enoate (VIII-16).** The reaction of **VIII-9** (130 mg, 1.0 mmol) and benzaldehyde (153 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 174 mg (74%) of the title compound as a white solid, m.p. 104–105 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5 H), 5.71–5.59 (m, 1 H), 5.09–4.97 (m, 2 H), 4.84 (d, *J* = 7.6 Hz, 1 H), 3.83 (s, 3 H), 3.54 (s, 1 H), 2.83 (d, *J* = 7.6 Hz, 1 H), 2.44–2.36 (m, 1 H), 2.01–1.93 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 138.7, 131.6, 128.3, 128.1, 127.8, 119.0, 80.6,

77.5, 52.9, 40.1; IR (film) 3490, 1734 cm^{-1}. Anal calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.11; H, 6.93.

(±)-(2*R,3*S**)-Methyl-2-hydroxy-2-(1-hydroxy-3-phenylpropyl)pent-4-enoate (VIII-17).** The reaction of **VIII-9** (130 mg, 1.0 mmol) and 3-phenylpropionaldehyde (201 μL, 1.5 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude product showed the formation of the desired product with >20:1 dr. Chromatographic purification afforded 195 mg (74%) of the title compound as a white solid, m.p. 60–62 °C. This material was judged to be of >20:1 dr by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.25 (m, 2 H), 7.23–7.15 (m, 3 H), 5.74–5.64 (m, 1 H), 5.12–5.05 (m, 2 H), 3.79–3.71 (m, 4 H), 3.57 (s, 1 H), 2.97–2.88 (m, 1 H), 2.71–2.62 (m, 1 H), 2.42–2.34 (m, 3 H), 1.96–1.87 (m, 1 H), 1.81–1.71 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 141.7, 131.7, 128.4, 128.3, 125.8, 119.2, 80.6, 74.4, 52.8, 39.5, 32.3, 31.9; IR (film) 3493, 1732 cm^{-1}. Anal calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.15; H, 7.62.



(±)-(2*R*,3*S*)-Methyl-2,3-dihydroxy-2-(4-methoxybenzyl)pent-4-enoate (VIII-18). The reaction of **VIII-10** (211 mg, 1.0 mmol) and acrolein (101 μL, 1.5 mmol) was conducted following the general procedure for the Wittig-aldol reaction. ^{1}H NMR analysis indicated that a ~25:75 mixture of aldol product **VIII-18** and rearranged product **VIII-10a** were present. This procedure afforded 44 mg (17%) of the title compound as a colorless oil and as a single diastereoisomer and 73 mg (26%) of rearranged product **VIII-10a** (described below). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.3 Hz, 2 H), 6.80 (d, *J* = 8.3 Hz, 2 H), 6.09–6.00 (m, 1 H), 5.45–5.34 (m, 2 H), 4.33 (t, *J* = 8.8 Hz, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.28 (s, 1 H), 2.92 (d, *J* = 13.9 Hz, 1 H), 2.82 (d, *J* = 13.7 Hz, 1 H), 2.32 (d, *J* = 9.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 158.6, 135.1, 130.9, 127.1, 119.0, 113.7, 80.9, 55.2, 52.8, 40.7.

Methyl 2-hydroxy-3-(4-methoxyphenyl)propanoate (VIII-10a).[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.43–4.39 (m, 1 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.06 (dd, *J* = 6.3, 13.9 Hz, 1 H), 2.91 (dd, *J* = 6.6, 13.9 Hz, 1 H), 2.76 (d, *J* = 6.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 158.5, 130.4, 128.2, 113.8, 71.3, 55.2, 52.4, 39.6.

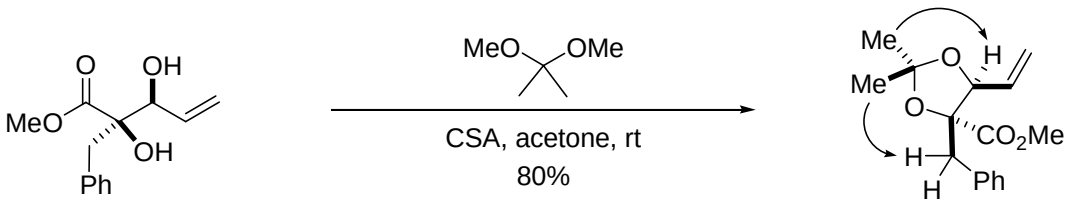
(±)-Methyl-2-hydroxy-3-phenylpropanoate (VIII-4)[22] The reaction of **VIII-1** (180 mg, 1.0 mmol) was conducted following the general procedure except that no aldehyde was added, and CH_2Cl_2 was used for extraction. This protocol afforded 148 mg

(82%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2 H), 7.25–7.17 (m, 3 H), 4.46–4.40 (m, 1 H), 3.74 (s, 3 H), 3.14–3.07 (m, 1 H), 2.98–2.87 (m, 2 H).

(*E*)-7-benzyl-5,10-dibutyl-8-methoxy-6,9-dioxa-5,10-diboratetradec-7-ene (VIII-7). The reaction of **VIII-1** (90 mg, 0.5 mmol) was conducted following the general procedure except that no aldehyde was added. After stirring for 15 min the crude reaction mixture was analyzed by mass spectrometry. A signal was observed with an isotopic distribution and exact mass in accord with the calculated value for **VIII-7**. MS (EI): 428.3650 (428.3633 calculated for $C_{26}H_{46}B_2O_3$, M +).

Assignment of stereochemistry

The stereochemistry of (2*R**,3*S**)-methyl-2-benzyl-2,3-dihydroxypent-4-enoate (**VIII-3**) was assigned by ^{1}H NMR nOe analysis of the corresponding acetonide derivative **VIII-3a** as shown below. The stereochemistry of the other 1,2-diol products was assigned based on analogy to the (2*R**,3*S**)-methyl-2-benzyl-2,3-dihydroxypent-4-enoate product.



VIII-3 **VIII-3a**

(±)-(4*R,5*S**)-Methyl-4-benzyl-2,2-dimethyl-5-vinyl-1,3-dioxolane-4-carboxylate (VIII-3a)**. A flame-dried flask was cooled under a stream of nitrogen and charged with **VIII-3 (**118 mg, 0.5 mmol), dry acetone (5 mL), 2,2-dimethoxypropane (0.7 mL, 5.7 mmol) and camphorsulfonic acid (14 mg, 0.06 mmol). The reaction mixture was stirred at rt for 25 h and then was concentrated *in vacuo*. The residue obtained was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluant to afford 111 mg (80%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.13 (m, 5 H), 6.10–5.99 (m, 1 H), 5.59–5.52 (m, 1 H), 5.46–5.40 (m, 1 H), 4.69 (d, *J* = 5.9 Hz, 1 H), 3.64 (s, 3 H), 3.06–3.00 (m, 1 H), 2.82–2.76 (m, 1 H), 1.67 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.7, 131.4, 130.0, 128.1, 126.7, 119.1, 110.2, 86.3, 81.4, 52.1, 40.6, 28.0, 25.3; IR (film) 1732 cm^{-1}. MS (ESI): 299.1262 (299.1259 calculated for $C_{16}H_{20}O_4$, M + Na^+).

(±)-(2*R*,3*S*,4*S*)-Methyl-2-allyl-2,3-dihydroxy-4-methylhexanoate (VIII-20).[7] The reaction of methyl *O*-allylglycolate **VIII-9** (131 mg, 1.0 mmol) and S-(+)-2-methylbutanal **VIII-19**[23] (220 mg, 2 mmol) was conducted following the general procedure. ^{1}H NMR analysis of the crude reaction mixture indicated that a 2:1 ratio of diastereoisomers was obtained. Chromatographic purification (10% ethyl acetate/hexanes) afforded 163 mg (64%) of the title compound as a colorless oil. This material was judged to be a 2:1 mixture of diastereoisomers by ^{1}H and ^{13}C NMR analysis. The data is 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* = 9.5 Hz, 1.33 H), 0.96–0.87 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 176.0, 131.84, 131.78, 119.3, 80.9, 78.6, 76.0, 53.1, 40.4, 40.3, 35.8, 35.1, 28.3, 22.2, 17.5, 12.8, 12.0, 11.9.

(4*S*)-4-Benzyl-3-(2-hydroxy-3-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (VIII-26). The reaction of **VIII-25** (101 mg, 0.3 mmol) and benzaldehyde (46 μL, 0.45 mmol) was conducted following the general procedure except that **VIII-25** was stirred at rt for 45 min before the aldehyde was added. ^{1}H NMR analysis of the crude reaction mixture indicated that **VIII-25** rearranged but did not undergo the aldol reaction. The diastereomeric ratio was observed to be 1.5:1. Chromatographic purification allowed the separation of the diastereoisomers. The first compound to elute was the minor isomer (8 mg, 8%) followed by the major isomer (23 mg, 23%, description below). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (m, 2 H), 7.31–7.28 (m, 1 H), 7.24–7.18 (m, 4 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 5.30–5.22 (m, 1 H), 4.65–4.57 (m, 1 H), 4.28–4.21 (m, 2 H), 3.79 (s, 3 H), 3.44 (d, *J* = 8.0 Hz, 1 H), 3.31 (dd, *J* = 3.3, 13.5 Hz, 1 H), 3.12 (dd, *J* = 4.3, 13.9 Hz, 1 H), 2.90–2.79 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 158.5, 153.2, 134.8, 130.6, 129.5, 129.1, 128.6, 127.5, 113.8, 71.8, 67.0, 55.6, 55.2, 39.6, 37.5.

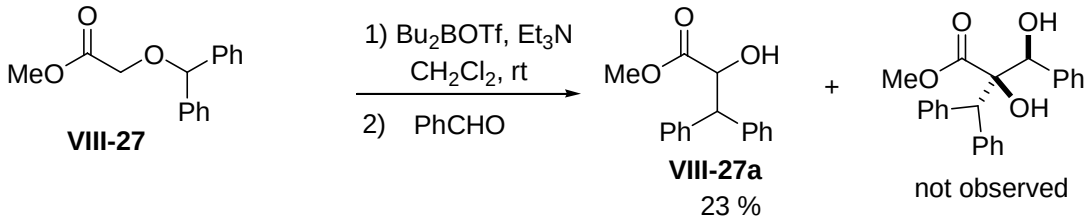
The major diastereoisomer of **VIII-26** was obtained as a solid, m.p. 86–88 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2 H), 7.31–7.28 (m, 1 H), 7.26–7.18 (m, 4 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.29–5.23 (m, 1 H), 4.77–4.70 (m, 1 H), 4.31 (t, *J* = 9.0 Hz, 1

H), 4.26 (dd, *J* = 3.4, 9.0 Hz, 1 H), 3.78 (s, 3 H), 3.25 (dd, *J* = 3.4, 13.4 Hz, 1 H), 3.22–3.17 (m, 2 H), 2.86–2.73 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 158.6, 153.0, 134.7, 130.7, 129.4, 129.1, 128.6, 127.6, 113.8, 71.8, 67.1, 55.2, 55.0, 40.0, 38.0; IR (film) 3497, 1781 cm^{-1}. Anal calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.37; H, 6.04; N, 3.79.

Methyl 2-(benzhydryloxy)acetate (VIII-27).[24] A flame-dried flask was cooled under a stream of nitrogen and charged with benzhydrol (9.2 g, 50 mmol), chloroacetic acid (9.5 g, 100 mmol) and THF (200 mL). The resulting mixture was cooled to 0 ^{o}C and solid NaH (20 g, 500 mmol, 60% in oil) was added in portions. The reaction mixture was warmed to rt then heated to reflux until the starting material was consumed as judged by TLC analysis (ca. 8 h). The reaction mixture was then cooled to 0 ^{o}C and quenched by the addition of water (10 mL), and 1 M HCl was then added until pH ~7. The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue obtained was used without purification in the next reaction.

A flame-dried flask was cooled under a stream of nitrogen and charged with crude 2-(benzhydryloxy)acetic acid (50 mmol) and DMF (50 mL). The mixture was cooled to 0 ^{o}C and K_2CO_3 (35 g, 250 mmol) was added followed by dropwise addition of iodomethane (9.3 mL, 150 mmol). The reaction mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 4 h). Water (100 mL) and ethyl

acetate (100 mL) were then added and the organic layer was separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue obtained was purified by flash chromatography using 10% ethyl acetate/hexanes as the eluent to afford 7.43 g (58%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.1 Hz, 4 H), 7.40 (t, *J* = 7.1 Hz, 4 H), 7.33 (tt, *J* = 7.3, 1.2 Hz, 2 H), 5.67 (s, 1 H), 4.20 (s, 2 H), 3.78 (s, 3 H).



Methyl 2-hydroxy-3,3-diphenylpropanoate (VIII-27a).[25] The reaction of **VIII-27** (130 mg, 1.0 mmol) and benzaldehyde (201 μL, 1.5 mmol) was conducted following the general procedure for the Wittig-aldol reaction. ^{1}H NMR analysis of the crude reaction mixture indicated that **VIII-27** rearranged but did not undergo the aldol reaction. This procedure afforded 60 mg (23%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.34 (m, 2 H), 7.33–7.17 (m, 8 H), 4.96 (dd, *J* = 3.9, 6.8 Hz, 1 H), 4.49 (d, *J* = 3.7 Hz, 1 H), 3.69 (s, 3 H), 2.78 (d, *J* = 6.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 141.2, 138.9, 129.3, 128.5, 128.42, 128.37, 127.1, 126.7, 73.4, 54.2, 52.5; IR (film) 3493, 1738 cm^{-1}. Anal calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.97; H, 6.38.

Methyl 2-(4-methoxybenzyloxy)acetate (VIII-10). [26] This compound was prepared on a 52 mmol scale using a procedure analogous to that employed for the synthesis of **VIII-27** except that *p*-methoxybenzyl alcohol (7.25 g, 52 mmol) was used in place of benzhydrol. This procedure afforded 1.8 g (17%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.6 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 4.56 (s, 2 H), 4.07 (s, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H).

Methyl 2-(methoxymethoxy)acetate (VIII-28).[27] A flame-dried flask was cooled under a stream of nitrogen and charged with methyl glycolate (4.5 g, 50 mmol) and methylene chloride (150 mL). The mixture was cooled to 0 ^{o}C and DIPEA (61 mL, 350 mmol) was added via syringe. MOM-Cl (11.4 mL, 150 mmol) was then added slowly and the reaction mixture was stirred at rt until the starting material was consumed as judged by TLC analysis (ca. 2 h). The reaction mixture was then washed with 1 M HCl (100 mL), and brine (100 mL), and the organic layer was separated. The organic layer was then dried over Na_2SO_4, filtered and concentrated. The residue obtained was distilled at 70 ^{o}C (water aspirator) to afford 1.61 g (24%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (s, 2 H), 4.18 (s, 2 H), 3.77 (s, 3 H), 3.40 (s, 3 H).

Methyl 2-(cyclopropylmethoxy)acetate (VIII-29). This compound was prepared

on a 50 mmol scale using a procedure analogous to that employed for the synthesis of **VIII-27** except that cyclopropylmethanol (3.6 g, 50 mmol) was used in place of benzhydrol. This procedure afforded 2.1 g (29%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (s, 2 H), 3.76 (s, 3 H), 3.39 (d, J = 7.1 Hz, 2 H), 1.15–1.06 (m, 1 H), 0.59–0.54 (m, 2 H), 0.27–0.22 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 76.1, 67.4, 51.5, 10.0; IR (film) 1756 cm^{-1}. Anal calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.03; H, 8.27.

Methyl 2-(cyclohexyloxy)acetate (VIII-30). This compound was prepared on a 50 mmol scale using a procedure analogous to that employed for the synthesis of **VIII-27** except that cyclohexanol (5.1 g, 50 mmol) was used in place of benzhydrol. This procedure afforded 2.8 g (32%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (s, 2 H), 3.72 (s, 3 H), 3.33–3.27 (m, 1 H), 1.95–1.87 (m, 2 H), 1.76–1.68 (m, 2 H), 1.55–1.47 (m, 1 H), 1.35–1.13 (m, 6 H).

Methyl 2-ethoxyacetate (VIII-31).[28] A flask was cooled under a stream of nitrogen and charged with ethoxy acetic acid (5.3 g, 50 mmol) and methanol (50 mL). The mixture was cooled to 0 ^{o}C and H_2SO_4 (0.3 mL, 5 mmol) was added dropwise. The reaction mixture was stirred at rt for 20 h. The mixture was cooled to 0 ^{o}C and quenched with a saturated solution of $NaHCO_3$ (50 mL). Diethyl ether (100 mL) was added and the organic layer was separated. The organic layer was then washed with brine, dried over

Na_2SO_4, filtered, and concentrated. The residue obtained was distilled at 40 ^oC (water aspirator) to afford 2.7 g (46%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 2 H), 3.54 (s, 3 H), 3.38 (q, *J* = 7.0 Hz, 2 H), 1.04 (t, *J* = 7.0 Hz, 3 H).

Benzyl 2-ethoxyacetate (VIII-32). A flame-dried flask was cooled under a stream of nitrogen and charged with CDI (10 g, 50 mmol) and THF (100 mL). Ethoxy acetic acid (4.8 mL, 50 mmol) was then added slowly and the reaction mixture was stirred at rt for 2 h. The mixture was then cooled to 0 ^oC and benzyl alcohol (5.7 mL, 55 mmol) was added. The mixture was stirred at rt for 3h. The reaction mixture was then diluted with ethyl acetate (100 mL) and water (100 mL). The organic layer was separated and washed with 1 M HCl (2 x 50 mL), saturated Na_2CO_3 (2 x 50 mL) and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated. The residue obtained was purified by column chromatography (20% ethyl acetate/hexanes) to afford 8.9 g (92%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5 H), 5.19 (s, 2 H), 4.11 (s, 3 H), 3.59 (q, *J* = 6.8 Hz, 2 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

2-(Benzyloxy)-*N*,*N*-dimethylacetamide (VIII-34). A flame-dried flask was cooled under a stream of nitrogen and charged with dimethylamine hydrochloride (4.1 g, 50 mmol) and methylene chloride (100 mL). The resulting solution was cooled to 0 $^\circ C$ and Et_3N was added dropwise (13 mL, 100 mmol). A solution of benzyloxyacetyl

chloride (4.62 g, 25 mmol) in methylene chloride (25 mL) was added slowly to the reaction mixture. The resulting mixture was then warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (ca. 22 h). The reaction mixture was then diluted with 1 M HCl (100 mL) and the organic layer was separated. The layer was washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (50 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 50% ethyl acetate/hexanes as the eluent to afford 3.13 g (65%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 4.62 (s, 2 H), 4.18 (s, 2 H), 2.99 (s, 3 H), 2.96 (s, 3 H).

Methyl 2-(cinnamyloxy)acetate (VIII-36).[29] This compound was prepared on a 50 mmol scale using a procedure analogous to that employed for the synthesis of **VIII-27** except that cinnamyl alcohol (6.7 g, 50 mmol) was used in place of benzhydrol. This procedure afforded 2.2 g (41%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.3 Hz, 2 H), 7.30 (t, J = 7.1 Hz, 2 H), 7.24 (t, J = 7.1 Hz, 1 H), 6.62 (d, J = 15.9 Hz, 1 H), 6.32–6.24 (m, 1 H), 4.25 (dd, J = 1.2, 6.3 Hz, 2 H), 4.13 (s, 2 H), 3.75 (s, 3 H).

Methyl 2-hydroxy-3-phenylpent-4-enoate (VIII-37). The reaction of **VIII-36** (207 mg, 1.0 mmol) and benzaldehyde (153 μL, 1.5 mmol) was conducted following the general procedure for the Wittig-aldol reaction. ^{1}H NMR analysis indicated that crude

reaction contained 80% of rearranged product **VIII-37** in a 2:1 ratio and 20% of aldol products. Chromatographic purification (10 % ethyl acetate/hexanes) allowed the isolation of the major diastereomer of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2 H), 7.27–7.20 (m, 3 H), 6.27–6.19 (m, 1 H), 5.27–5.19 (m, 2 H), 4.54 (q, *J* = 4.2 Hz, 1 H), 3.80–3.75 (m, 1 H), 3.70 (s, 3 H), 2.68 (d, *J* = 7.1 Hz, 1 H).

Equation 82. A flame-dried flask was cooled under a stream of nitrogen and charged with KHMDS (300 mg, 1.5 mmol) and THF (2.5 mL). The resulting solution was cooled to 0 °C and **VIII-34** (97 mg, 0.5 mmol) was added neat to the solution. The mixture was allowed to warm to rt and was stirred for 30 min. The reaction mixture was then diluted with water (5 mL) and methylene chloride (5 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% methanol/methylene chloride as the eluent to afford 30 mg (31%) of the title compound as a colorless oil and as a 2:1 mixture of amides **VIII-38** and **VIII-39** determined by ^{1}H NMR analysis. Data are from the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.15 (m, 4.66 H), 5.16 (d, *J* = 5.9 Hz, 0.33 H), 4.70 (d, *J* = 6.1 Hz, 0.33 H), 4.59 (q, *J* = 5.6 Hz, 0.66 H), 3.70 (d, *J* = 7.8 Hz, 0.66 H), 3.02 (s, 1 H), 2.97 (s, 2 H), 2.95–2.85 (m, 1.25 H), 2.80 (s, 2 H), 2.77 (s, 1 H), 2.34 (s, 1 H).

References

[1] Reproduced in part with permission from Beaudoin Bertrand, M.; Wolfe, J. P. "Tandem Wittig Rearrangement/Aldol Reactions for the Synthesis of Glycolate Aldols" *Org. Lett* **2006**, *8*, 4661–4663. © 2006 American Chemical Society.

[2] Ester **VIII-2** was prepared through an aldol reaction between acrolein and the lithium enolate of **VIII-1** at –78 °C.

[3] The mechanism of [1,2]-Wittig rearrangement of α-lithio ether is believed to proceed via C-O bond homolysis and radical recombination. However, the conditions used in the boron-enolate [1,2]-Wittig rearrangement are quite Lewis acidic, and this transformation may proceed via a different mechanism.

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[5] In most cases only one stereoisomer was observed by ^{1}H NMR analysis of crude reaction mixtures. Product stereochemistry was assigned through ^{1}H NMR nOe analysis of an acetonide derivative of **VIII-3**. See the Supporting Information for complete details.

[6] PMB oxygen protecting groups can be removed under Lewis acidic conditions. See: Wuts, P. G. M.; Greene, T. W. In *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience, Hoboken, 2007; pp.127–129.

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[12] Longer reaction times (up to 24 h) did not lead the rearrangement of **VIII-23** and **VIII-24**.

[13] Use of bases such as NaHMDS, LiHMDS and KHMDS with **VIII-1** led to decomposition of the starting material.

[14] Substrate **VIII-36** underwent the following aldol reaction in low conversion (~20%).

[15] A literature report indicates that a 1:1.5 mixture of [1,2]- and [2,3]-Wittig rearrangement products was obtained when α-alkoxy lactams were treated with LiHMDS

in THF at rt. See: Garbi, D. Y.; Allain, L.; Chorki, F.; Ourevitch, M.; Crousse, B.; Bonnet-Delpon, D.; Nakai, T.; Begue, J. –P. *Org. Lett.* **2001**, *3*, 2529–2531.

[16] Use of an *N*-sulfonyl alkyl imine with **VIII-1** under the optimized reaction conditions did not lead to the formation of aldol products.

[17] These aspects of the research are currently being investigated by other members of the laboratory.

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