Stereoselective Annulation Reactions for the Asymmetric Synthesis of Tricyclic Guanidine Natural Products and Related Polycyclic Alkaloids

by

Nicholas R. Babij

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry) in the University of Michigan 2014

Doctoral Committee:

Professor John P. Wolfe, Chair
Assistant Professor Pavel Nagorny
Professor Melanie S. Sanford
Assistant Professor Matthew B. Soellner
Dedication

To Uncle Z.

I know how much you love reading and writing. Hopefully this will keep you busy for a bit.
Acknowledgments

First and foremost, I would like to thank my advisor, Dr. Wolfe, for allowing me to complete my graduate studies in his lab. I genuinely enjoyed my time in graduate school and most of that is a credit to him. I am particularly thankful for the freedom he allowed me during the course of my research. During my 5 years in his lab, I was able to grow as an independent thinker and chemist, in large part, because I had the opportunity to pursue research ideas and topics that I personally thought were interesting. Overall, I had the opportunity to learn from one of the greatest chemists in the world and I will always cherish that.

I also want to acknowledge all of those that played a significant mentorship role in my development as a chemist. Which begins with my undergraduate advisor, Prof. Andrew Duncan, who got me interested in organic chemistry all the way back during my sophomore year at Willamette and pushed me to pursue my doctorate degree here at Michigan. Secondly, I would like to thank Dr. Montgomery for the opportunity to rotate in his lab during my first year; it was a tremendous learning experience. I would also like to acknowledge Dr. Sanford, Dr. Nagorny, and Dr. Soellner for serving on my committee and giving me invaluable feedback during my time in graduate school. I was also incredibly fortunate to be mentored by some exceptionally gifted graduate students at Michigan, including Dr. Zack Buchan, Dr. Georgia Lemen, and Dr. Dani Schultz. I also had the opportunity to learn from an amazing group of students in the Wolfe group including Dr. Peter Mai, Dr. Joshua Neukom, Dr. Matthew Leathen, and Dr. Amanda Ward.

I am also grateful for all of the current students in the Wolfe group that I have had the opportunity to work with over the years. In particular, I want to thank Renata Everett for being an incredible bench mate for nearly three full years. Brett Hopkins was also an amazing colleague and I am very thankful I had the opportunity to work alongside him for so long. I also want to acknowledge all of the students I had the chance to mentor during my time in the Wolfe group including April Tang, Blane Zavesky, Grace McKenna, and Kortney Kersten. Mentoring
such a young group of talented and passionate students was an incredibly challenging, yet, rewarding experience. I also want to thank Ryan Fornwald for all of the help he gave me on my final research project; it was an incredible experience to try to find solutions to some incredibly difficult problems with such a talented chemist. Last but not least, I want to thank Justin Tham. We started in the Wolfe group at the same time and quickly became best friends. It’s a friendship that will last a lifetime.

I also want to thank all of my friends from Ann Arbor that have supported me during my time in graduate school including Jordan Walk, Taylor Haynes, Nathan Cichowicz, Brendan Clifford, Meg and Jim Zamberlan, Andrea Lawson, Elizabeth Stewart, and Pam Munson. You made the five years I spent in Ann Arbor very special.

Finally, I want to thank my family for always being there for me. I want to first acknowledge my Bearcat Hoop family: once a Bearcat always a Bearcat. Marcus Uchida and Simon Currie you are my best friends. Thanks for everything. Allison Knauff, if nothing else, graduate school will always be where I met you. Grandma, thank you for always loving me. I can’t wait to add the final piece to your present. Steph, Chris and Ali you are the most amazing younger sisters I could ask for. I am so proud of you. And lastly, Mom and Dad you are the single greatest reason any of this is possible. I cannot adequately express how thankful I am for everything you have done for me. Quite simply, I love you!
Table of Contents

Dedication ............................................................................................................................. ii

Acknowledgments .................................................................................................................. iii

List of Figures ........................................................................................................................ vii

List of Tables ........................................................................................................................ viii

List of Schemes ........................................................................................................................ ix

List of Abbreviations ............................................................................................................. xi

Abstract ................................................................................................................................. xiii

Chapter 1: Annulation Strategies for the Total Synthesis of Tricyclic Guanidine Alkaloids I

1.1 Introduction: Biological Properties and Structural Diversity ........................................ 1
1.2 Biomimetic Syntheses ...................................................................................................... 3
1.3 Total Syntheses: Previous Annulation Strategies ............................................................ 4
1.4 Limitations of Current Synthetic Methods ........................................................................ 11
1.5 Pd-Catalyzed Carboamination Reactions ........................................................................ 12

Chapter 2: Asymmetric Total Synthesis of (±)-Merobatzelladine B ....................................... 18

2.1 Introduction ....................................................................................................................... 18
2.2 Synthetic Plan and Model Studies .................................................................................... 19
2.3 Total Synthesis of (±)-Merobatzelladine B .................................................................... 20
2.4 Conclusions ...................................................................................................................... 22
2.5 Experimental ................................................................................................................... 22

Chapter 3: Desymmetrization of meso-2,5-Diallylpyrrolidinyl Ureas via Asymmetric Pd-
Catalyzed Carboamination: Stereocontrolled Synthesis of Bicyclic Ureas ......................... 36

3.1 Introduction ....................................................................................................................... 36
3.2 Optimization and Scope of Desymmetrization Transformation .................................... 37
List of Figures

Figure 1.1 Tricyclic guanidine natural products................................................................. 2
Figure 2.1 Polycyclic guanidine natural products.............................................................. 18
Figure 3.1 Bioactive guanidine alkaloids prepared from bicyclic urea and guanidine precursors.
........................................................................................................................................... 36
Figure 4.1 Biologically active tricyclic guanidine natural products................................. 79
Figure 5.1 Tetraponerine natural products.......................................................................... 104
List of Tables

Table 3.1 N-aryl group effects.................................................................................................................. 38
Table 3.2 Desymmetrization Reaction Scope. .......................................................................................... 39
Table 4.1 Ligand screen and solvent optimization..................................................................................... 82
Table 4.2 N-Protecting group effects. ...................................................................................................... 83
Table 4.3 Synthesis of 5-6 trans-bicyclic sulfamides. ............................................................................. 84
Table 4.4 Asymmetric desymmetrization of meso-2,5-diallylpyrroldinyl sulfamides......................... 85
Table 5.1 Synthesis of 5-6 cis-bicyclic ureas........................................................................................... 107
List of Schemes

Scheme 1.1 Total synthesis of crambescidin alkaloids via biomimetic annulation strategy ........ 3
Scheme 1.2 biomimetic synthesis of batzelladine alkaloids by Snider and Bhutani ............ 4
Scheme 1.3 Overman’s total synthesis of ptilomycalin A and other crambescidin alkaloids via tethered Biginelli condensation reactions ................................................................. 5
Scheme 1.4 Tethered Biginelli condensation annulation to access trans-core of isocrambescidins by Overman .................................................................................................................... 6
Scheme 1.5 Batzelladine alkaloid synthesis via tethered Biginelli condensation reactions by Overman ............................................................................................................................... 7
Scheme 1.6 Nagasawa’s total synthesis of (–)-crambescidin 359 via 1,3-dipolar cycloadditions. 8
Scheme 1.7 Cycloaddition/ Mitsunobu annulation sequence for batzelladine alkaloids by Nagasawa. ........................................................................................................................................ 9
Scheme 1.8 Gin’s asymmetric total syntheses of batzelladines A and D ....................... 10
Scheme 1.9 Crambidine synthesis via [4 + 2] annulation and hydroamination by Gin .......... 10
Scheme 1.10 Elliott’s synthesis of batzelladine C methyl ester via a three-component annulation. ........................................................................................................................................ 11
Scheme 1.11 Evan’s total synthesis of batzelladine D via stereoselective radical cyclization .... 11
Scheme 1.12 General scheme of Pd-catalyzed carboamination reactions and representative nitrogen-containing heterocyclic products ................................................................. 13
Scheme 1.13 Proposed catalytic cycle for Pd-catalyzed carboamination reactions that proceed via syn-aminopalladation. .................................................................................................. 13
Scheme 1.14 Stereochemical rationale for 5- and 6-membered ring-forming carboaminations .. 14
Scheme 1.15 Pd-catalyzed carboamination reactions that proceed via anti-addition .......... 15
Scheme 1.16 Proposed catalytic cycle for Pd-catalyzed carboamination reactions that proceed via anti-aminopalladation. ...................................................................................................... 16
Scheme 1.17 Synthesis of bicyclic products via Pd-catalyzed carboaminations ............... 17
Scheme 2.1 Iterative carboamination strategy for tricyclic guanidine synthesis ............. 19
Scheme 2.2 Model studies: synthesis of bicyclic ureas by Pd-catalyzed carboamination. ........ 20
Scheme 2.3 Total synthesis of (+)-merobatzelladine B .......................................................... 21
Scheme 3.1 Synthesis of bicyclic ureas through Pd-catalyzed asymmetric desymmetrization. .. 37
Scheme 3.2 Synthesis of meso-pyrrolidinyl urea substrates. .............................................. 38
Scheme 3.3 Deprotection of desymmetrization product ...................................................... 40
Scheme 3.4 Synthesis of tricyclic guanidine derivative ....................................................... 41
Scheme 3.5 Synthesis of 9-epi-batzelladine K ................................................................. 41
Scheme 3.6 Synthesis of ent-3-5c to determine absolute stereochemistry ....................... 73
Scheme 4.1 Synthesis of bicyclic ureas via syn-aminopalladation ........................................ 80
Scheme 4.2 Synthesis of cyclic ureas via anti-aminopalladation .......................................... 80
Scheme 4.3 Synthesis of trans-bicyclic ureas via anti-aminopalladation ............................ 81
Scheme 4.4 Synthesis of 6-6 bicyclic sulfamides .................................................................. 84
Scheme 4.5 Plausible catalytic cycle ................................................................................... 86
Scheme 4.6 Stereochemical rationale for the synthesis of bicyclic sulfamides ..................... 87
Scheme 4.7 Possible boat-like intermediates ..................................................................... 88
Scheme 5.1 Total synthesis of tetraponerine alkaloids via amino nitrile alkylations ............ 105
Scheme 5.2 Synthetic strategy towards the core of the tetraponerines via Pd-catalyzed carboamination reactions ......................................................................................... 106
Scheme 5.3 Proposed synthesis of the tetraponerine alkaloids from bicyclic ureas and sulfamides .................................................................................................................. 106
Scheme 5.4 Synthesis of 6-6 cis-bicyclic urea via a Pd-catalyzed carboamination reaction .... 107
Scheme 5.5 Synthesis of trans-bicyclic cyclic sulfamides ...................................................... 108
Scheme 5.6 Initial synthetic efforts towards tetraponerine T-5 ............................................. 109
Scheme 5.7 Reduction of urea bridge ............................................................................... 109
Scheme 5.8 Removal of sulfamide bridge via LiAlH₄ ......................................................... 110
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>All</td>
<td>allyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DTBP</td>
<td>2,6-di-tert-butylpyridine</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>(Me),t-BuXPhos</td>
<td>2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-tri-iso-propylbiphenyl</td>
</tr>
<tr>
<td>MeOTf</td>
<td>methyl trifluoromethanesulfonate</td>
</tr>
</tbody>
</table>
Ms ..............................................................methanesulfonyl
NMO ...................................................................N-methylmorpholine 4-oxide
PG .................................................................protecting group
Ph .....................................................................phenyl
PMB ..................................................................para-methoxybenzyl
PMP ..................................................................para-methoxyphenyl
PPTS ..............................................................pyridinium para-toluenesulfonate
Pr ..................................................................propyl
tetra-n-butylammonium fluoride
TBDMS .........................................................tert-butyldimethylsilyl
TBDPS .........................................................tert-butyldiphenylsilyl
TBS ..........................................................tert-butyldimethylsilyl
Tf .................................................................trifluoromethylsulfonyl
TFA .............................................................. trifluoroacetic acid
THF .............................................................tetrahydrofuran
TMS ..........................................................trimethylsilyl
para-toluenesulfonic acid

p-TSOH ................................................................para-toluenesulfonic acid
Abstract

Natural products and molecules derived from natural products have historically been one of the primary sources of new pharmaceuticals including antibiotics, antimalarials and anticancer drugs. However, many natural products cannot be isolated in sufficient quantities for commercialization due to insufficient natural resources, elevated costs of extractions and/or environmental factors; thus, pharmaceutical companies attempt to synthetically generate these compounds on scales large enough in order to serve the public.

Tricyclic guanidine alkaloids are a class of natural products that exhibit a wide range of interesting biological properties including anti-HIV, antibacterial and anti-tumor activity but face practical isolation challenges. Unfortunately, current methods for the synthesis of these molecules suffer from an inability to provide access to stereochemically different cores and fail to facilitate the synthesis of analogs in a straightforward manner. To address these limitations, the research outlined in this thesis focused on the development of annulation strategies that can be utilized for the synthesis of polycyclic guanidines of any given stereochemical configuration and that are amenable to rapid analog construction.

In all, this dissertation describes the synthesis of tricyclic guanidine natural products and structurally related alkaloids from bicyclic ureas and sulfamides that were prepared in a concise and stereocontrolled manner via Pd-catalyzed carboamination reactions. Chapters 2 and 3 of this dissertation detail the development of Pd-catalyzed carboamination reactions that are believed to proceed via syn-aminopalladation. This chemistry was utilized to accomplish the first total synthesis of (+)-merobatzelladine B. Additionally, an asymmetric variant of this methodology allows for the construction of bicyclic ureas via the desymmetrization of meso-pyrrolidinyl ureas, in good yields, diastereo- and enantioselectivities. The utility of the desymmetrization methodology was demonstrated by transforming one of the bicyclic urea products into 9-epi-batzelladine K. In an effort to synthesize the natural stereoisomer of batzelladine K, Pd-catalyzed carboamination reactions that are believed to proceed via anti-aminopalladation were explored.
The optimization of this chemistry, along with the scope and limitations of the methodology, is described in chapter 4. Lastly, the final chapter of this dissertation details the application of the carboamination methodology developed in chapters 2-4 towards the total synthesis of the tetraponerine alkaloids.
Chapter 1

Annulation Strategies for the Total Synthesis of Tricyclic Guanidine Alkaloids

1.1 Introduction: Biological Properties and Structural Diversity

Tricyclic guanidine natural products (Figure 1.1) comprise a class of marine alkaloids that exhibit remarkable biological properties, including antiviral, antimicrobial, and antifungal activity.\(^1\)\(^-\)\(^5\) Several members of the batzelladine family, a subset of this class of natural products, are known to inhibit protein-protein interactions associated with the replication of HIV-1 in cells, and thus have gained significant attention due to their therapeutic potential for the AIDS virus.\(^6\) Batzelladines A and B are known to inhibit the binding of HIV glycoprotein gp-120 to CD4 on human T-cells.\(^7\) Other batzelladine alkaloids, such as batzelladine F, induce dissociation of the protein tyrosine kinase p56\(^{\text{lk}}\) complex from CD4.\(^8\) Additionally, several members of the crambescidin family, including crambescidin 800, show nanomolar toxicity against a number of human cancer cell lines.\(^9\) The wide-ranging biological activity of these compounds can in part be attributed to the cationic nature of the guanidinium functional group that can participate in a large number of non-covalent molecular interactions.\(^10\)

In all, the structurally unique tricyclic guanidinium ring system (hydro-5,6,6a-triazaacenaphthlene) that defines this class of natural products can be found in over 30 different alkaloids. While each of these natural products share this common structural motif, the substituents that decorate the tricyclic core of these molecules leads to significant structural diversity and wide-ranging biological properties. For instance, a large number of these molecules including batzelladine F and ptilomycalin A feature pendant esters that tether the tricyclic core to a diverse array of different functional groups, including other tricyclic guanidine subunits.\(^1\)\(^11\)

Interestingly, differences in the ester side chains dramatically alter the biological properties of the natural products. For example, batzelladine A inhibits the binding of HIV glycoprotein gp120 to CD4 receptors as mentioned above, where as batzelladine D has no known biological activity.\(^7\)
Furthermore, several tricyclic guanidine alkaloids do not feature an ester side chain, yet exhibit interesting biological properties such as the antibacterial and antimalarial activity of merobatzelladines A and B. The other area of structural diversity within this family of alkaloids is the C1 and C8 alkyl chains, which vary in terms of length, units of unsaturation, and oxidation. Remote oxidation of the alkyl branches is characteristic of the crambescidin alkaloids, including ptilomycalin A and crambescidin 359, which feature two spirocyclic hemiaminals in addition to the tricyclic guanidine framework.

In addition to structural diversity, the batzelladine and crambescidin alkaloids feature different stereochemical configurations of the tricyclic core. As highlighted in Figure 1.1, both the trans- and cis-configurations of the pyrrolidine subunit are prevalent in this class of natural products. Batzelladine F highlights this stereochemical diversity as it contains two distinct configurations.
tricyclic guanidine subunits, with each featuring one of the pyrrolidine configurations.\textsuperscript{11,13} The stereochemical diversity is generally limited to the configuration of the pyrrolidine unit, as all of the alkaloids in this class feature a trans relationship between the C4 (and/or C6) proton and the C1 (and/or C8) alkyl chain, except, merobatzelladines A and B.\textsuperscript{12,14} Both natural products feature a cis relationship between the C6 proton and the C8 alkyl chain as highlighted in Figure 1.1.

### 1.2 Biomimetic Syntheses

The architecturally complex structures of tricyclic guanidine natural products, in addition to their remarkable biological properties, make this class of alkaloids ideal targets for total synthesis. Shortly after the isolation of ptilomycalin A,\textsuperscript{1} the parent member of this family, Snider and Murphy identified a potential biosynthetic pathway for the formation of these natural products. As shown in Scheme 1.1, Snider proposed that the methyl ester of ptilomycalin A (1-1) could be constructed in a single step from addition of guanidine to bis-Michael acceptor 1-2.\textsuperscript{15} This proposal was predicated on the idea that a double Michael addition would afford the pyrrolidine ring, and subsequent imine and hemiaminal formation would generate the final four rings. Ultimately, Snider was able to validate this hypothesis by converting bis-enone 1-2 to the methyl ester of ptilomycalin A (1-1) in just four steps. A related biomimetic strategy was simultaneously explored by Murphy, and culminated in the total synthesis of crambescidin 359, a molecule that features the same pentacyclic core of ptilomycalin A but absent the ester side chain.\textsuperscript{16}

**Scheme 1.1** Total synthesis of crambescidin alkaloids via biomimetic annulation strategy.
Additionally, Snider utilized a similar synthetic sequence to complete the racemic total synthesis of batzelladine E (Scheme 1.2). Intermolecular axial delivery of a hydride to hemiaminal 1-3, effected the stereoselective synthesis of the natural product.\textsuperscript{17} This report marked the first synthesis of a member of the batzelladine family and remains the only synthesis of batzelladine E to date. Recently, Bhutani applied this biomimetic strategy to synthesize racemic batzelladine K,\textsuperscript{18} and 50 derivatives in an effort to evaluate these compounds for potential biological applications.\textsuperscript{19}

**Scheme 1.2** Biomimetic synthesis of batzelladine alkaloids by Snider and Bhutani.

While this work does suggest that this is a plausible biogenetic route for the synthesis of several alkaloids including ptilomycalin A, crambescidin 359, and batzelladine K, the origin of stereoselection for natural products containing a trans-2,5 pyrrolidine such as batzelladine A or isocrambescidin 800 is unclear. However, based on the work conducted by Snider as shown in Scheme 1.1, the bicyclic isourea (1-4) formed via the bis-enone conjugate addition was generated with ~4:1 selectivity in favor of the trans-pyrrolidine configuration.\textsuperscript{15} Thus, this may be a plausible synthetic pathway for natural products with the trans configuration, although the precise biosynthetic mechanism of the third annulation is unclear.

**1.3 Total Syntheses: Previous Annulation Strategies**

In addition to the biomimetic research detailed above, a number of groups have targeted the total synthesis of these alkaloids by developing new synthetic methodologies. The Overman group has remarkably reported the enantioselective synthesis of ten tricyclic guanidine alkaloids over the course of the past 20 years.\textsuperscript{20} This unbelievable feat is a tribute to the incredible versatility of the intramolecular Biginelli reaction they first developed during their landmark
synthesis of ptilomycalin A in 1995. Specifically, the tethered Biginelli condensation of 1-5 and β-ketoester 1-6 generated bicyclic urea 1-7 in good yield and 7.5:1 diastereoselectivity in favor of the cis-pyrrolidine (Scheme 1.3). Acid-mediated spirocyclization of 1-7 afforded tricyclic urea 1-8 with high stereoselectivity. However, the ester C7 stereocenter was epimeric to that of the natural product, and thus required base induced epimerization prior to completion of the synthesis. The final two rings of the pentacyclic alkaloid were fashioned in a similar manner to the biomimetic strategy developed by Snider and Murphy as described in Scheme 1.1. Despite being the first synthesis of any member in the tricyclic guanidine class of natural products, this synthetic route generated ptilomycalin A on a gram scale, permitting further biological studies to be conducted. Shortly thereafter, the group reported a second generation approach towards this family of alkaloids, which was more convergent and culminated in the total syntheses of crambsidins 657 and 800, neofolitispates 2 and ptilomycalin A. Further evolution of this annulation strategy provided crambsidins 359 and 431.

**Scheme 1.3** Overman’s total synthesis of ptilomycalin A and other crambsidin alkaloids via tethered Biginelli condensation reactions.

Given the stereochemical diversity displayed within this family of natural products, the Overman group sought to develop reactions conditions that would selectively afford products of the Biginelli condensation reaction with a trans-pyrrolidine. Simply switching to a guanidine substrate 1-9 (Scheme 1.4) from ureido aminal 1-5 (Scheme 1.3) led to a reversal in selectivity, specifically providing the trans-isomer 1-10 with 7:1 diastereoselectivity. The success in
effecting this change in selectivity was highlighted in the total syntheses of isocrambescidins 657 and 800.\(^{25}\)

**Scheme 1.4** Tethered Biginelli condensation annulation to access \textit{trans}-core of isocrambescidins by Overman.

In addition to their work directed towards members of the crambescidin family, the Overman group successfully completed the first enantioselective synthesis of a batzelladine alkaloid (batzelladine D).\(^{26}\) The tethered Biginelli annulation reaction of 1-11 and \(\beta\)-ketoester 1-12 afforded bicyclic core 1-13 with \(\sim 6\!:\!1\) diastereoselectivity in favor of the \textit{trans}-isomer (Scheme 1.5). Following annulation of the third ring via an intramolecular \(S_N^2\) reaction, hydrogenation of the alkene in 1-14, which was installed via the Biginelli reaction, afforded a mixture of products (1-15 and 1-16). The unselective nature of this step is a major limitation of the Biginelli annulation chemistry for the synthesis of batzelladine alkaloids. In spite of this limitation, this chemistry was further utilized to complete the first total synthesis of batzelladine F, and establish the constitution and relative stereochemistry of the natural product.\(^{11,27,28}\) Notably, the \textit{syn}-isomer displayed in one of the two tricyclic guanidine subunits was accessed by employing the intramolecular Biginelli annulation reaction to close the third and final ring, as opposed to the second ring in all of the chemistry described above. Lastly, the total synthesis of dehydrobatzelladine C was accomplished by utilizing the Biginelli chemistry to access a key intermediate.\(^{29}\) Advantageously, this synthesis did not require the problematic unselective olefin hydrogenation due to the oxidized core of the molecule.
Scheme 1.5 Batzelladine alkaloid synthesis via tethered Biginelli condensation reactions by Overman.

The Nagasawa group reported the first total synthesis of (−)-crambescidin 359 through an iterative sequence of 1,3-dipolar cycloaddition reactions (Scheme 1.6). The key sequence served to install the entirety of the alkaloid’s carbon framework. Interestingly, both cycloaddition reactions proceeded with complete regio- and stereocontrol. However, the cycloaddition sequence stereoselectively generated trans-pyrrolidine 1-17, whereas the pyrrolidine in crambescidin 359 has a cis configuration. To address this unfavorable stereochemical outcome, the authors used a two-step epimerization reaction sequence, which generated the desired cis-pyrrolidine (1-18) as a separable mixture of diastereomers (7:1 crude dr). Having successfully stereoselectively constructed the pyrrolidine ring and the carbon framework of the natural product, annulation of the remaining four rings was accomplished in a single step from bis-ketone 1-19, in a similar fashion to the biomimetic work developed by Snider and Murphy highlighted above (Scheme 1.1).
Scheme 1.6 Nagasawa’s total synthesis of (−)-crambescidin 359 via 1,3-dipolar cycloadditions.

The Nagasawa group expanded upon their initial work by completing the total synthesis of both (+)-batzelladine A and (−)-batzelladine D (Scheme 1.7).31–33 These syntheses took advantage of the selective formation of the *trans*-2,5-disubstituted pyrrolidine (1-20) generated following the iterative sequence of 1,3 dipolar cycloadditions. Importantly, the ester side chains displayed in the natural products were easily incorporated, as conjugated alkenes served as viable substrates for the cycloaddition reactions. Furthermore, the cycloaddition reaction sequence stereoselectively introduced alcohol functionality, which facilitated annulation of the six-membered rings via sequential Mitsunobu reactions. Notably, the Nagasawa group employed the same general cycloaddition/Mitsunobu synthetic strategy to complete the first total synthesis of (+)-batzelladine K.34
In 2006, the Gin group reported the asymmetric synthesis of batzelladines A and D, which highlighted their recently developed [4 + 2] annulation reactions between vinyl carbodiimides and chiral N-alkyl imines (Scheme 1.8).\textsuperscript{35} This strategy provided an expedient route towards the construction of the bicyclic core common to several members of the batzelladine family. Specifically regarding the total synthesis of \((\text{--})\)-batzelladine D, vinyl carbodiimide 1-21 was coupled with enantiopure 3,4-dihydropyrrole 1-22 to afford the desired dihydropyrimidine 1-23 in good yield and as a single diastereomer. The configuration of the pyrrolidine subunit was determined to be \textit{trans} after detailed NMR experiments. The stereochemical outcome of this reaction was rationalized based on steric factors although the exact mechanism of the [4 + 2] annulation is unclear. In addition to the [4 + 2] annulation methodology developed to construct the bicyclic core of batzelladines A and D, the Gin group introduced a new annulation strategy for closing the third ring of these natural products. Annulation of the final ring in batzelladine D was accomplished via an intramolecular halo-amination of olefin 1-24. The tricyclic product was generated with complete stereocontrol as the final stereocenter in batzelladine D was established.
Scheme 1.8 Gin’s asymmetric total syntheses of batzelladines A and D.

In 2010, Gin expanded upon the [4 + 2] annulation chemistry developed in his group to accomplish the total synthesis of (–)-crambidine (Scheme 1.9).\textsuperscript{36} In an effort to access the more highly oxidized core displayed in the natural product, thioimidiate 1-25 was used as the coupling partner in the key annulation reaction. Closure of the final ring of the alkaloid was again accomplished via addition across a multiple bond, specifically the Au-catalyzed hydroamination of alkyne 1-26.

Scheme 1.9 Crambidine synthesis via [4 + 2] annulation and hydroamination by Gin.

The methyl ester of batzelladine C was first synthesized in 2009, leading to the unambiguous assignment of the relative and absolute stereochemistry of the natural product.\textsuperscript{37} The unknown C8 stereocenter was installed via a three-component coupling of alkylidenepyrrolidine 1-27, hexanal, and TMS-isothiocyanate (Scheme 1.10). While the diastereoselectivity of the reaction
was modest (2:1), this permitted the synthesis of both possible stereoisomers of the methyl ester of batzelladine C. Annulation of the final ring was accomplished via an intramolecular iodo-cyclization based on the work developed by Gin described above (Scheme 1.8).

**Scheme 1.10** Elliott’s synthesis of batzelladine C methyl ester via a three-component annulation.

In 2007, Evans utilized a stereoselective intramolecular radical cyclization to afford a key intermediate in the synthesis of (–)-batzelladine D (Scheme 1.11). Homolytic cleavage of alkyl iodide 1-28 when treated with tributyltin hydride and triethylborane initiated the key diastereoselective cyclization. Annulation of the third and final ring of batzelladine D was accomplished via intramolecular guanylation of methyl isourea 1-29.

**Scheme 1.11** Evan’s total synthesis of batzelladine D via stereoselective radical cyclization.

In all, the groups of Overman, Nagasawa, Gin and Evans have successfully synthesized 14 different crambescidin and batzelladine natural products. Importantly, a number of these syntheses established the relative and absolute stereochemical configuration of the synthetic target, in addition to other alkaloids in the family based on analogous assignments. Lastly, several of these natural products and synthetic analogs were prepared on scales large enough to permit further biological testing including structure-activity relationship studies.

**1.4 Limitations of Current Synthetic Methods**

Overall, the synthetic challenge posed by the structural and stereochemical complexity of tricyclic guanidine natural products has inspired the development of a number of new methodologies and led to several extraordinary total syntheses as highlighted above. However, general methods that provide access to stereochemically different cores are exceedingly rare.
and versatile strategies for the construction of tricyclic guanidines remain highly desirable. Specifically, biomimetic pathways for the synthesis of members of the batzelladine family are currently limited to racemic routes and are limited to alkaloids featuring a cis-pyrrolidine. Furthermore, no methods have been successfully demonstrated to afford tricyclic guanidine products with a cis relationship between the C6 proton and C8 alkyl chain as observed in merobatzelladines A and B. Moreover, given the rich biological history of this class of alkaloids, approaches that facilitate the synthesis of analogs in a straightforward manner are of tremendous interest, yet strikingly uncommon. To address these limitations, the research described in the dissertation is centered on the development of annulation strategies for the synthesis of polycyclic guanidines of any given stereochemical configuration and that are amenable to rapid analog construction.

1.5 Pd-Catalyzed Carboamination Reactions

Over the past decade, the Wolfe group has successfully developed a series of Pd-catalyzed annulation reactions that afford nitrogen-containing heterocycles from simple starting materials (Scheme 1.12). Alkene substrates bearing a pendant amine are cross-coupled with an aryl or alkenyl halide in the presence of a palladium catalyst and base to afford various heterocyclic products including pyrazolidines, piperazines, and benzodiazepines. These reactions effect the formation of two new bonds and up to two new stereocenters. These annulation reactions have been proven to be efficient for heterocyclic scaffolds of varying ring sizes, and generally proceed with high levels of stereocontrol. Importantly, a large number of analogs of a particular heterocycle can be easily generated from a single substrate due to the commercial availability of the electrophilic coupling partners.
Scheme 1.12 General scheme of Pd-catalyzed carboamination reactions and representative nitrogen-containing heterocyclic products.

In most cases, the Pd-catalyzed annulation reactions are believed to proceed via the catalytic cycle shown below in Scheme 1.13.\textsuperscript{47,48} Oxidative addition of the aryl (or alkenyl) halide to the Pd(0) catalyst affords complex 1-30. Deprotonation of the substrate with base and coordination of the amine to the Pd-metal center affords the key Pd(aryl)amido species 1-31. Migratory insertion of the alkene into the Pd-N bond results in \textit{syn}-aminopalladation and reductive elimination generates the desired heterocyclic product and regenerates the Pd(0) catalyst.

Scheme 1.13 Proposed catalytic cycle for Pd-catalyzed carboamination reactions that proceed via \textit{syn}-aminopalladation.
The high stereoselectivity generally observed in these transformations can be attributed to the highly organized nature of the transition state for the stereocenter-forming syn-aminopalladation event (Scheme 1.14). For instance, the selectivity observed for the formation of cis-2,5 disubstituted pyrrolidines likely arises from transition state 1-32, where the substituent on the backbone of the substrate occupies a pseudo-axial position in order to minimize A(1,3)-strain with the N-protecting group. Additionally, carboamination reactions that facilitate the formation of 6-membered rings, including the synthesis of piperazines and morpholines, are believed to proceed via boat-like transition states such as 1-33.45,49

**Scheme 1.14** Stereochemical rationale for 5- and 6-membered ring-forming carboaminations.

Recently, a series of Pd-catalyzed carboamination reactions have been shown to go through an alternative mechanistic pathway, one in which the aminopalladation step results in anti-addition of the two components across the alkene, rather than syn-addition. As shown in Scheme 1.15, 5-membered cyclic sulfamides and ureas have been synthesized via the cross-coupling of substrates 1-34 and 1-35 with phenyl triflate. Deuterium labeling studies indicated that these products were formed as a result of anti-addition across the olefin. These results are in stark contrast to most of the difunctionalization reactions that have been developed in the Wolfe lab over the past decade. Importantly, this chemistry has the potential to greatly expand the number of products that can be synthetized via Pd-catalyzed carboamination reactions. For example, substrates containing 1,2-disubstituted alkenes such as 1-36 can be converted into products (1-37) that could not be constructed using carboamination reactions that proceed via syn-aminopalladation.
Scheme 1.15 Pd-catalyzed carboamination reactions that proceed via *anti*-addition.

A plausible catalytic cycle for the aforementioned transformation is shown in Scheme 1.16. This mechanism is initiated via oxidative addition of an aryl triflate to the Pd(0) catalyst. The non-coordinating nature of the triflate anion may lead to cationic complex 1-38, which can then coordinate to the olefin of the substrate. As opposed to the migratory insertion observed previously in Wolfe group chemistry, the aminopalladation step for these transformations is believed to occur via outer-sphere nucleophilic attack of the amino-group onto the olefin, resulting in *anti*-addition across the alkene. Reductive elimination from intermediate 1-39 affords the desired heterocyclic product and regenerates the Pd(0) catalyst.
Overall, Pd-catalyzed carboamination reactions have proven to be of tremendous utility for the construction of nitrogen-containing heterocycles. As such, we envisioned that carboamination reactions could serve as the foundation for a novel annulation strategy towards the synthesis of tricyclic guanidine natural products. This approach was particularly attractive as it was anticipated that tricyclic guanidines with different stereochemical configurations could be synthesized from a single precursor (Scheme 1.17). This aspect of the research was particularly important for two reasons: 1) this class of alkaloids displays a wide range of stereochemical diversity and 2) existing methodology for the construction of these alkaloids is generally limited to the synthesis of a single stereoisomer. Additionally, this strategy was attractive for its potential to rapidly generate analogs from a late stage intermediate without any changes to the general synthetic strategy. Specifically, a library of analogs could be easily prepared from a single precursor by simply changing the electrophilic coupling partner employed during the carboamination reaction. To this end, our goal was to develop a series of novel carboamination reactions that could be utilized for the construction of polycyclic guanidines of any given stereochemical configuration and which would facilitate the rapid synthesis of analogs.
Scheme 1.17 Synthesis of bicyclic products via Pd-catalyzed carboaminations.

As depicted in Scheme 1.17, our general strategy was to construct stereochemically-different bicyclic products via the cross-coupling of alkenyl halides and 2-allyl pyrrolidinyl substrates 1-40. Chapters 2 and 3 detail our development of Pd-catalyzed carboamination reactions that proceed via syn-aminopalladation and afford bicyclic ureas 1-41 with high levels of diastereoselectivity. The utility of this chemistry was demonstrated in the asymmetric synthesis of merobatzelladine B and 9-epi-batzelladine K. Additionally, chapter 4 details the optimization and scope of carboamination reactions that proceed via anti-aminopalladation and afford bicyclic sulfamides 1-42 with good stereocontrol. The chemistry described in chapter 4 highlights that the diastereoselectivity of carboamination reactions can be reversed by simply employing reaction conditions that favor an anti-aminopalladation mechanism. Furthermore, these carboamination products could serve as key intermediates in the synthesis of members of the batzelladine family, including batzelladine K, which were previously inaccessible via the methodology developed in chapters 2 and 3. In all, the research detailed in this dissertation demonstrates that the stereochemical outcome of carboamination reactions can be controlled through judicious choice of substrate, catalyst, and reaction conditions. We report herein our findings on the use of Pd-catalyzed carboamination reactions as an annulation strategy for the stereoselective synthesis of tricyclic guanidine natural products, their analogs, and related polycyclic alkaloids.
Chapter 2

Asymmetric Total Synthesis of (+)-Merobatzelladine B

2.1 Introduction

In 2009, Matsunaga et al. reported the isolation of merobatzelladines A and B from the marine sponge *monanchora sp.* (Figure 2.1). These compounds are members of a new subclass of the batzelladine alkaloids that possess the signature tricyclic guanidine core common to all batzelladines, but display a unique stereochemical feature that differs from other members in this family. The C8 alkyl substituents in merobatzelladines A and B are positioned in a *syn*-relationship with the C6 hydrogen atoms, whereas other related natural products, such as batzelladines A, E, or F, contain an *anti*-relationship between these groups. Merobatzelladines A and B exhibit moderate antimicrobial activity against *Vibrio anguillarum*, and also show inhibitory activity against the K1 strain of *Plasmodium falciparum* (IC$_{50}$ = 0.48 µg/mL and 0.97 µg/mL, respectively). Given the rich biological activity of the related batzelladine alkaloids, it is possible that merobatzelladines A and B may exhibit additional useful properties that have yet to be reported.

Figure 2.1 Polycyclic guanidine natural products.
Given the importance of polycyclic guanidine alkaloids, several different approaches have been employed for the synthesis of these compounds. As detailed in chapter 1, the most widely utilized routes typically generate the fused ring system through condensation reactions, cycloaddition reactions, radical cyclizations, and substitution reactions. Although these routes have proven highly useful, none provide a means for generation of a C–C bond adjacent to the ring (such as the C8′–C4H9 bond in merobatzelladine B) during the ring-closing event. In addition, none of these routes has been employed for the generation of molecules with the syn-relationship between the C8 alkyl group and the C6 H-atom such as that displayed in merobatzelladines A and B. This chapter describes the first total synthesis of merobatzelladine B, which provides the natural product as a single stereoisomer in high optical purity, and represents a new strategy for the construction of polycyclic guanidine alkaloids.

2.2 Synthetic Plan and Model Studies

Our approach to the synthesis of merobatzelladine B was centered around the use of Pd-catalyzed alkene carboamination reactions for the formation of two of the three rings in the natural product. As shown in Scheme 2.1, we envisioned that a Pd-catalyzed carboamination between vinyl bromide and an appropriately functionalized γ-aminoalkene derivative 2-1 would generate cis-disubstituted pyrrolidine 2-2 with high stereocontrol. A second carboamination reaction between allylpyrrolidine derivative 2-3 and 1-bromo-1-butene would afford bicyclic product 2-4, which could then be transformed to the polycyclic guanidine natural product through functional group interconversion and ring-closure via an intramolecular S_N2 reaction.

Scheme 2.1 Iterative carboamination strategy for tricyclic guanidine synthesis.

Our prior studies on Pd-catalyzed alkene carboamination reactions have illustrated that the conversion of N-Boc-γ-aminoalkenes to 2,5-disubstituted pyrrolidines typically proceeds in good yield with > 20:1 diastereoselectivity favoring the cis-isomer. As such, the transformation of 2-1 to 2-2 appeared quite feasible; however, the likelihood of success in the planned Pd-catalyzed carboamination between 2-3 and an alkenyl halide was less clear. The generation of
six-membered rings via Pd-catalyzed carboamination is considerably more difficult than formation of five-membered rings,\textsuperscript{44,45,49} and this has not previously been accomplished with an unsaturated urea substrate.\textsuperscript{55,56} To test the feasibility of this key transformation, we examined the Pd-catalyzed carboamination of 2-allyl-pyrrolidine-derived urea 2-5 with simple aryl and alkenyl halides. After optimization of conditions, we found that a catalyst composed of Pd\(_2\)(dba)\(_3\)/PCy\(_3\) provided satisfactory results in these reactions (Scheme 2.2). The bicyclic urea products 2-6a and 2-6b were obtained in good yield and high diastereoselectivity, which may arise via cyclization through boat-like transition state 2-7.\textsuperscript{45,47–49} The alternative boat-like transition state 2-8, which leads to the minor diastereomer, appears to suffer from significant steric interactions between the alkene and the pyrrolidinyl ring. Moreover, cyclization through a chair-like transition state appears to be less accessible due to poor overlap between the alkene pi-system and the Pd–N bond.\textsuperscript{45,49}

**Scheme 2.2** Model studies: synthesis of bicyclic ureas by Pd-catalyzed carboamination.

![Scheme 2.2 Model studies: synthesis of bicyclic ureas by Pd-catalyzed carboamination.](image)

\section*{2.3 Total Synthesis of (+)-Merobatzelladine B}

Having illustrated the feasibility of our approach to the generation of fused bicyclic ureas, we undertook the synthesis of merobatzelladine B by constructing an appropriately functionalized \(\gamma\)-aminoalkene derivative for the pyrrolidine-forming carboamination. As shown in Scheme 2.2, the amine-bearing stereocenter was generated via a highly efficient asymmetric Mannich reaction of sulfinyl imine 2-9.\textsuperscript{57,58} The stereocontrolled reduction of ketone 2-10 proved quite challenging,\textsuperscript{59} and after examining many different reducing agents we found that the combination of NaBH\(_4\) and CeCl\(_3\) led to formation of 2-11 with 3:1 diastereoselectivity. However, the two diastereomers were separable by column chromatography, and 2-11 was isolated as a single stereoisomer in 63\% yield. Protection of the alcohol as a benzyl ether followed by exchange of the sulfinyl group for a Boc-group provided 2-12 in 91\% yield over three steps and 99\% ee.

With intermediate 2-12 in hand, the key sequence of carboamination reactions was undertaken. The Pd/P(2-furyl)\(_3\)-catalyzed carboamination of 2-12 with \(E\)-2-bromovinyltrimethylsilane...
provided pyrrolidine 2-13 in 68% yield and with excellent stereocontrol (>20:1 dr). Treatment of 2-13 with TFA led to cleavage of the Boc group and protodesilylation of the alkene. The resulting pyrrolidine was coupled with p-methoxybenzylisocyanate to generate pyrrolidinyl urea 2-14 in 72% yield over the two-step sequence. The Pd/PCy₃-catalyzed carboamination of 2-14 with Z-1-bromo-1-butene proceeded smoothly to yield bicyclic urea 2-15 in 91% yield and >20:1 dr.

**Scheme 2.3** Total synthesis of (+)-merobatzelladine B.

Bicyclic urea 2-15 was converted to guanidinium salt 2-16 in 89% yield by treatment with POCl₃ followed by addition of ammonia. This transformation was conducted under rigorously anhydrous conditions to avoid HCl-mediated side reactions. The tetrafluoroborate counterion was introduced during the workup procedure by washing a dichloromethane solution of the crude guanidine product with aqueous NaBF₄. This anion exchange was essential to avoid complications during the subsequent ring-closing step. The use of the analogous guanidinium chloride salt in the ring-closing reaction led to the formation of a chlorinated side product resulting from the substitution of chloride for hydroxide. A diastereomeric side product resulting from double inversion at C1 was also formed. Use of the BF₄⁻ salt prevented the formation of these side products.
Guanidinium salt 2-16 was then transformed to the natural product in a three-step sequence involving initial hydrogenation with Pd/C to effect reduction of the alkene and cleavage of the benzyl ether protecting group. Ring-closure was achieved via intramolecular Mitsunobu reaction, and deprotection of the N-PMB group provided merobatzelladine B in 41% yield over the three step sequence from 2-16. The synthetic alkaloid was obtained in enantiopure form \([\alpha]^{23}_D + 40.1 \ (c \ 0.7, \text{MeOH})\); [lit.]: \([\alpha]^{23}_D + 27 \ (c \ 0.15 \text{MeOH})\]}, and NMR spectra were identical to the data previously reported for the natural product.12

2.4 Conclusions

In summary, we have developed the first asymmetric total synthesis of (+)-merobatzelladine B, which confirms the structural and stereochemical assignments of the natural product. Our route afforded the desired alkaloid in 15 steps and 6.7% overall yield from commercially available pent-4-enal. The results described above represent a fundamentally new strategy for the stereocontrolled synthesis of polycyclic guanidine natural products. This new approach allows for formation of a carbon-carbon bond during the ring-closing event, and is the first route shown to provide access to alkaloids with a syn-relationship between the C6 hydrogen atom and the C8 alkyl group. This strategy could potentially be employed to access other guanidine alkaloids that contain this stereochemical feature, and could also be used for the generation of novel analogs of the batzelladine alkaloids. In addition, this work also illustrates the feasibility of forming 5,6-fused bicyclic urea ring systems via Pd-catalyzed carboamination, which could be of value for preparation of other interesting biologically active heterocycles.

The work described in this chapter was published in Angewandte Chemie International Edition.60

2.5 Experimental

General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium and tri-(2-furyl)phosphine were purchased from Strem Chemical Co. and used without further purification. Tricyclohexylphosphonium tetrafluoroborate was purchased from Acros Chemical Co. and used without further purification. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. POCl3 was purified by distillation under N2 prior to use. tert-Butyl 2-allylpyrrolidine-1-carboxylate,61 and
(E)-1-bromodec-1-ene\textsuperscript{62} were prepared according to published procedures. Toluene, THF, methylene chloride and diethyl ether were purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by either \textsuperscript{1}H NMR or capillary GC analysis of crude reaction mixtures. Yields refer to isolated yields of compounds estimated to be \( \geq 95\% \) pure as determined by \textsuperscript{1}H NMR.

**Experimental Procedures and Compound Characterization Data**

\((Z)-1\text{-bromobut-1-ene}\). This compound was prepared via a modification of a published procedure by Ellman.\textsuperscript{63} A flame-dried flask equipped with a stirbar was cooled under vacuum, backfilled with \( N_2 \) and charged with (\( E \))-2-pentenoic acid (10 ml, 100 mmol) and methylene chloride (100 mL). The resulting solution was cooled to 0 °C and bromine (11 mL, 220 mmol) was slowly added over 15 min. The solution was gradually warmed to rt, at which time the \( N_2 \) line was replaced with a vent needle, and then stirred overnight. The solvent and excess bromine were carefully removed by stirring under a stream of \( N_2 \) in the back of a ventilation hood. The crude material was dissolved in DMF (100 mL) and \( \text{Et}_3\text{N} \) (15 mL, 110 mmol) was slowly added to the reaction flask (open to air) over the course of 5 min. Within minutes a precipitate formed and the reaction was stirred for a total of ca. 15 min. The DMF solution was transferred to a distillation flask to remove most of the precipitate. The precipitate was washed with DMF (2 x 15 mL) and each wash was added to the distillation flask. The resulting solution was subjected to atmospheric pressure distillation and the fraction collected from 60–115 °C was transferred to a separatory funnel. The solution was washed with saturated aqueous NH\textsubscript{4}Cl (10 mL) and dried over anhydrous sodium sulfate to afford 7.6 g (56%) of the title compound as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 6.13–6.06 (m, 2 H), 2.24–2.17 (m, 2 H), 1.02 (t, \( J = 7.6 \) Hz, 3 H). Spectroscopic properties were identical to those previously reported.
(±)-2-Allyl-N-(4-methoxyphenyl)pyrrolidine-1-carboxamide (2-5). A round bottomed flask equipped with a stirbar was charged with tert-butyl 2-allylpyrrolidine-1-carboxylate (465 mg, 2.2 mmol) and methylene chloride (2.2 mL). The resulting solution was cooled to 0 °C and trifluoroacetic acid (2.2 mL, 28.7 mmol) was added. The solution was gradually warmed to rt and stirred until the starting material had been consumed as judged by TLC analysis (ca. 30 min). The reaction mixture was diluted with water, basified with NH₄OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in methylene chloride (11 mL) and 4-methoxyphenyl isocyanate (285 µL, 2.2 mmol) was added. The reaction mixture was stirred at rt until starting material had been completely consumed as judged by TLC analysis (ca. 1 h). The crude reaction mixture was concentrated in vacuo, and purified by flash chromatography on silica gel to afford 300 mg (53%) of the title compound as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, J = 9.5 Hz, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 6.07 (s, 1 H), 5.82 (ddt, J = 17.0, 10.0, 7.5 Hz, 1 H), 5.13-5.07 (m, 2 H), 4.07-4.04 (m, 1 H), 3.78 (s, 3 H), 3.45-3.42 (m, 2 H), 2.60-2.55 (m, 1 H), 2.22-2.16 (m, 1 H), 2.04-1.93 (m, 3 H), 1.83-1.79 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 154.3, 135.2, 132.2, 121.7, 117.4, 114.1, 57.2, 55.5, 46.3, 38.7, 29.5, 23.8; IR (film) 3306, 1639 cm⁻¹. MS (ESI) 261.1599 (261.1598 calcd for C₁₅H₂₀N₂O₂, M + H⁺).

(±)-(3R*,4aR*)-2-(4-Methoxyphenyl)-3-(4-methylbenzyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (2-6a). A flame-dried Schlenk tube was cooled under a stream of N₂ and charged with Pd₂(dba)₃ (6.4 mg, 0.007 mmol), PCy₃•HBF₄ (10.3 mg, 0.028 mmol) and NaOttBu (50 mg, 0.52 mmol). The flask was purged with N₂, then a solution of 2-5 (83 mg, 0.35 mmol) in toluene (3.5 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. 4-Bromotoluene (89 µL, 0.52 mmol) was added and the flask was heated to 110 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH₄Cl (3 mL) and ethyl acetate (3 mL) were added. The organic layer was filtered through a plug of silica gel and the
silica gel was washed with ethyl acetate (10 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Analysis of the crude material by $^1$H NMR revealed the product had been formed as a 14:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 78 mg (70%) of the title compound as a pale yellow oil with 14:1 dr. Data are for the major isomer. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.19 (d, $J = 9.0$ Hz, 2 H), 7.06 (d, $J = 8.0$ Hz, 2 H), 6.92–6.90 (m, 4 H), 3.96 (dt, $J = 11.5$, 4.5 Hz, 1 H), 3.82 (s, 3 H), 3.82–3.76 (m, 1 H), 3.60 (dt, $J = 11.5$, 7.5 Hz, 1 H), 3.55–3.51 (m, 1 H), 3.02 (dd, $J = 13.8$, 3.8 Hz, 1 H), 2.64 (dd, $J = 13.5$, 11.0 Hz, 1 H), 2.30 (s, 3 H), 2.13 (dt, $J = 12.0$, 5.5 Hz, 1 H), 2.05–1.95 (m, 2 H), 1.88–1.82 (m, 1 H), 1.54 (dt, $J = 12.5$, 2.5 Hz, 1 H) 1.50–1.44 (m, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 157.5, 154.4, 135.9, 135.5, 134.8, 130.1, 129.2, 128.8, 114.2, 60.4, 55.4, 52.5, 46.1, 38.1, 33.8, 29.5, 23.4, 20.9; IR (film) 1640 cm$^{-1}$. MS (ESI) 351.2071 (351.2071 calcd for C$_{22}$H$_{26}$N$_2$O$_2$, M + H$^+$).

(±)-(E,3R*,4aR*)-2-(4-Methoxyphenyl)-3-(undec-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (2-6b). A flame-dried Schlenk tube was cooled under a stream of N$_2$ and charged with Pd$_2$(dba)$_3$ (6.4 mg, 0.007 mmol), PCy$_3$•HBF$_4$ (10.3 mg, 0.028 mmol) and NaOEtBu (67 mg, 0.70 mmol). The flask was purged with N$_2$, then a solution of 2-5 (83 mg, 0.35 mmol) in toluene (3.5 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. A solution of (E)-1-bromodec-1-ene (153 mg, 0.70 mmol) in toluene (1 mL) was added and the flask was heated to 110 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH$_4$Cl (3 mL) and ethyl acetate (3 mL) were added. The organic layer was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (10 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Analysis of the crude material by $^1$H NMR revealed the product had been formed as a 18:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 98 mg (77%) of the title compound as a pale yellow oil with 18:1 dr. Data are for the major isomer. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.13 (d, $J = 9.0$ Hz, 2 H), 6.86 (d, $J = 9.0$ Hz, 2 H), 6.81 (d, $J = 9.0$ Hz, 2 H), 6.60 (d, $J = 9.0$ Hz, 2 H), 6.47 (d, $J = 9.0$ Hz, 2 H), 5.91 (d, $J = 9.0$ Hz, 2 H), 5.84 (d, $J = 9.0$ Hz, 2 H), 5.70 (d, $J = 9.0$ Hz, 2 H), 5.57 (d, $J = 9.0$ Hz, 2 H), 5.44 (d, $J = 9.0$ Hz, 2 H), 5.31 (d, $J = 9.0$ Hz, 2 H), 5.11 (d, $J = 9.0$ Hz, 2 H), 5.00 (d, $J = 9.0$ Hz, 2 H), 4.85 (d, $J = 9.0$ Hz, 2 H), 4.70 (d, $J = 9.0$ Hz, 2 H), 4.60 (d, $J = 9.0$ Hz, 2 H), 4.50 (d, $J = 9.0$ Hz, 2 H), 4.40 (d, $J = 9.0$ Hz, 2 H), 4.30 (d, $J = 9.0$ Hz, 2 H), 4.20 (d, $J = 9.0$ Hz, 2 H), 4.10 (d, $J = 9.0$ Hz, 2 H), 4.00 (d, $J = 9.0$ Hz, 2 H), 3.90 (d, $J = 9.0$ Hz, 2 H), 3.80 (d, $J = 9.0$ Hz, 2 H), 3.70 (d, $J = 9.0$ Hz, 2 H), 3.60 (d, $J = 9.0$ Hz, 2 H), 3.50 (d, $J = 9.0$ Hz, 2 H), 3.40 (d, $J = 9.0$ Hz, 2 H), 3.30 (d, $J = 9.0$ Hz, 2 H), 3.20 (d, $J = 9.0$ Hz, 2 H), 3.10 (d, $J = 9.0$ Hz, 2 H), 3.00 (d, $J = 9.0$ Hz, 2 H), 2.90 (d, $J = 9.0$ Hz, 2 H), 2.80 (d, $J = 9.0$ Hz, 2 H), 2.70 (d, $J = 9.0$ Hz, 2 H), 2.60 (d, $J = 9.0$ Hz, 2 H), 2.50 (d, $J = 9.0$ Hz, 2 H), 2.40 (d, $J = 9.0$ Hz, 2 H), 2.30 (d, $J = 9.0$ Hz, 2 H), 2.20 (d, $J = 9.0$ Hz, 2 H), 2.10 (d, $J = 9.0$ Hz, 2 H), 2.00 (d, $J = 9.0$ Hz, 2 H), 1.90 (d, $J = 9.0$ Hz, 2 H), 1.80 (d, $J = 9.0$ Hz, 2 H), 1.70 (d, $J = 9.0$ Hz, 2 H), 1.60 (d, $J = 9.0$ Hz, 2 H), 1.50 (d, $J = 9.0$ Hz, 2 H), 1.40 (d, $J = 9.0$ Hz, 2 H), 1.30 (d, $J = 9.0$ Hz, 2 H), 1.20 (d, $J = 9.0$ Hz, 2 H), 1.10 (d, $J = 9.0$ Hz, 2 H), 1.00 (d, $J = 9.0$ Hz, 2 H), 0.90 (d, $J = 9.0$ Hz, 2 H), 0.80 (d, $J = 9.0$ Hz, 2 H), 0.70 (d, $J = 9.0$ Hz, 2 H), 0.60 (d, $J = 9.0$ Hz, 2 H), 0.50 (d, $J = 9.0$ Hz, 2 H), 0.40 (d, $J = 9.0$ Hz, 2 H), 0.30 (d, $J = 9.0$ Hz, 2 H), 0.20 (d, $J = 9.0$ Hz, 2 H), 0.10 (d, $J = 9.0$ Hz, 2 H), 0.00 (d, $J = 9.0$ Hz, 2 H).
Hz, 2 H), 5.42 (dt, J = 15.5, 7.5 Hz, 1 H), 5.16 (dt, J = 15.0, 7.0 Hz, 1 H), 3.79 (s, 3 H), 3.76–3.73 (m, 1 H), 3.68–3.62 (m, 1 H), 3.58 (dt, J = 11.5, 7.5 Hz, 1 H), 3.50–3.46 (m, 1 H), 2.39 (dt, J = 13.5, 5.0 Hz, 1 H), 2.24 (ddt, J = 13.0, 2.0, 1.5 Hz, 1 H), 2.00–2.11 (m, 2 H), 2.00–1.91 (m, 3 H), 1.85–1.78 (m, 1 H), 1.62 (dt, J = 12.3, 5.0 Hz, 1 H), 1.49 (ddt, J = 12.0, 10.0, 7.5 Hz, 1 H), 1.30–1.23 (m, 12 H), 0.87 (t, J = 7.0 Hz, 3 H); 13C NMR (125 MHz, CDCl3) δ 157.5, 154.4, 135.7, 134.2, 129.3, 125.4, 58.7, 55.4, 52.5, 46.0, 35.9, 33.9, 32.5, 31.8, 30.3, 29.4, 29.2, 29.1, 23.4, 22.6, 14.1 (one carbon signal is absent due to incidental equivalence); IR (film) 1640 cm⁻¹. MS (ESI) 399.3009 (399.3006 calcd for C25H38N2O2, M + H⁺).

(+)-(S₈)-2-Methyl-N-(pent-4-en-1-ylidene)propane-2-sulfinamide (2-9). This compound was prepared according to a published procedure by Ellman. A flame-dried flask was cooled under a stream of N₂ and charged with pent-4-enal (1.38 mL, 14 mmol) and THF (40 mL). Titanium ethoxide (4.2 mL, 20 mmol) was added and the reaction mixture was stirred at rt for 5 min. (S)-tert-butanesulfinamide (1.21 g, 10 mmol) was added in one portion and the mixture was stirred overnight (ca. 14 h) at rt. The reaction mixture was poured into brine (40 mL) and stirred for 10 min. Ethyl acetate (20 mL) was added, the mixture was filtered through celite and the celite was washed with ethyl acetate (100 mL). The mixture was transferred to a separatory funnel, brine (20 mL) was added, and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 1.62 g (87%) of the title compound as a colorless oil: [α]²³D +244.8 (c 5.5, CH₂Cl₂). 1H NMR (500 MHz, CDCl₃) δ 8.08 (t, J = 4.5 Hz, 1 H), 5.84 (ddt, J = 17.0, 10.0, 4.5 Hz, 1 H), 5.08 (dd, J = 17.0, 1.5 Hz, 1 H), 5.02 (dd, J = 10.0, 1.5 Hz, 1 H), 2.63 (td, J = 7.5, 4.0 Hz, 2 H), 2.40 (q, J = 7.0 Hz, 2 H), 1.19 (s, 9 H); 13C NMR (125 MHz, CDCl₃) δ 168.8, 136.7, 115.8, 56.5, 35.2, 29.3, 22.3; IR (film) 1621 cm⁻¹. MS (ESI) 188.1101 (188.1104 calcd for C₉H₁₇NOS, M + H⁺).
(−)-(S<sub>s</sub>,S<sub>s</sub>)-2-Methyl-N-(7-oxododec-1-en-5-yl)propane-2-sulfinamide (2-10). This compound was prepared via a modification of a published procedure by Davis. A flame-dried flask was cooled under a stream of N₂, charged with diethyl ether (80 mL), and cooled to −78 °C. Solid KHMDS (5.6 g, 28.0 mmol) was added and the reaction mixture was stirred for 5 min at −78 °C. Heptan-2-one (3.43 mL, 24.0 mmol) was slowly added to the reaction flask and the mixture was stirred at −78 °C for 1 h. A solution of 2-9 (1.50 g, 8.0 mmol) in diethyl ether (10 mL) was added to the reaction flask and stirred at −78 °C for 2 h. The reaction was quenched with saturated aqueous NH₄Cl (10 mL) at −78 °C and gradually warmed to rt. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with water (1 x 10 mL) and then the combined aqueous layers were extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 1.95 g (81%) of the title compound as a pale yellow oil: [α]<sup>23</sup> <sub>D</sub> +47.8 (c 3.2, CH₂Cl₂).<sup>1</sup>H NMR (400 MHz, CDCl₃) δ 5.77 (ddt, J = 16.8, 10.0, 6.8 Hz, 1 H), 5.04–4.96 (m, 2 H), 4.07 (d, J = 9.2 Hz, 1 H), 3.53 (oct, J = 4.8 Hz, 1 H), 2.90 (dd, J = 17.6, 5.6 Hz, 1 H), 2.77 (dd, J = 17.6, 4.4 Hz, 1 H), 2.39 (t, J = 7.6 Hz, 2 H), 2.24–2.02 (m, 2 H), 1.78–1.67 (m, 1 H), 1.60–1.50 (m, 3 H), 1.38–1.18 (m, 4 H), 1.22 (s, 9 H), 0.88 (t, J = 7.0 Hz, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl₃) δ 210.8, 137.7, 115.2, 55.8, 53.2, 48.0, 43.8, 34.7, 31.2, 30.4, 23.1, 22.6, 22.4, 13.9; IR (film) 3216, 1708 cm⁻¹. MS (ESI) 302.2155 (302.2148 calcd for C₁₆H₃₁NO₂S, M + H⁺).

(−)-(S<sub>s</sub>,S<sub>s</sub>,S<sub>s</sub>)-N-(7-Hydroxododec-1-en-5-yl)-2-methylpropane-2-sulfinamide (2-11). A flame-dried flask was cooled under a stream of N₂ and charged with 2-10 (322 mg, 1.1 mmol) and THF (11 mL). The reaction flask was cooled to 0 °C, CeCl₃•7H₂O (831 mg, 2.2 mmol) was added, and the mixture was stirred for 5 min. NaBH₄ (600 mg, 15.9 mmol) was added in a single portion and the resulting solution was stirred until the starting material had been consumed as
judged by ESI* MS analysis (ca. 2 h). The reaction mixture was slowly quenched with water (3 mL) and the mixture was transferred to a separatory funnel. 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 sodium sulfate, filtered, and concentrated in vacuo. Analysis of the crude material by 1H NMR revealed the product had been formed as a 3:1 mixture of diastereomers. The crude material was purified by flash chromatography on silica gel to afford 204 mg (63%) of the title compound as a colorless oil with >20:1 dr: [α]23D +55.1 (c 2.1, CH2Cl2). 1H NMR (500 MHz, CDCl3) δ 5.79 (ddt, J = 17.3, 10.3, 6.8 Hz, 1 H), 5.03–4.95 (m, 2 H), 3.79 (m, 1 H), 3.65 (d, J = 8.0 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.36 (d, J = 4.5 Hz, 1 H), 2.21–2.04 (m, 2 H), 1.80 (ddd, J = 14.5, 10.5, 4.0 Hz, 1 H), 1.64–1.21 (m, 11 H), 1.23 (s, 9 H), 0.87 (t, J = 7.0 Hz, 3 H); 13C NMR (125 MHz, CDCl3) δ 138.0, 115.0, 67.8, 55.8, 53.9, 42.6, 37.8, 36.3, 31.9, 30.3, 25.5, 22.7, 22.6, 14.0; IR (film) 3243 cm-1. MS (ESI) 304.2314 (304.2305 calcd for C16H33NO2S, M + H+).

(+)-(S5S,5S,7S)-N-[7-(Benzyloxy)dodec-1-en-5-yl]-2-methylpropane-2-sulfinamide (2-S1). A flame-dried flask was cooled under a stream of N2 and charged with 2-11 (345 mg, 1.1 mmol) and THF (11 mL). The reaction was cooled to 0 ºC and NaH (65 mg, 1.6 mmol, 60% suspension in mineral oil) was added. The reaction flask was stirred for 5 min at 0 ºC and then benzyl bromide (190 µL, 1.6 mmol) was added and the resulting mixture was stirred overnight at rt. The reaction was quenched with water (10 mL) and the mixture was transferred to a separatory funnel. 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 sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 428 mg (96%) of the title compound as a colorless oil. The enantipurity was determined to be 99% ee by chiral HPLC analysis (Regis Tech. (R,R) WHELK-O1, 0.46 cm x 25 cm, 5% iPrOH/hexanes, 1.0 mL/min, l = 254 nm, RT = 8.57 and 11.82 min). [α]23D +63.4 (c 2.1, CH2Cl2).

1H NMR (500 MHz, CDCl3) δ 7.37–7.24 (m, 5 H) 5.79 (ddt, J = 17.5, 11.5, 6.5 Hz, 1 H), 5.04–4.96 (m, 2 H), 4.60 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 11.0 Hz, 1 H), 4.13 (d, J = 6.0 Hz, 1 H),
3.76–3.69 (m, 1 H), 3.54–3.47 (m, 1 H), 2.18–2.03 (m, 2 H), 1.84 (ddd, J = 15.0, 9.5, 3.0 Hz, 1 H), 1.76–1.51 (m, 5 H), 1.35–1.24 (m, 6 H), 1.07 (s, 9 H), 0.89 (t, J = 6.8 Hz, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 138.5, 138.2, 128.3, 128.1, 127.6, 114.9, 76.9, 71.0, 55.4, 53.9, 39.1, 35.4, 33.0, 32.0, 30.0, 24.8, 22.7, 22.6, 14.0; IR (film) 3257 cm\(^{-1}\). MS (ESI) 394.2777 (394.2774 calcd for C\(_{23}\)H\(_{39}\)NO\(_2\)S, M + H\(^+\)).

(+)-(5S,7S)-tert-Butyl 7-(benzyloxy)dodec-1-en-5-ylcarbamate (2-12). A flame-dried flask was cooled under a stream of N\(_2\) and charged with (2-S1) (426 mg, 1.1 mmol) and methanol (5.5 mL). A solution of anhydrous hydrochloric acid (1.1 mL, 4.4 mmol, 4 M in dioxane) was added and the mixture was stirred at rt for 1 h, at which time TLC analysis indicated that the starting material had been completely consumed. The reaction mixture was diluted with water (5 mL) and CH\(_2\)Cl\(_2\) (5 mL), basified with NH\(_4\)OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in THF (11 mL), solid di-tert-butyldicarbonate (264 mg, 1.2 mmol) was added and the reaction mixture was stirred at rt for 3 h. 1 M NaOH (5 mL) was added and the resulting biphasic mixture was stirred overnight at rt. The mixture was transferred to a separatory funnel, 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 sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 401 mg (95%) of the title compound as a colorless oil: \([\alpha]^{23}_D+31.8\) (c 1.5, CH\(_2\)Cl\(_2\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.41–7.32 (m, 4 H), 7.30–7.26 (m, 1 H), 5.81 (ddt, J = 17.0, 10.0, 7.5 Hz, 1 H), 5.01 (dd, J = 17.3, 1.8 Hz, 1 H), 4.95 (d, J = 10.0 Hz, 1 H), 4.79 (d, J = 14.0 Hz, 1 H), 4.55 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 11.0 Hz, 1 H), 3.84–3.76 (m, 1 H), 3.60–3.52 (m, 1 H), 2.18–2.02 (m, 2 H), 1.74–1.47 (m, 6 H), 1.44 (s, 9 H), 1.37–1.24 (m, 6 H), 0.90 (t, J = 7.3 Hz, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 155.5, 138.6, 138.3, 128.3, 128.1, 127.5, 114.6, 78.6, 76.3, 71.3, 47.9, 39.2, 34.8, 33.8, 32.0, 30.4, 28.4, 24.7, 22.6, 14.0; IR (film) 3347, 1702 cm\(^{-1}\). MS (ESI) 390.3004 (390.3003 calcd for C\(_{24}\)H\(_{39}\)NO\(_3\), M + H\(^+\)).
(+)-(E,2S,2’S,5R)-tert-Butyl 2-[2’-(benzyloxy)heptyl]-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate (2-13). A flame-dried Schlenk flask was cooled under a stream of N₂ and charged with Pd₂(dba)₃ (18.3 mg, 0.02 mmol), tri-(2-furyl)phosphine (18.6 mg, 0.08 mmol) and NaOtBu (200 mg, 2.08 mmol). The flask was purged with N₂, then a solution of 2-12 (406 mg, 1.04 mmol) in distilled xylenes (5.2 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. (E)-(2-bromovinyl)trimethylsilane (319 µL, 2.08 mmol) was added and the flask was heated to 140 ºC and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH₄Cl (5 mL) and ethyl acetate (5 mL) were added. The mixture was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (20 mL). The mixture was transferred to a separatory funnel, water was added (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 sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 347 mg (68%) of the title compound as a pale brown oil. This compound was found to exist as a mixture of rotamers as judged by 1H and 13C NMR analysis; data are for the mixture. [α]²⁰D +14.5 (c 0.7, CH₂Cl₂). 1H NMR (500 MHz, CDCl₃) δ 7.38–7.26 (m, 5 H), 6.00–5.91 (m, 1 H), 5.69 (d, J = 18.5 Hz, 1 H), 4.57–4.42 (m, 2 H), 3.99–3.60 (m, 2 H), 3.58–3.24 (m, 1 H), 2.59–2.52 (m, 1 H), 2.37–2.18 (m, 1 H), 2.02–1.81 (m, 3 H), 1.78–1.63 (m, 2 H), 1.59–1.23 (m, 9 H), 1.46 (s, 9 H), 0.90 (t, J = 7.3 Hz, 3 H), 0.04 (s, 9 H); 13C NMR (125 MHz, CDCl₃) δ 154.5, 143.1, 138.9, 133.1, 128.3, 127.8, 127.5, 127.4, 79.0, 78.1, 70.7, 57.5, 57.1, 41.7, 40.8, 34.0, 32.0, 30.2, 28.6, 28.4, 24.8, 22.6, 14.1, 0.0, −1.0, −1.2, −1.4; IR (film) 1693 cm⁻¹. MS (ESI) 488.3553 (488.3554 calcd for C₂₉H₃₉NO₃Si, M + H⁺).
(+)-(2R,2'S,5S)-2- Allyl-5-[2'-(benzyloxy)heptyl]-N-(4-methoxybenzyl)pyrrolidine-1-carboxamide (2-14). A round bottomed flask equipped with a stirbar was charged with 2-13 (397 mg, 0.81 mmol) and methylene chloride (1.6 mL). The resulting solution was cooled to 0 °C and trifluoroacetic acid (1.6 mL, 20.9 mmol) was added. The solution was gradually warmed to rt and stirred until the starting material had been consumed as judged by TLC analysis (ca. 15 min). The reaction mixture was diluted with water, basified with NH₄OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in methylene chloride (8 mL) and 4-methoxybenzyl isocyanate (159 µL, 0.97 mmol) was added. The reaction mixture was stirred at rt until starting material had been completely consumed as judged by TLC analysis (ca. 1 h). The crude reaction mixture was concentrated in vacuo, and purified by flash chromatography on silica gel to afford 282 mg (72%) of the title compound as a colorless oil: [α]²³_D +52.7 (c 4.3, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃) δ 7.31–7.24 (m, 3 H), 7.22–7.18 (m, 2 H), 6.97 (d, J = 9.0 Hz, 2 H), 6.73 (d, J = 9.0 Hz, 2 H), 5.96–5.88 (m, 1 H), 5.78 (ddt, J = 17.8, 10.3, 7.5 Hz, 1 H), 5.07 (dd, J = 17.5, 2.0 Hz, 1 H), 5.03 (dd, J = 11.5, 2.0 Hz, 1 H), 4.49 (d, J = 11.5 Hz, 1 H), 4.20 (d, J = 11.5 Hz, 1 H), 4.13 (dd, J = 14.5, 5.5 Hz, 1 H), 4.10–4.05 (m, 1 H), 4.02 (dd, J = 14.5, 5.5 Hz, 1 H), 3.94–3.88 (m, 1 H), 3.76 (s, 3 H), 3.68–3.62 (m, 1 H), 2.64–2.57 (m, 1 H), 2.27–2.20 (m, 1 H), 2.05–1.89 (m, 2 H), 1.76–1.55 (m, 5 H), 1.56–1.42 (m, 1 H), 1.34–1.22 (m, 6 H), 0.89 (t, J = 7.0 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 158.3, 158.3, 138.2, 135.3, 132.5, 128.7, 128.3, 127.4, 126.8, 116.8, 113.5, 75.8, 67.4, 57.9, 55.1, 54.9, 43.6, 40.5, 40.3, 32.2, 31.8, 31.8, 28.7, 24.6, 22.5, 13.9; IR (film) 3361, 1642 cm⁻¹. MS (ESI) 479.3271 (479.3268 calcd for C₃₈H₄₂N₂O₃, M + H⁺).

(+)-(Z,2'S,3R,4aR,7S)-7-[2'-(Benzylloxy)heptyl]-2-(4-methoxybenzyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (2-15). A flame-dried Schlenk tube was cooled under a stream of N₂ and charged with Pd₂(dba)₃ (8.0 mg, 0.009 mmol), PCy₃•HBF₄ (12.9
mg, 0.04 mmol) and NaO'Bu (56 mg, 0.58 mmol). The flask was purged with N₂, then a solution of 2-14 (138 mg, 0.29 mmol) in toluene (1.5 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. A solution of (Z)-1-bromobut-1-ene (78.3 mg, 0.58 mmol) in toluene (1 mL) was added and the flask was heated to 110 °C and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH₄Cl (2 mL) and ethyl acetate (2 mL) were added. The mixture was filtered through a plug of silica gel and the silica gel was washed with ethyl acetate (10 mL). The mixture was transferred to a separatory funnel, water was added (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 sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 139 mg (91%) of the title compound as a pale yellow oil: [α]$_D$ +35.3 (c 2.7, CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.37–7.29 (m, 3 H), 7.28–7.23 (m, 2 H), 7.17 (d, $J$ = 8.4 Hz, 2 H), 6.83 (d, $J$ = 8.4 Hz, 2 H), 5.51–5.42 (m, 1 H), 5.22–5.12 (m, 2 H), 4.55 (d, $J$ = 11.4 Hz, 1 H), 4.49 (d, $J$ = 11.4 Hz, 1 H), 4.02 (d, $J$ = 15.2 Hz, 1 H), 4.01–3.94 (m, 1 H), 3.77 (s, 3 H), 3.60–3.48 (m, 2 H), 3.24–3.16 (m, 1 H), 2.46–2.38 (m, 1 H), 2.26 (dd, $J$ = 13.2, 3.6 Hz, 1 H), 2.19–2.10 (m, 1 H), 2.05–1.81 (m, 6 H), 1.65–1.20 (m, 11 H), 0.94 (t, $J$ = 7.4 Hz, 3 H) 0.89 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 158.5, 154.6, 139.0, 134.4, 131.3, 128.7, 128.2, 127.7, 127.3, 124.4, 113.7, 78.9, 70.9, 56.8, 55.1, 53.6, 52.2, 47.3, 39.0, 34.1, 32.0, 31.3, 31.0, 30.9, 29.7, 24.7, 22.6, 20.8, 14.0, 14.0; IR (film) 1631 cm$^{-1}$. MS (ESI) 533.3737 (533.3738 calcd for C$_{34}$H$_{48}$N$_2$O$_3$, M + H$^+$).

![Chemical Structure](image-url)
of ammonia (6.4 mL, 2 M in ethanol) was added. The mixture was stirred at rt until the starting material had been consumed as judged by ESI+ MS analysis (ca. 15 min). The reaction mixture was concentrated and dissolved in methylene chloride (5 mL). Water (5 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer was washed with saturated aqueous NaBF₄ (3 x 10 mL). The combined aqueous layers were extracted with methylene chloride (3 x 10 mL). The combined organics layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 88 mg (89%) of the title compound as a pale brown oil: [α]²³ D +59.9 (c 3.6, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.21 (m, 5 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 5.99 (s, 2 H), 5.62–5.51 (m, 1 H), 5.20–5.12 (m, 1 H), 4.63 (d, J = 17.0 Hz, 1 H), 4.58 (d, J = 17.5 Hz, 1 H), 4.57 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 11.0 Hz, 1 H), 4.09–4.06 (m, 1 H), 3.80 (s, 3 H), 3.68–3.62 (m, 1 H), 3.61–3.52 (m, 2 H), 2.56–2.44 (m, 1 H), 2.36–2.20 (m, 2 H), 2.19–2.08 (m, 2 H), 2.02–1.93 (m, 4 H), 1.78–1.56 (m, 4 H), 1.43–1.20 (m, 7 H), 0.95 (t, J = 7.5 Hz, 3 H) 0.87 (t, J = 7.0 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 159.5, 151.5, 137.7, 136.2, 128.4, 128.2, 127.8, 127.4, 125.8, 122.3, 114.7, 77.2, 71.4, 57.6, 55.9, 55.3, 55.3, 52.6, 51.2, 38.3, 32.5, 32.0, 31.8, 31.2, 29.8, 29.5, 24.9, 22.5, 20.9, 13.9; IR (film) 3366, 3252, 1592 cm⁻¹. MS (ESI) 532.3908 (532.3898 calcd for C₃₄H₄₉N₅O₂, M + H⁺).

**(+)-Merobatzelladine B.** A glass vial equipped with a magnetic stirbar was charged with 2-16 (43 mg, 0.07 mmol), Pd/C (43 mg), and methanol (3 mL). The glass vial was placed in a stainless steel bomb equipped with a regulator. The vessel was pressurized to 45 psig with H₂ and stirred overnight (ca. 14 h) at rt under a hydrogen atmosphere (45 psig). Complete consumption of starting material was confirmed with ESI+ analysis. The mixture was filtered through a plug of celite and washed with methanol (20 mL). The crude product was transferred to a round-bottomed flask and concentrated in vacuo. The Mitsunobu reaction was carried out based on a published procedure by Nagasawa. The crude product was dissolved in toluene (3.5 mL) and PPh₃ (22 mg, 0.08 mmol) was added. The reaction flask was cooled to 0 °C and DIAD
(16.3 µL, 0.083 mmol) was added. The reaction mixture was stirred at 0 °C until the starting material had been consumed as judged by ESI+ MS analysis (ca. 1 h). The reaction was quenched with a drop of water and concentrated in vacuo. The material was purified by flash chromatography on silica (EtOAc, 2:98 MeOH:CH₂Cl₂, 10:90 MeOH:CH₂Cl₂) to provide N-p-methoxybenzyl merobatzealladine B in ca. 70% purity (the remaining impurities were not identified). The PMB deprotection was carried out using the procedure of Gin, with slight modifications. This material was dissolved in methylene chloride (2 mL) and trifluoroacetic acid (6 mL, 78 mmol) was added. The reaction mixture was refluxed overnight (ca. 15 h). The crude material was concentrated in vacuo and then purified by flash chromatography on silica gel to afford 11.9 mg (41%) of the title compound as a pale brown oil. Spectroscopic properties are identical to those reported for the natural product. [α]$_{23}^\text{D}$ +40.1 (c 0.7, MeOH) [lit. Error! Bookmark not defined. [α]$_{25}^\text{D}$ +27 (c 0.15, MeOH)].

**Assignment of Stereochemistry of 2-6a and 2-6b**

The relative stereochemistry of compound 2-6a was assigned on the basis of observed $^1$H NMR nOe experiments. Significant nOe relationships are shown below.

The relative stereochemistry of compound 2-6b was assigned on the basis of observed $^1$H NMR nOe experiments. Significant nOe relationships are shown below.
Chapter 3
Desymmetrization of \textit{meso}-2,5-Diallylpyrrolidinyl Ureas via Asymmetric Pd-Catalyzed Carboamination: Stereocontrolled Synthesis of Bicyclic Ureas

3.1 Introduction

Catalytic asymmetric desymmetrization reactions are powerful and efficient tools for the synthesis of chiral molecules.\textsuperscript{65–67} These transformations convert simple achiral substrates into complex enantioenriched products through the differentiation of two enantiotopic groups, and can generate complex structures bearing multiple stereocenters in a highly controlled fashion. As such, the development of asymmetric desymmetrization reactions that allow for the construction of important structural motifs is of considerable utility.

As mentioned in chapters 1 and 2, tricyclic guanidines are an interesting class of compounds that could potentially be accessed via catalytic asymmetric desymmetrization reactions (Figure 3.1). These scaffolds are displayed in a wide variety of biologically active natural products,\textsuperscript{2–6} including the batzelladine alkaloids\textsuperscript{7,68–70} (e.g., batzelladine K), the merobatzelladine alkaloids (e.g., merobatzelladine B),\textsuperscript{12,14} and the crambescidin alkaloids (e.g., crambescidin 359).\textsuperscript{9,71,72} Many synthetic routes to these compounds involve the generation of a fused-bicyclic urea or guanidine derivative (e.g., 3-1), which is then transformed to the tricyclic guanidine in subsequent steps.\textsuperscript{20,31,35,38,60} As such, development of a concise asymmetric synthesis of 3-1 could provide access to a broad array of interesting alkaloids.

\textbf{Figure 3.1} Bioactive guanidine alkaloids prepared from bicyclic urea and guanidine precursors.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{guanidine_alkaloids.png}
\caption{Bioactive guanidine alkaloids prepared from bicyclic urea and guanidine precursors.}
\end{figure}
Chapter 2 described our asymmetric synthesis of the tricyclic guanidine natural product (+)-merobatzelladine B, which featured a new strategy for the construction of bicyclic ureas and polycyclic guanidines via Pd-catalyzed carboamination reactions of enantiomerically enriched 2-allylpyrrolidine-1-carboxamide derivatives 3-2 (Scheme 3.1). These reactions provided bicyclic urea products 3-3 in good yield with excellent diastereoselectivity, but control of absolute stereochemistry required the chiral-auxiliary mediated introduction of the C2 stereocenter during the fairly lengthy asymmetric synthesis of 3-2 (7–9 steps).

Scheme 3.1 Synthesis of bicyclic ureas through Pd-catalyzed asymmetric desymmetrization.

A potentially more attractive route to enantiomerically enriched bicyclic ureas and related bi- and tricyclic guanidines would involve the asymmetric Pd-catalyzed desymmetrization of meso-2,5-diallylpyrrolidinyl urea 3-4. This approach would allow for facile introduction of different R-substituents, and the alkene present in product 3-5 provides a convenient handle for further elaboration to tricyclic guanidine products or more highly substituted urea derivatives. In addition, the meso-substrate 3-4 can be prepared in only four steps. Our preliminary studies in this area are described in this chapter. These transformations represent the first examples of asymmetric desymmetrizations of bis-alkene substrates in intermolecular Pd-catalyzed alkene carboamination reactions, and also the first examples of six-membered ring formation in an asymmetric Pd-catalyzed alkene carboamination.  73–78

3.2 Optimization and Scope of Desymmetrization Transformations

meso-Pyrrolidinyl urea substrates 3-4 were readily prepared in just four steps following the synthetic route detailed in Scheme 3.2. The three-component coupling of 4-pentenal, tert-butyl carbamate and allyl trimethylsilane afforded racemic N-Boc-γ-aminoalkene 3-6 in a single step. cis-2,5-disubstituted pyrrolidine 3-7 was generated as a single diastereomer from a Pd-catalyzed carboamination cross-coupling reaction between substrate 3-6 and 2-bromovinyl trimethylsilane. The high stereoselectivity observed for this transformation is based on transition state 1-32 as depicted in Scheme 1.14. Pyrrolidine 3-7 was converted to various meso-substrates 3-4 upon treatment with TFA and an N-aryl isocyanate. This relatively short synthetic sequence permitted
the preparation of these compounds on a multi-gram scale, and makes this route an attractive approach for future total synthesis endeavors.

**Scheme 3.2 Synthesis of meso-pyrrolidinyl urea substrates.**

In initial experiments we elected to employ a catalyst composed of Pd\(_2\)(dba)\(_3\)/(S)-Siphos-PE for desymmetrization reactions of 3-4, as we previously illustrated this complex provides good results in related asymmetric carboamination reactions of simple N-allyl urea derivatives.\(^{79-85}\) We decided to first optimize the structure of the urea N-aryl group, as prior studies in our lab suggested this group may have a significant influence on the level of asymmetric induction.\(^{79}\) Thus, we explored the coupling of Z-1-bromobutene with ureas 3-4 bearing different N-aryl substituents. As shown in Table 3.1, the use of electron-poor p-cyanophenyl or p-nitrophenyl N-aryl groups resulted in the formation of products 3-5 with the highest levels of both diastereoselectivity and enantioselectivity. However, these electron-poor substrates were transformed in modest chemical yield due to competing cleavage of the urea moiety (entries 5–6). Use of the electron-rich p-methoxyphenyl group led to improved yields but with lower levels of stereocontrol. After some exploration we found that a substrate bearing a p-chlorophenyl group was transformed to the desired product with both good chemical yield and stereoselectivity (entry 3). The reaction of the analogous p-bromophenyl derivative proceeded in low yield because of competing oligomerization of the substrate (entry 4).

**Table 3.1 N-aryl group effects.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product</th>
<th>Yield(%)(^{[b]})</th>
<th>dr(^{[c]})</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeOC(_6)H(_4)</td>
<td>3-5a</td>
<td>65</td>
<td>7:1</td>
<td>86:14</td>
</tr>
<tr>
<td>2</td>
<td>3,4-MeOC(_6)H(_4)</td>
<td>3-5b</td>
<td>41</td>
<td>7:1</td>
<td>82:18</td>
</tr>
</tbody>
</table>
As shown in Table 3.2, the asymmetric desymmetrization reactions of 3-4c are effective with a number of different alkenyl and aryl bromide electrophiles. The main side products generated in these reactions were cis-2,5-diallylpyrrolidine (resulting from competing urea cleavage) and an unsaturated bicyclic urea that is generated by competing β-hydride elimination of an intermediate alkylpalladium complex. In the reaction of 3-4c with E-1-bromohexene a regioisomeric side product bearing a 2-hex-1-enyl group was also generated.\textsuperscript{86}

**Table 3.2 Desymmetrization Reaction Scope.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield(%)</th>
<th>dr[(\text{er})]</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Z-butene</td>
<td>3-5c</td>
<td>76</td>
<td>&gt;20:1[(\text{d})]</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>E-hexene</td>
<td>3-5g</td>
<td>50[(\text{f})]</td>
<td>&gt;20:1[(\text{d})]</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>Z-hexene</td>
<td>3-5h</td>
<td>61</td>
<td>&gt;20:1[(\text{d})]</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td>2-methyl propene</td>
<td>3-5i</td>
<td>48</td>
<td>10:1</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>2-propene</td>
<td>3-5j</td>
<td>55</td>
<td>20:1[(\text{d})]</td>
<td>88:12</td>
</tr>
<tr>
<td>6</td>
<td>4-MeC(_6)H(_4)</td>
<td>3-5k</td>
<td>84</td>
<td>8:1</td>
<td>92:8</td>
</tr>
<tr>
<td>7</td>
<td>4-MeOC(_6)H(_4)</td>
<td>3-5l</td>
<td>70</td>
<td>7:1</td>
<td>92:8</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>3-5m</td>
<td>83</td>
<td>6:1</td>
<td>90:10</td>
</tr>
<tr>
<td>9</td>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>3-5n</td>
<td>74</td>
<td>5:1</td>
<td>85:15</td>
</tr>
<tr>
<td>10</td>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>3-5n</td>
<td>55[(\text{d})]</td>
<td>11:1[e]</td>
<td>90:10</td>
</tr>
<tr>
<td>11</td>
<td>4-F(_3)COC(_6)H(_4)</td>
<td>3-5o</td>
<td>68</td>
<td>7:1</td>
<td>87:13</td>
</tr>
<tr>
<td>12</td>
<td>4-F(_3)COC(_6)H(_4)</td>
<td>3-5o</td>
<td>51[(\text{d})]</td>
<td>18:1[(\text{d})]</td>
<td>92:8</td>
</tr>
<tr>
<td>13</td>
<td>3-MeOC(_6)H(_4)</td>
<td>3-5p</td>
<td>72</td>
<td>5:1</td>
<td>87:13</td>
</tr>
</tbody>
</table>

[a] Conditions: 1.0 equiv substrate, 1.5 equiv (Z)-1-bromobutene, 1.5 equiv NaO\(_\text{Bu}\), 2 mol % Pd\(_2\)(dba), 8 mol % (S)-Siphos-PE, Toluene (0.2 M), 100 °C, 2h. [b] Isolated yield (average of two or more runs). [c] Diastereomeric ratio of the pure isolated material. Diastereomeric ratios of the isolated materials were identical to those of the crude products except for entry 3. [d] The diastereomeric ratio of the crude material was 12:1. The product was isolated in 76% yield with 20:1 dr. [e] This material contained a small amount of the corresponding aniline derivative. [f] The reaction was conducted at 120 °C for 16 h. The isolated material contained ca. 8% of unreacted substrate.
<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>2-naphthyl</td>
<td>3-5q</td>
<td>75</td>
<td>7:1</td>
<td>88:12</td>
</tr>
<tr>
<td>15</td>
<td>2-MeC₆H₄</td>
<td>3-5r</td>
<td>81</td>
<td>5:1</td>
<td>71:29</td>
</tr>
</tbody>
</table>

[a] Conditions: 1.0 equiv substrate, 1.5 equiv R–Br, 1.5 equiv NaOTBu, 2 mol % Pd₂dba₃, 8 mol % (S)-Siphos-PE, Toluene (0.2 M), 100 °C, 2h. [b] Isolated yield (average of two or more runs). [c] Diastereomeric ratio of the pure isolated material. Diastereomeric ratios of the isolated materials were identical to those of the crude products unless otherwise noted. [d] The diastereomeric ratio of the crude material was 10–12:1. [e] The diastereomeric ratio of the crude material was 6:1 [f] This material contained 15% of the analogous 2-hex-1-enyl regioisomer. [g] The reaction was conducted using NaOMe as base instead of NaOBu.

The best enantioselectivities were obtained when either alkenyl bromides, electron-rich aryl bromides, or electron-neutral aryl bromides were employed as substrates. Diastereoselectivities were generally higher with the alkenyl electrophiles than with aryl electrophiles. Use of sterically hindered aryl bromides (entries 14–15) or electron-poor aryl bromides (entries 9, 11, and 13) led to lower diastereo- and enantioselectivities. Selectivities improved when NaOMe was used in place of NaOEtBu in reactions of electron-poor aryl bromides (entries 10 and 12), although yields decreased in these cases.

### 3.3 Deprotection and Synthesis of Tricyclic Guanidine Derivative

To further demonstrate the utility of the asymmetric desymmetrization reactions, we examined the deprotection of 3-5c and the conversion of 3-5c to tricyclic guanidine derivatives. As shown in Scheme 3.3, cleavage of the N-p-chlorophenyl group can be accomplished via Pdcatalyzed amination with acetamide, followed by oxidation of the resulting N-aryl amide (3-8) with ceric ammonium nitrate. This sequence afforded 3-9 in 65% yield over two steps.

**Scheme 3.3** Deprotection of desymmetrization product.

The conversion of 3-5c to tricyclic guanidine 3-10 was carried out as shown in Scheme 3.4. Treatment of 3-5c with POCl₃ followed by NH₃ provided bicyclic guanidine 3-11 in 78% yield. Wacker oxidation of 3-11 afforded hemiaminal 3-12, which was then transformed to tricyclic product 3-10 in 70% yield with 5:1 dr via reductive amination with NaBH₄CN. Preliminary
efforts to cleave the N-aryl group from 3-10 were unsuccessful. Overall, the synthesis of 3-10, which is structurally related to the batzelladine and merobatzelladine alkaloids, was accomplished in 5 steps and 41% yield from meso-2,5-diallylpyrrolidinyl urea 3-4c. In addition, this is the first example of a Wacker oxidation/ring-closure sequence to generate a tricyclic guanidine.

**Scheme 3.4** Synthesis of tricyclic guanidine derivative.

3.4 Synthesis of 9-epi-Batzelladine K

Finally, 3-5c was converted to tricyclic guanidine 3-13, which is an unnatural stereoisomer of batzelladine K, as shown in Scheme 3.5. To avoid problems with base-mediated epimerization of the C4 stereocenter, the Pd-catalyzed amination with acetamide was carried out prior to Wacker oxidation of the alkene. This two-step sequence provided 3-14 in 65% yield. Reduction of the alkene followed by CAN deprotection generated urea 3-15, which was converted to guanidine aminal 3-16 by O-methylation and treatment with ammonia. The reduction of 3-16 proceeded with modest diastereoselectivity (3:1 dr), but upon purification 9-epi-batzelladine K was isolated as a single stereoisomer in 48% yield over three steps from 3-15.

**Scheme 3.5** Synthesis of 9-epi-batzelladine K.
3.5 Conclusions

In conclusion we have developed a concise route to enantiomerically enriched bicyclic ureas via Pd-catalyzed desymmetrizing carboamination reactions of meso-diallylpyrrolidinyl ureas. These transformations effect formation of both a C–N and a C–C bond, and provide products bearing three stereocenters with good levels of diastereoselectivity and enantioselectivity. These reactions illustrate the potential utility of asymmetric Pd-catalyzed alkene carboamination for desymmetrization processes and provide synthetically valuable products in a straightforward manner.

The work described in this chapter was published in Angewandte Chemie International Edition.88

3.6 Experimental

General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware unless otherwise noted. Tris(dibenzylidene)acetone dipalladium, tri(2-furyl)phosphine, and (S)-Siphos-PE were purchased from Strem Chemical Co. and used without purification. Tricyclohexylphosphonium tetrafluoroborate was purchased from Acros Chemical Co. and used without further purification. 2-Di-tert-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl was purchased from Sigma-Aldrich and used without further purification. All other reagents were obtained from commercial sources and were used as obtained unless otherwise noted. NaOtBu and CuCl were stored in the glove box and removed prior to use. BF3•OEt2 and POCl3 were purified by distillation under N2 prior to use. (Z)-1-bromobutene63 was prepared according to a slight modification of a literature procedure; the preparation was conducted at rt instead of using microwave heating as described in chapter 2. (Z)-1-bromohexene,62 and (E)-1-bromohexene62 were prepared according to published procedures. Toluene, THF, diethyl ether and dichloromethane were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by 1H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in Chapter 3 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Chapter 3. Structural and stereochemical assignments were made on the basis of 2-D
COSY, and NOESY experiments. Ratios of diastereomers were determined by $^1$H NMR analysis. The reported optical rotation values refer to measurements taken of the isolated mixtures of diastereomers upon which chemical yields were based. Ratios of enantiomers were determined by HPLC analysis. Although diastereomers were not easily separable by chromatography, for most examples (with the exception of 3-5i and 3-5j) it was possible to separate small amounts of the pure (>20:1 dr) major diastereomer for chiral HPLC analysis.

Preparation and Characterization of meso-N-Aryl-2,5-Diallylpyrrolidine-1-Carboxamide Substrates

(±)-tert-Butyl octa-1,7-dien-4-ylcarbamate (3-6). The title compound was prepared by modifying a procedure published by Veenstra.$^{89}$ A flame-dried flask was cooled under a stream of N$_2$, charged with dichloromethane (60 mL) and cooled to 0 °C. Pent-4-enal (2.96 mL, 30 mmol), allyltrimethylsilane (4.77 mL, 30 mmol) and tert-butyl carbamate (3.5 g, 30 mmol) were added to the flask and the resulting solution was stirred for 15 min at 0 °C. Distilled BF$_3$•OEt$_2$ (2.3 mL, 18 mmol) was added and the reaction mixture was stirred for 30 min at 0 °C. The mixture was gradually warmed to rt and stirred for 30 min. The reaction was then quenched with saturated aqueous NaHCO$_3$ (20 mL) and stirred for 5 min at rt. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous NaHCO$_3$ (20 mL) and then the combined aqueous layers were extracted with dichloromethane (15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 3.8 g (56%) of the title compound as a clear colorless oil. This compound was found to exist as a mixture of rotamers as judged by $^1$H and $^{13}$C NMR analysis; data are for the mixture. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.84–5.73 (m, 2 H), 5.10–4.95 (m, 4 H), 4.33 (d, br, $J = 7.5$ Hz, 1 H), 3.66 (d, br, $J = 4.5$ Hz, 1 H), 2.26–2.07 (m, 4 H), 1.60–1.55 (m, 1 H), 1.48–1.40 (m, 1 H), 1.43 (s, 9 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 155.5, 138.0, 134.4, 117.7, 114.9, 79.0, 49.6, 39.5, 33.9, 30.2, 28.4; IR (film) 3337,1684 cm$^{-1}$. MS (ESI) 248.1621 (248.1621 calcd for C$_{13}$H$_{23}$NO$_2$, M + Na$^+$).
(±)-(E,2R*,5S*)-tert-Butyl 2-allyl-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate (3-7).

A flame-dried Schlenk flask was cooled under a stream of N₂ and charged with Pd₂(dba)₃ (81 mg, 0.089 mmol), tri(2-furyl)phosphine (82 mg, 0.36 mmol) and NaOttBu (853 mg, 8.9 mmol). The flask was purged with N₂, then a solution of 3-6 (1.0 g, 4.4 mmol) in freshly distilled xylenes (22.2 mL) was added via syringe and the resulting mixture was stirred at rt for 5 min. (E)-(2-bromovinyl)trimethylsilane (1.36 mL, 8.9 mmol) was added and the flask was heated to 137 ºC and stirred overnight (ca. 14 h). The mixture was cooled to room temperature and saturated aqueous NH₄Cl (10 mL) and ethyl acetate (10 mL) were added. The layers were separated, the organic layer was filtered through a plug of silica gel, and the silica gel was washed with ethyl acetate (20 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 1.11 g (77%) of the title compound as a dark red-brown oil. This compound was found to exist as a mixture of rotamers as judged by ¹H and ¹³C NMR analysis; data are for the mixture. ¹H NMR (500 MHz, CDCl₃) δ 5.98–5.92 (m, 1 H), 5.78–5.70 (m, 1 H), 5.68 (d, J = 18.5 Hz, 1 H), 5.06–5.01 (m, 2 H), 3.92–3.68 (m, 2 H), 2.64–2.41 (m, 2 H), 2.34 (dt, J = 8.0, 13.0 Hz, 1 H), 2.09 (dt, J = 8.0, 13.0 Hz, 1 H), 1.87–1.82 (m, 2 H), 1.68–1.64 (m, 2 H), 1.46 (s, 9 H), 0.03 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 154.7, 143.2, 135.4, 132.9, 116.8, 79.0, 58.0, 57.9, 42.1, 42.0, 40.0, 39.8, 28.5, –1.2; IR (film) 1692 cm⁻¹. MS (ESI) 346.2174 (346.2173 calcd for C₁₈H₃₃NO₂Si, M + Na⁺).

General Procedure for Synthesis of meso-N-Aryl-2,5-Diallylpyrrolidine-1-Carboxamide Substrates 3-4. A round-bottom flask equipped with a stirbar was charged with 3-7 (1.0 equiv) and dichloromethane (0.2 M). Trifluoroacetic acid (1.0 M) was added to the flask and the mixture was heated to reflux and stirred overnight. The solution was cooled to rt, diluted with water, basified with NH₄OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude
product was dissolved in dichloromethane (0.2 M) and the appropriate isocyanate (1.1 equiv) was added. The reaction mixture was stirred at rt until starting material had been completely consumed as judged by TLC analysis (ca. 1 h). The crude reaction mixture was concentrated in vacuo, and purified by flash chromatography on silica gel.

(2S,5R)-2,5-Diallyl-N-(4-methoxyphenyl)pyrrolidine-1-carboxamide (3-4a). The title compound was prepared from 3-7 (2.13 g, 6.6 mmol) and 4-methoxyphenyl isocyanate (940 µL, 7.3 mmol) in two steps via the general procedure described above. This procedure afforded 1.2 g (61%) of the title compound as a white solid: mp = 63–65 °C. 1H NMR (700 MHz, CDCl₃) δ 7.25 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 9.1 Hz, 2 H), 6.33 (s, 1H), 5.91–5.85 (m, 2 H), 5.20–5.15 (m, 4 H), 3.99–3.96 (m, 2 H), 3.77 (s, 3 H), 2.55 (dt, J = 14.0, 7.0 Hz, 2 H), 2.24 (dt, J = 7.0, 14.0 Hz, 2 H), 2.02–1.97 (m, 2 H), 1.78–1.74 (m, 2 H); 13C NMR (175 MHz, CDCl₃) δ 155.5, 155.2, 135.2, 132.3, 121.4, 118.0, 114.1, 58.8, 55.5, 40.2, 29.5; IR (film) 3311, 1635 cm⁻¹. MS (ESI) 301.1917 (301.1911 calcd for C₁₈H₂₄N₂O₂, M + H⁺).

(2S,5R)-2,5-Diallyl-N-(3,4-dimethoxyphenyl)pyrrolidine-1-carboxamide (3-4b). The title compound was prepared from 3-7 (965 mg, 2.98 mmol) and 3,4-dimethoxyphenyl isocyanate (488 µL, 3.3 mmol) in two steps via the general procedure described above. This procedure afforded 542 mg (55%) of the title compound as a tan solid: mp = 112–114 °C. 1H NMR (500 MHz, CDCl₃) δ 7.27 (d, J = 2.1 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 1 H), 6.62 (dd, J = 2.8, 8.4 Hz, 1
H), 6.36 (s, 1H), 5.91–5.86 (m, 2 H), 5.21–5.16 (m, 4 H), 4.01–3.97 (m, 2 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 2.57 (dt, J = 6.3, 13.3 Hz, 2 H), 2.25 (dt, J = 7.7, 13.3 Hz, 2 H), 2.03–1.99 (m, 2 H), 1.79–1.75 (m, 2 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 155.1, 149.1, 144.8, 135.2, 133.0, 118.1, 111.4, 110.9, 104.7, 58.7, 56.2, 55.9, 40.2, 29.5; IR (film) 3327, 1635 cm\(^{-1}\). MS (ESI) 331.2018 (331.2016 calcd for C\(_{19}\)H\(_{26}\)N\(_2\)O\(_3\), M + H\(^{+}\)).

\((2S,5R)-2,5\text{-Diallyl-N-(4-chlorophenyl)pyrrolidine-1-carboxamide (3-4c)}\). The title compound was prepared from 3-7 (1.05 g, 3.2 mmol) and 4-chlorophenyl isocyanate (541 mg, 3.5 mmol) in two steps via the general procedure described above. This procedure afforded 574 mg (58%) of the title compound as a white solid: mp = 91–93 \(^{\circ}\)C. \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.30 (d, J = 9.0 Hz, 2 H), 7.21 (d, J = 9.0 Hz, 2 H), 6.51 (s, 1H), 5.91–5.85 (m, 2 H), 5.22–5.16 (m, 4 H), 4.00–3.95 (m, 2 H), 2.55 (dt, J = 14.0, 6.5 Hz, 2 H), 2.25 (dt, J = 14.0, 7.5 Hz, 2 H), 2.03–1.97 (m, 2 H), 1.79–1.74 (m, 2 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 154.5, 137.9, 135.1, 128.7, 127.4, 120.3, 118.3, 58.9, 40.1, 29.6; IR (film) 3318, 1640 cm\(^{-1}\). MS (ESI) 327.1242 (327.1235 calcd for C\(_{17}\)H\(_{21}\)ClN\(_2\)O, M + Na\(^{+}\)).

\((2S,5R)-2,5\text{-Diallyl-N-(4-bromophenyl)pyrrolidine-1-carboxamide (3-4d)}\). The title compound was prepared from 3-7 (1.2 g, 3.7 mmol) and 4-bromophenyl isocyanate (806 mg, 4.1 mmol) in two steps via the general procedure described above. This procedure afforded 827 mg (64%) of the title compound as an off-white solid: mp = 101–104 \(^{\circ}\)C. \(^{1}\)H NMR (700 MHz, CDCl\(_3\))
δ 7.37 (d, J = 7.7 Hz, 2 H), 7.25 (d, J = 7.7 Hz, 2 H), 6.49 (s, 1H), 5.91–5.85 (m, 2 H), 5.21–5.17 (m, 4 H), 3.99–3.97 (m, 2 H), 2.55 (dt, J = 6.3, 14.0 Hz, 2 H), 2.25 (dt, J = 7.0, 14.0 Hz, 2 H), 2.03–1.99 (m, 2 H), 1.80–1.77 (m, 2 H); 13C NMR (175 MHz, CDCl₃) δ 154.5, 138.4, 135.1, 131.7, 120.7, 118.3, 115.0, 58.9, 40.1, 29.6; IR (film) 3316, 1635 cm⁻¹. MS (ESI) 349.0912 (349.0910 calcd for C₁₇H₂₁BrN₂O, M + H⁺).

(2S,5R)-2,5-Diallyl-N-(4-cyanophenyl)pyrrolidine-1-carboxamide (3-4e). The title compound was prepared from 3-7 (1.12 g, 3.46 mmol) and 4-cyanophenyl isocyanate (549 mg, 3.81 mmol) in two steps via the general procedure described above. This procedure afforded 613 mg (60%) of the title compound as a off-white solid: mp = 76–79 °C. ¹H NMR (700 MHz, CDCl₃) δ 7.36 (d, J = 7.7 Hz, 2 H), 7.25 (d, J = 7.7 Hz, 2 H), 6.49 (s, 1H), 5.92–5.86 (m, 2 H), 5.21–5.17 (m, 4 H), 4.02–3.96 (m, 2 H), 2.55 (dt, J = 6.3, 14.0 Hz, 2 H), 2.25 (dt, J = 7.0, 14.0 Hz, 2 H), 2.03–1.99 (m, 2 H), 1.80–1.77 (m, 2 H); ¹³C NMR (175 MHz, CDCl₃) δ 153.9, 143.5, 135.0, 133.1, 119.2, 118.6, 118.6, 105.1, 59.1, 39.9, 29.6; IR (film) 3365, 1652 cm⁻¹. MS (ESI) 296.1756 (296.1757 calcd for C₁₈H₂₁N₃O, M + H⁺).

(2S,5R)-2,5-Diallyl-N-(4-nitrophenyl)pyrrolidine-1-carboxamide (3-4f). The title compound was prepared from 3-7 (660 mg, 2.04 mmol) and 4-nitrophenyl isocyanate (368 mg, 2.24 mmol)
in two steps via the general procedure described above. This procedure afforded 366 mg (57%) of the title compound as a pale-yellow solid: mp = 96–97 ºC. 1H NMR (700 MHz, CDCl₃) δ 8.15 (d, J = 9.1 Hz, 2 H), 7.50 (d, J = 9.1 Hz, 2 H), 6.93 (s, 1H), 5.94–5.88 (m, 2 H), 5.25–5.21 (m, 4 H), 4.04–4.01 (m, 2 H), 2.56 (dt, J = 7.0, 13.3 Hz, 2 H), 2.29 (dt, J = 7.0, 14.0 Hz, 2 H), 2.07–2.03 (m, 2 H), 1.83–1.79 (m, 2 H); 13C NMR (175 MHz, CDCl₃) δ 153.7, 145.5, 142.2, 135.0, 125.1, 118.8, 117.8, 59.2, 39.9, 29.7; IR (film) 3331, 1652 cm⁻¹. MS (ESI) 316.1656 (316.1656 calcd for C₁₇H₂₁N₃O₃, M + H⁺).

Preparation and Characterization of Bicyclic Urea Products

**General Procedure for Synthesis of Racemic Bicyclic Ureas (for HPLC assays).** A flame-dried Schlenk tube was cooled under vacuum and charged with the appropriate meso-N-aryl-2,5-diallylpyrrolidin-1-carboxamide substrate (1.0 equiv), Pd₂(dba)₃ (0.02 equiv), PCy₃•HBF₄ (0.08 equiv), and NaOtBu (1.5 equiv). The flask was evacuated and purged with N₂. Toluene (0.2 M) was added via syringe and the resulting mixture was stirred at rt for 2 min. The appropriate aryl or alkenyl bromide (1.5 equiv) was added and the tube was heated to 100 ºC and stirred for 2 h. The mixture was cooled to room temperature and saturated aqueous NH₄Cl (5 mL/mmol substrate) and ethyl acetate (5 mL/mmol substrate) were added. The layers were separated, the organic layer was filtered through a plug of silica gel, and the silica gel was washed with ethyl acetate (5 mL/mmol substrate). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

**General Procedure for Synthesis of Enantiomerically-Enriched Bicyclic Ureas 3-5**

A flame-dried Schlenk tube was cooled under vacuum and charged with the appropriate meso-N-aryl-2,5-diallylpyrrolidin-1-carboxamide substrate 3-4 (1.0 equiv), Pd₂(dba)₃ (0.02 equiv), (S)-Siphos-PE (0.08 equiv), and NaOtBu or NaOMe (1.5 equiv). The flask was evacuated and purged with N₂. Toluene (0.2 M) was added via syringe and the resulting mixture was stirred at rt for 2 min. The appropriate aryl or alkenyl bromide (1.5 equiv) was added and the tube was heated to 100 ºC. The solution was stirred for 2 h or until the starting material was completely consumed as judged by TLC analysis. The mixture was cooled to room temperature and
saturated aqueous NH₄Cl (5 mL/mmol substrate) and ethyl acetate (5 mL/mmol substrate) were added. 6 M HCl was used instead of NH₄Cl to remove aniline side products if column chromatography could not separate the desired product from aniline side products. The layers were separated, the organic layer was filtered through a plug of silica gel, and the silica gel was washed with ethyl acetate (5 mL/mmol substrate). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

(+)-(Z,3S,4aS,7R)-7-allyl-2-(4-methoxyphenyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5a). The general procedure was employed for the coupling of 3-4a (60 mg, 0.2 mmol) and (Z)-1-bromobut-1-ene (150 µL, 0.3 mmol, 2.0 M solution in toluene), using a catalyst composed of Pd₂dba₃ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 48 mg (68%) of the title compound as a brown oil and as a 7:1 mixture of diastereomers as determined by ¹H NMR analysis: [α]²³D +9.5 (c 4.3, CH₂Cl₂). Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 7.14 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 5.77–5.71 (m, 1 H), 5.43 (dt, J = 7.0, 11.2 Hz, 1 H), 5.12–5.08 (m, 1 H), 5.03 (d, J = 17.5 Hz, 1 H), 5.00 (d, J = 9.8 Hz, 1 H), 3.99 (dt, J = 2.1, 9.1 Hz, 1 H), 3.82–3.78 (m, 1 H), 3.79 (s, 3 H), 3.65 (ddt, J = 2.1, 4.9, 11.2 Hz, 1 H), 2.80 (dd, J = 5.6, 13.3 Hz, 1 H), 2.29–2.27 (m, 1 H), 2.18–2.15 (m, 2 H), 2.08 (dt, J = 8.4, 13.3 Hz, 1 H) 1.99–1.88 (m, 4 H), 1.83 (dd, J = 6.3, 12.6 Hz, 1 H) 1.68–1.60 (m, 2 H), 0.89 (t, J = 7.7 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 157.6, 154.2, 135.8, 135.1, 134.6, 129.3, 124.2, 116.8, 114.1, 58.3, 57.3, 55.4, 52.7, 37.8, 31.3, 31.0, 30.9, 27.8, 20.7, 14.0; IR (film) 1642 cm⁻¹. MS (ESI) 355.2382 (355.2380 calcd for C₂₂H₃₀N₂O₂, M + H⁺). The enantiopurity was determined to be 86:14 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 2.5% IPA/Hexanes, 0.75 mL/min, λ 245 nm, RT= 44.2 and 49.1 min).
(+)-(Z,3S,4aS,7R)-7- Allyl-2-(3,4-dimethoxyphenyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5b). The general procedure was employed for the coupling of 3-4b (66 mg, 0.2 mmol) and (Z)-1-bromobut-1-ene (150 µL, 0.3 mmol, 2.0 M solution in toluene), using a catalyst composed of Pd₂dba₃ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 30 mg (39%) of the title compound as a brown oil and as a 7:1 mixture of diastereomers as determined by ¹H NMR analysis: [α]²³° +7.0 (c 2.9, CH₂Cl₂). Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 6.83 (d, J = 8.4 Hz, 1 H), 6.78–6.77 (m, 2 H), 5.77–5.71 (m, 1 H), 5.44 (dt, J = 7.0, 10.5 Hz, 1 H) 5.13–5.09 (m, 1 H), 5.03 (d, J = 16.8 Hz, 1 H), 5.00 (d, J = 16.8 Hz, 1 H), 4.01 (dt, J = 2.8, 9.1 Hz, 1 H), 3.86 (s, 6 H), 3.85–3.81 (m, 1 H), 3.66 (ddt, J = 2.1, 5.6, 11.2 Hz, 1 H), 2.80 (dd, J = 5.6, 12.6 Hz, 1 H), 2.30–2.28 (m, 1 H), 2.18–2.15 (m, 2 H), 2.07 (dt, J = 8.4, 13.3 Hz, 1 H) 2.00–1.96 (m, 1 H), 1.93–1.87 (m, 3 H), 1.83 (dd, J = 7.0, 12.6 Hz, 1 H) 1.69–1.63 (m, 2 H), 0.89 (t, J = 7.7 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 154.1, 148.9, 147.2, 135.8, 135.4, 134.7, 124.2, 120.1, 116.8, 112.3, 111.1, 58.5, 57.3, 56.0, 55.9, 52.7, 37.8, 31.3, 31.1, 30.9, 27.7, 20.7, 14.1; IR (film) 1641 cm⁻¹. MS (ESI) 385.2486 (385.2486 calcd for C₂₃H₂₂N₂O₃, M + H⁺). The enantiopurity was determined to be 82:18 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, λ 205 nm, RT= 20.4 and 23.5 min).
(–)-(Z,3S,4aS,7R)-7-Allyl-2-(4-chlorophenyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5c). The general procedure was employed for the coupling of 3-4c (305 mg, 1.0 mmol) and (Z)-1-bromobut-1-ene (750 µL, 1.5 mmol, 2.0 M solution in toluene), using a catalyst composed of Pd2dba3 (18.3 mg, 0.02 mmol), and (S)-Siphos-PE (40.4 mg, 0.08 mmol). This procedure afforded 288 mg (80%) of the title compound as a yellow oil: [α]23D −14.3 (c 5.3, CH2Cl2). 

1H NMR (700 MHz, CDCl3) δ 7.31 (d, J = 8.4 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H), 5.77–5.71 (m, 1 H), 5.45 (dt, J = 7.0, 10.5 Hz, 1 H), 5.12–5.08 (m, 1 H), 5.04 (d, J = 16.8 Hz, 1 H), 5.01 (d, J = 16.8 Hz, 1 H), 4.01 (dt, J = 2.8, 9.1 Hz, 1 H), 3.90 (dt, J = 4.2, 10.5 Hz, 1 H), 3.66 (ddt, J = 2.1, 4.9, 11.2 Hz, 1 H), 2.78 (dd, J = 5.6, 12.6 Hz, 1 H), 2.23–2.15 (m, 3 H), 2.07 (dt, J = 6.3, 13.3 Hz, 1 H) 1.99 (dt, J = 6.3, 11.2 Hz, 1 H), 1.93–1.88 (m, 3 H), 1.84 (dd, J = 6.3, 12.6 Hz, 1 H) 1.69–1.64 (m, 2 H), 0.90 (t, J = 7.7 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 153.7, 140.8, 135.6, 134.9, 131.2, 129.3, 128.9, 123.8, 117.0, 58.0, 57.4, 52.8, 37.7, 31.3, 31.0, 30.9, 27.8, 20.7, 14.0; IR (film) 1643 cm⁻¹. MS (ESI) 359.1887 (359.1885 calcd for C21H27ClN2O, M + H⁺). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, λ 190 nm, RT= 13.4 and 18.1 min).

(–)-(Z,3S,4aS,7R)-7-Allyl-2-(4-bromophenyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5d). The general procedure was employed for the coupling of 3-4d (70 mg, 0.2 mmol) and (Z)-1-bromobut-1-ene (150 µL, 0.3 mmol, 2.0 M solution in toluene), using a catalyst composed of Pd2dba3 (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 15 mg (18%) of the title compound as a brown oil and as a 18:1 mixture of diastereomers as determined by 1H NMR analysis: [α]23D −21.1 (c 0.5, CH2Cl2). This material also contained ca. 20% of an unidentified side product. Data are for the major isomer. 

1H NMR (700 MHz, CDCl3) δ 7.46 (d, J = 8.4 Hz, 2 H), 7.14 (d, J = 8.4 Hz, 2 H), 5.77–5.71 (m,
1 H), 5.45 (dt, J = 7.0, 11.2 Hz, 1 H), 5.12–5.08 (m, 1 H), 5.04 (d, J = 17.5 Hz, 1 H), 5.01 (d, J = 10.5 Hz, 1 H), 4.01 (dt, J = 2.8, 8.4 Hz, 1 H), 3.90 (dt, J = 4.9, 10.5 Hz, 1 H), 3.66 (ddt, J = 2.8, 5.6, 11.2 Hz, 1 H), 2.78 (dd, J = 5.6, 12.6 Hz, 1 H), 2.23–2.15 (m, 3 H), 2.07 (dt, J = 8.4, 13.3 Hz, 1 H) 1.99 (dt, J = 5.6, 11.9 Hz, 1 H), 1.95–1.88 (m, 3 H), 1.84 (dd, J = 6.3, 12.6 Hz, 1 H) 1.69–1.63 (m, 2 H), 0.90 (t, J = 7.7 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 153.6, 141.4, 135.6, 134.9, 131.9, 129.7, 123.8, 119.2, 117.0, 57.9, 57.4, 52.7, 37.7, 31.3, 31.0, 30.8, 27.7, 20.7, 14.0; IR (film) 1645 cm−1. MS (ESI) 403.1379 (403.1380 calcd for C21H27BrN2O, M + H+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, λ 205 nm, RT= 14.5 and 20.0 min).

(−)-4-[(Z,3S,4aS,7R)-7-Allyl-1-oxo-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-2(1H)-yl]benzonitrile (3-5e). The general procedure was employed for the coupling of 3-4e (59 mg, 0.2 mmol) and (Z)-1-bromobut-1-ene (150 µL, 0.3 mmol, 2.0 M solution in toluene), using a catalyst composed of Pd2dba3 (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 29 mg (41%) of the title compound as a brown oil and as a 17:1 mixture of diastereomers as determined by 1H NMR analysis: [α]23D –71.0 (c 2.9, CH2Cl2). This material also contained ca. 5% of 4-aminobenzonitrile. Data are for the major isomer. 1H NMR (700 MHz, CDCl3) δ 7.62 (d, J = 9.1 Hz, 2 H), 7.39 (d, J = 9.1 Hz, 2 H), 5.76–5.71 (m, 1 H), 5.45 (dt, J = 7.0, 11.2 Hz, 1 H), 5.12–5.08 (m, 1 H), 5.04 (d, J = 16.1 Hz, 1 H), 5.02 (d, J = 9.1 Hz, 1 H), 4.07 (dt, J = 4.9, 10.5 Hz, 1 H), 4.02 (dt, J = 2.1, 8.4, Hz 1 H), 3.68 (ddt, J = 2.1, 5.6, 11.2 Hz, 1 H), 2.76 (dd, J = 6.3, 12.6 Hz, 1 H), 2.23 (d, J = 12.6 Hz, 1 H), 2.20–2.14 (m, 2 H), 2.06 (dt, J = 8.4, 13.3 Hz, 1 H), 2.03–2.00 (m, 1 H), 1.97–1.85 (m, 4 H), 1.71–1.63 (m, 2 H), 0.89 (t, J = 7.7 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 153.1, 146.6, 135.3, 135.2, 132.6, 127.8, 123.4, 118.9, 115.3, 114.0.
117.2, 108.5, 57.7, 57.4, 52.7, 37.4, 31.4, 31.0, 30.8, 27.7, 20.7, 14.0; IR (film) 1648 cm$^{-1}$. MS (ESI) 350.2227 (350.2227 calcd for C$_{22}$H$_{27}$N$_3$O, M + H$^+$). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, $\lambda$ 205 nm, RT= 33.2 and 42.9 min).

(-)-(Z,3S,4aS,7R)-7-allyl-2-(4-nitrophenyl)-3-(pent-2-en-1-yl)hexahydropyrrrolo[1,2-c]pyrimidin-1(2H)-one (3-5f). A modification of the general procedure was employed for the coupling of 3-4f (63 mg, 0.2 mmol) and (Z)-1-bromobut-1-ene (150 µL, 0.3 mmol, 2.0 M solution in toluene), using a catalyst composed of Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). In contrast to the general procedure, this reaction was run overnight (16 h) at 120 °C. This procedure afforded 18 mg (24%) of the title compound as a yellow oil and as a 20:1 mixture of diastereomers as determined by $^1$H NMR analysis: $[\alpha]_D^{23}$ –281.3 (c 1.1, CH$_2$Cl$_2$). This material also contained ca. 8% of unreacted starting material and ca. 3% of a bicyclic urea side product lacking the butenyl group (tentatively assigned as 7-allyl-3-methyl-2-(4-nitrophenyl)-4a,5,6,7-tetrahydropyrrrolo[1,2-c]pyrimidin-1(2H)-one). Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 8.21 (d, $J = 9.1$ Hz, 2 H), 7.46 (d, $J = 9.1$ Hz, 2 H), 5.77–5.71 (m, 1 H), 5.46 (dt, $J = 7.0$, 11.2 Hz, 1 H), 5.12 (ddt, $J = 2.1$, 8.4, 17.5 Hz, 1 H), 5.07–5.03 (m, 2 H), 4.15 (dt, $J = 4.9$, 9.8 Hz, 1 H), 4.05 (dt, $J = 2.8$, 9.1 Hz, 1 H), 3.70 (ddt, $J = 2.8$, 5.6, 11.2 Hz, 1 H), 2.78 (dd, $J = 5.6$, 13.3 Hz, 1 H), 2.25 (d, $J = 13.3$ Hz, 1 H), 2.23–2.16 (m, 2 H), 2.10–2.02 (m, 2 H) 1.97–1.87 (m, 4 H), 1.73–1.66 (m, 2 H), 0.90 (t, $J = 7.7$ Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 153.0, 148.5, 144.4, 135.3, 135.3, 127.2, 124.1, 123.3, 117.3, 57.8, 57.4, 52.7, 37.3, 31.5, 31.0, 30.8, 27.7, 20.8, 14.0; IR (film) 1649 cm$^{-1}$. MS (ESI) 370.2126 (370.2125 calcd for C$_{21}$H$_{27}$N$_3$O$_3$, M + H$^+$). The enantiopurity was determined to be 96:4 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 1.5 mL/min, $\lambda$ 310 nm, RT= 19.1 and 26.2 min).
(--)(E,3S,4aS,7R)-7-Allyl-2-(4-chlorophenyl)-3-(hept-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5g). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and (E)-1-bromohex-1-ene (49 mg, 0.3 mmol), using a catalyst composed of Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). 6 M HCl was used in the workup to remove 4-chloroaniline side product. This procedure afforded 44 mg (57%) of the title compound as a yellow oil: [a]$^2_{D}$ = –30.3 (c 1.9, CH$_2$Cl$_2$). This material also contained ca. 15% of a regioisomeric bicyclic urea product generated from the coupling of 3-4c and 2-bromohex-1-ene (tentatively assigned as (3S,4aS,7R)-7-allyl-2-(4-chlorophenyl)-3-(2-methylenehexyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one). Data are for the major isomer.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.31 (d, $J$ = 9.0 Hz, 2 H), 7.17 (d, $J$ = 9.0 Hz, 2 H), 5.78–5.70 (m, 1 H), 5.41–5.36 (m, 1 H), 5.17–5.10 (m, 1 H), 5.05–5.00 (m, 2 H), 4.00 (dt, $J$ = 2.5, 8.5 Hz, 1 H), 3.92–3.87 (m, 1 H), 3.65 (ddt, $J$ = 2.5, 5.5, 11.0 Hz, 1 H), 2.79 (dd, $J$ = 6.0, 13.5 Hz, 1 H), 2.28–2.23 (m, 2 H), 2.10–1.98 (m, 3 H), 1.95–1.87 (m, 3 H), 1.84 (dd, $J$ = 6.5, 12.5 Hz, 1 H) 1.69–1.62 (m, 2 H), 1.29–1.26 (m, 4 H), 0.87 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.7, 140.9, 135.6, 134.6, 131.2, 129.4, 128.8, 125.1, 116.9, 57.9, 57.4, 52.6, 37.7, 36.9, 32.2, 31.4, 30.8, 27.8, 22.1, 13.9 (one carbon signal is absent due to incidental equivalence); IR (film) 1643 cm$^{-1}$. MS (ESI) 387.2207 (387.2198 calcd for C$_{22}$H$_{31}$ClN$_2$O, M + H$^+$). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 1.5% IPA/Hexanes, 1.5 mL/min, $\lambda$ 205 nm, RT= 20.0 and 37.5 min).
The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and (Z)-1-bromohex-1-ene (49 mg, 0.3 mmol), using a catalyst composed of Pd_{2}dba_{3} (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). 6 M HCl was used in the workup to remove 4-chloroaniline side product. This procedure afforded 47 mg (61%) of the title compound as a yellow brown oil: [α]^{23}_{D} -14.8 (c 3.5, CH_{2}Cl_{2}). Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 7.31 (d, J = 9.1 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H), 5.77–5.71 (m, 1 H), 5.45 (dt, J = 7.0, 11.2 Hz, 1 H), 5.15–5.11 (m, 1 H), 5.05–5.00 (m, 2 H), 4.01 (dt, J = 2.8, 8.4 Hz, 1 H), 3.91–3.88 (m, 1 H), 3.66 (ddt, J = 2.1, 4.9, 11.2 Hz, 1 H), 2.78 (dd, J = 8.4, 13.3 Hz, 1 H), 2.24–2.14 (m, 3 H), 2.07 (dt, J = 8.4, 14.0 Hz, 1 H), 2.00–1.97 (m, 1 H) 1.95–1.83 (m, 4 H), 1.70–1.62 (m, 2 H), 1.25–1.24 (m, 4 H), 0.86 (t, J = 7.0 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 153.7, 140.8, 135.6, 133.4, 131.3, 129.4, 128.9, 124.4, 117.0, 58.1, 57.4, 52.8, 37.7, 31.6, 31.3, 31.0, 30.8, 27.8, 27.2, 22.3, 13.9; IR (film) 1642 cm⁻¹. MS (ESI) 387.2203 (387.2198 calcd for C_{23}H_{31}ClN_{2}O, M + H⁺). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 1.5% IPA/Hexanes, 1.5 mL/min, λ 254 nm, RT= 20.9 and 36.2 min).

The general procedure was employed for the coupling of 3-4c (61
56 mg, 0.2 mmol) and 1-bromo-2-methyl-1-propene (31 µL, 0.3 mmol), using a catalyst composed of Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 37 mg (52%) of the title compound as a yellow oil and as a 10:1 mixture of diastereomers as determined by $^1$H NMR analysis: [α]$^3_D$ –37.9 (c 2.2, CH$_2$Cl$_2$). Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.30 (d, $J$ = 7.7 Hz, 2 H), 7.18 (d, $J$ = 9.1 Hz, 2 H), 5.74 (dddd, $J$ = 6.3, 7.7, 10.5, 16.8 Hz, 1 H), 5.04 (dd, $J$ = 2.1, 16.8 Hz, 1 H), 5.01 (d, $J$ = 10.5 Hz, 1 H), 4.89 (dt, $J$ = 1.4, 7.0 Hz, 1 H), 4.00 (dt, $J$ = 2.8, 9.1 Hz, 1 H), 3.88–3.85 (m, 1 H), 3.66 (ddt, $J$ = 2.8, 5.6, 11.2 Hz, 1 H), 2.79 (dd, $J$ = 6.3, 12.6 Hz, 1 H), 2.21–2.16 (m, 2 H), 2.09–2.04 (m, 2 H), 2.02–1.99 (m, 1 H), 1.95–1.89 (m, 1 H), 1.84 (dd, $J$ = 7.0, 12.6 Hz, 1 H) 1.68–1.62 (m, 2 H), 1.64 (s, 3 H), 1.47 (s, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 153.7, 140.9, 135.6, 134.9, 131.1, 129.3, 128.8, 119.6, 117.0, 58.3, 57.4, 52.8, 37.7, 32.2, 31.1, 30.9, 27.7, 25.7, 17.9; IR (film) 1643 cm$^{-1}$. MS (ESI) 359.1895 (359.1885 calcd for C$_{21}$H$_{27}$ClN$_2$O, M + H$^+$). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, λ 254 nm, RT= 13.8 and 24.0 min).

(--)(3S,4aS,7R)-7-Allyl-2-(4-chlorophenyl)-3-(2-methylallyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5j). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 2-bromopropene (89 µL, 1.0 mmol), using a catalyst composed of Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 39 mg (56%) of the title compound as a yellow oil and as a 20:1 mixture of diastereomers as determined by $^1$H NMR analysis: [α]$^3_D$ –33.5 (c 2.9, CH$_2$Cl$_2$). Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.31 (d, $J$ = 8.4 Hz, 2 H), 7.19 (d, $J$ = 9.1 Hz, 2 H), 5.77–5.71 (m, 1 H), 5.06–5.01 (m, 2 H), 4.79 (s, 1 H), 4.66 (s, 1 H), 4.09–4.06 (m, 1 H), 4.00 (dt, $J$ = 2.8, 8.4 Hz, 1 H), 3.66 (ddt, $J$ = 2.8, 4.9, 11.2 Hz, 1 H), 2.79 (dd, $J$ = 6.3, 12.6 Hz, 1 H), 2.27–2.23 (m, 2 H),
2.12 (dd, J = 11.2, 14.0 Hz, 1 H) 2.07 (dt, J = 8.4, 13.3 Hz, 1 H), 2.03–1.99 (m, 1 H), 1.95–1.89 (m, 1 H), 1.85 (dd, J = 7.0, 12.6 Hz, 1 H) 1.68–1.64 (m, 2 H), 1.55 (s, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 153.7, 141.5, 140.7, 135.6, 131.2, 129.3, 128.9, 117.0, 113.9, 57.5, 55.8, 52.6, 41.8, 37.7, 30.8, 30.5, 27.8, 22.0; IR (film) 1641 cm\(^{-1}\). MS (ESI) 345.1735 (345.1728 calcd for C\(_{20}\)H\(_{25}\)ClN\(_2\)O, M + H\(^+\)). The enantiopurity was determined to be 88:12 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 3% IPA/Hexanes, 0.75 mL/min, \(\lambda\) 254 nm, RT= 22.8 and 28.4 min).

\[(\text{–})(3S,4aS,7R)-7-	ext{Allyl-2-}(4-	ext{chlorophenyl})-3-(4-	ext{methylbenzyl})\text{hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5k).}\]

The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 4-bromotoluene (37 µL, 0.3 mmol), using a catalyst composed of Pd\(_2\)dba\(_3\) (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 66 mg (83%) of the title compound as a pale yellow oil and as a 8:1 mixture of diastereomers as determined by \(^1\)H NMR analysis: [\(\alpha\)\(^{23}\)\(_D\)] –125.6 (c 3.1, CH\(_2\)Cl\(_2\)). Data are for the major isomer. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.36 (d, \(J = 8.4\) Hz, 2 H), 7.26 (d, \(J = 8.4\) Hz, 2 H), 7.06 (d, \(J = 8.4\) Hz, 2 H), 6.86 (d, \(J = 7.7\) Hz, 2 H), 5.77–5.71 (m, 1 H), 5.04 (d, \(J = 16.8\) Hz, 1 H), 5.01 (d, \(J = 10.5\) Hz, 1 H), 4.10 (dt, \(J = 4.9\) 11.2 Hz, 1 H), 4.03 (dt, \(J = 2.8\), 8.4 Hz 1 H), 3.76 (ddt, \(J = 2.8\), 5.6, 11.2 Hz, 1 H), 2.90 (dd, \(J = 2.8\), 13.3 Hz, 1 H), 2.81–2.78 (m, 1 H), 2.53 (dd, \(J = 11.2\), 14.0 Hz, 1 H), 2.30 (s, 3 H), 2.09–2.04 (m, 2 H), 2.00 (dt, \(J = 5.6\), 11.9 Hz, 1 H), 1.96–1.91 (m, 1 H), 1.85 (dd, \(J = 5.6\), 12.6 Hz, 1 H) 1.64–1.59 (m, 1 H), 1.56 (dt, \(J = 6.3\), 12.6 Hz, 1 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 153.6, 140.8, 136.2, 135.6, 134.5, 131.3, 129.3, 129.3, 129.0, 128.9, 117.0, 59.8, 57.5, 52.6, 39.2, 37.6, 30.8, 30.1, 27.8, 21.0; IR (film) 1642 cm\(^{-1}\). MS (ESI) 395.1887 (395.1885 calcd for C\(_{24}\)H\(_{27}\)ClN\(_2\)O, M + H\(^+\)). The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, \(\lambda\) 254 nm, RT= 17.3 and 19.4 min).
(−)(3S,4aS,7R)-7-allyl-2-(4-chlorophenyl)-3-(4-methoxybenzyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5l). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 4-bromoanisole (38 µL, 0.3 mmol), using a catalyst composed of Pd$_3$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 58 mg (70%) of the title compound as a pale yellow oil and as a 8:1 mixture of diastereomers as determined by $^1$H NMR analysis: $[\alpha]_{D}^{23} -169.4$ (c 2.2, CH$_2$Cl$_2$). Data are for the major isomer.

$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.35 (d, $J = 8.4$ Hz, 2 H), 7.25 (d, $J = 8.4$ Hz, 2 H), 6.89 (d, $J = 9.1$ Hz, 2 H), 6.79 (d, $J = 8.4$ Hz, 2 H), 5.77–5.71 (m, 1 H), 5.04 (d, $J = 17.5$ Hz, 1 H), 5.01 (d, $J = 10.5$ Hz, 1 H), 4.08 (dt, $J = 4.2$, 11.2 Hz, 1 H), 4.03 (dt, $J = 2.1$, 8.4 Hz, 1 H), 3.77 (s, 3 H), 3.77–3.72 (m, 1 H), 2.87 (dd, $J = 3.5$, 14.0 Hz, 1 H), 2.80 (dd, $J = 6.3$, 14.0 Hz, 1 H), 2.51 (dd, $J = 11.2$, 13.3 Hz, 1 H), 2.09–2.04 (m, 2 H), 2.00 (dt, $J = 5.6$, 11.9 Hz, 1 H), 1.96–1.91 (m, 1 H), 1.85 (dd, $J = 7.0$, 12.6 Hz, 1 H) 1.65–1.54 (m, 2 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 158.3, 153.6, 140.8, 135.6, 131.3, 130.0, 129.6, 129.3, 129.0, 117.0, 114.0, 59.9, 57.5, 55.2, 52.6, 38.7, 37.6, 30.8, 30.1, 27.8; IR (film) 1642 cm$^{-1}$. MS (ESI) 411.1834 (411.1834 calcd for C$_{24}$H$_{27}$ClN$_2$O$_2$, M + H$^+$). The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 3% IPA/Hexanes, 0.75 mL/min, λ 204 nm, RT= 49.3 and 55.7 min).
(−)-(3S,4aS,7R)-7-Allyl-3-benzyl-2-(4-chlorophenyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5m). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and bromobenzene (32 µL, 0.3 mmol), using a catalyst composed of Pd₂dba₃ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 63 mg (83%) of the title compound as a pale brown foam oil and as a 7:1 mixture of diastereomers as determined by ¹H NMR analysis: [α]²³D −61.2 (c 5.6, CH₂Cl₂). Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 7.36 (d, J = 9.1 Hz, 2 H), 7.27–7.25 (m, 4 H), 7.21–7.20 (m, 1 H), 6.98 (d, J = 7.0 Hz, 2 H), 5.75–5.71 (m, 1 H), 5.05–5.00 (m, 2 H), 4.14 (dt, J = 4.9, 11.2 Hz, 1 H), 4.03 (dt, J = 2.1, 8.4 Hz, 1 H), 3.77 (ddt, J = 2.1, 4.9, 11.2 Hz, 1 H), 2.94 (dd, J = 3.5, 14.0 Hz, 1 H), 2.80 (dd, J = 6.3, 13.3 Hz, 1 H), 2.57 (dd, J = 11.2, 14.0 Hz, 1 H), 2.10–2.04 (m, 2 H), 2.03–2.00 (m, 1 H), 1.97–1.91 (m, 1 H), 1.86 (dd, J = 6.3, 12.6 Hz, 1 H) 1.66–1.54 (m, 2 H); ¹³C NMR (175 MHz, CDCl₃) δ 153.6, 140.8, 137.6, 135.6, 131.4, 129.3, 129.1, 129.0, 128.6, 126.6, 117.0, 59.7, 57.5, 52.7, 39.6, 37.6, 30.8, 30.2, 27.8; IR (film) 1642 cm⁻¹. MS (ESI) 381.1736 (381.1728 calcd for C₂₃H₂₅ClN₂O, M + H⁺). The enantiopurity was determined to be 90:10 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, λ 245 nm, RT= 21.1 and 24.2 min).

(−)-(3S,4aS,7R)-7-Allyl-2-(4-chlorophenyl)-3-[4-(trifluoromethyl)benzyl]hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5n). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 4-bromobenzotrifluoride (42 µL, 0.3 mmol), using a catalyst composed of Pd₂dba₃ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 66 mg (74%) of the title compound as a pale yellow oil and as a 5:1 mixture of diastereomers as determined by ¹H NMR analysis: [α]²¹D −46.1 (c 6.0, CH₂Cl₂). Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 7.51 (d, J = 7.7 Hz, 2 H), 7.36 (d, J = 9.1 Hz, 2 H), 7.24 (d, J = 9.1 Hz, 2 H), 7.09 (d, J
= 7.7 Hz, 2 H), 5.77–5.71 (m, 1 H), 5.05–5.01 (m, 2 H), 4.16 (dt, \(J = 4.2, 11.2\) Hz, 1 H), 4.03 (dt, \(J = 2.1, 9.1\) Hz, 1 H), 3.76 (ddt, \(J = 2.1, 5.6, 11.9\) Hz, 1 H), 3.00 (dd, \(J = 3.5, 14.0\) Hz, 1 H), 2.79 (dd, \(J = 5.6, 13.3\) Hz, 1 H), 2.66 (dd, \(J = 11.2, 13.3\) Hz, 1 H), 2.09–2.00 (m, 3 H), 1.98–1.93 (m, 1 H), 1.87 (dd, \(J = 6.3, 11.9\) Hz, 1 H) 1.66–1.56 (m, 2 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 153.5, 141.7, 140.6, 135.5, 131.6, 129.4, 129.3, 129.1, 125.6 (q, \(J = 3.3\) Hz), 124.0 (q, \(J = 270\) Hz), 117.1, 59.5, 57.6, 52.6, 39.6, 37.6, 30.8, 30.3, 27.8; IR (film) 1642 cm\(^{-1}\). MS (ESI) 449.1600 (449.1602 calcd for \(\text{C}_{24}\text{H}_{24}\text{ClF}_{3}\text{N}_{2}\text{O}, \text{M} + \text{H}^+\)). The enantiopurity was determined to be 85:15 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, \(\lambda = 205\) nm, RT= 19.9 and 27.5 min).

\((-\text{)}-(3\text{S},4\text{aS},7\text{R})\text{-7-Allyl-2-(4-chlorophenyl)-3-[4-(trifluoromethyl)benzyl]hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5n).} \)

A modified general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 4-bromobenzotrifluoride (42 \(\mu\)L, 0.3 mmol) using NaOMe (16.2 mg, 0.3 mmol) as base and a catalyst composed of Pd\(_2\)dba\(_3\) (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 54 mg (60%) of the title compound as a pale yellow oil and as a 10:1 mixture of diastereomers as determined by \(^1\)H NMR analysis: \([\alpha]_{23}^{D} = -51.1\) (c 2.3, CH\(_2\)Cl\(_2\)). The enantiopurity was determined to be 90:10 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, \(\lambda = 205\) nm, RT= 19.4 and 26.7 min). Spectroscopic data were identical to those provided above.
(−)-(3S,4aS,7R)-7-allyl-3-benzyl-2-(4-chlorophenyl)-3-[4-(trifluoromethoxy)benzyl]hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5o). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 1-bromo-4-(trifluoromethoxy)benzene (45 µL, 0.3 mmol), using a catalyst composed of Pd₂dba₃ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 63 mg (68%) of the title compound as a pale yellow oil and as a 8:1 mixture of diastereomers as determined by ¹H NMR analysis: [α]²³D −48.7 (c 5.7, CH₂Cl₂). Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 7.35 (d, J = 9.1 Hz, 2 H), 7.24 (d, J = 9.1 Hz, 2 H), 7.10 (d, J = 7.7 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 5.77–5.71 (m, 1 H), 5.05–5.01 (m, 2 H), 4.13 (dt, J = 4.2, 11.2 Hz, 1 H), 4.03 (dt, J = 2.8, 8.4 Hz, 1 H), 3.75 (ddt, J = 2.8, 4.9, 11.2 Hz, 1 H), 2.93 (dd, J = 4.2, 14.0 Hz, 1 H), 2.79 (dd, J = 6.3, 13.3 Hz, 1 H), 2.60 (dd, J = 10.5, 14.0 Hz, 1 H), 2.10–2.00 (m, 3 H), 1.98–1.92 (m, 1 H), 1.86 (dd, J = 6.3, 12.6 Hz, 1 H) 1.67–1.57 (m, 2 H); ¹³C NMR (175 MHz, CDCl₃) δ 153.5, 147.9, 140.7, 136.7, 135.5, 131.5, 130.3, 129.3, 129.1, 121.2, 117.0, 59.6, 57.5, 52.6, 39.1, 37.6, 30.8, 30.3, 27.8 (the CF₃ carbon signal could not be determined due to the appearance of carbon signals from the minor diastereomer in the CF₃ region of the spectrum); IR (film) 1642 cm⁻¹. MS (ESI) 465.1557 (465.1551 calcd for C₂₄H₂₄ClF₃N₂O₂, M + H⁺). The enantiopurity was determined to be 88:12 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, λ 245 nm, RT= 17.1 and 19.8 min).
(−)-(3S,4aS,7R)-7-Allyl-3-benzyl-2-(4-chlorophenyl)-3-[4-(trifluoromethoxy)benzyl]hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5o). A modified general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 1-bromo-4-(trifluoromethoxy)benzene (45 µL, 0.3 mmol) using NaOMe (16.2 mg, 0.3 mmol) as base and a catalyst composed of Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 48 mg (52%) of the title compound as a pale yellow oil and as an 17:1 mixture of diastereomers as determined by $^1$H NMR analysis: [α]$^2$D $\approx$ −55.6 (c 1.5, CH$_2$Cl$_2$). The enantiopurity was determined to be 93:7 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, $\lambda$ 245 nm, RT= 16.8 and 19.8 min). Spectroscopic data were identical to those provided above.

(−)-(3S,4aS,7R)-7-Allyl-2-(4-chlorophenyl)-3-(3-methoxybenzyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5p). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 3-bromoanisole (38 µL, 0.3 mmol), using a catalyst composed of Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 61 mg (74%) of the title compound as a yellow brown solid and as a 5:1 mixture of diastereomers as determined by $^1$H NMR analysis: [α]$^2$D $\approx$ −65.1 (c 2.8, CH$_2$Cl$_2$). Mp = 132–137 °C. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.36 (d, $J$ = 8.4 Hz, 2 H), 7.25 (d, $J$ = 9.1 Hz, 2 H), 7.18 (t, $J$ = 8.4 Hz, 1 H), 6.74 (dd, $J$ = 2.1, 8.4 Hz, 1 H), 6.57 (d, $J$ = 7.0 Hz, 1 H), 6.50 (s, 1 H), 5.77–5.71 (m, 1 H), 5.04 (dd, $J$ = 1.4, 16.8 Hz, 1 H), 5.01 (dd, $J$ = 1.4, 9.8 Hz, 1 H), 4.14 (dt, $J$ = 4.2, 11.2 Hz, 1 H), 4.03 (dt, $J$ = 2.1, 8.4 Hz, 1 H), 3.77 (s, 3 H), 3.78–3.73 (m, 1 H), 2.91 (dd, $J$ = 3.5, 13.3 Hz, 1 H), 2.80 (dd, $J$ = 5.6, 13.3 Hz, 1 H), 2.54 (dd, $J$ = 11.2, 14.0 Hz, 1 H), 2.10–2.04 (m, 2 H), 2.03–1.99 (m, 1 H), 1.96–1.91 (m, 1 H), 1.85 (dd, $J$ = 6.3, 12.6 Hz, 1 H), 1.65–1.56 (m, 2 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 159.7, 153.6, 140.7, 139.2, 135.6, 131.4, 129.6, 129.3, 129.0, 121.4, 117.0, 115.3, 111.3, 59.6, 57.5, 55.2, 52.7, 39.7, 37.6, 30.8, 30.3, 27.8; IR
(-)-(3S,4aS,7R)-7-Allyl-2-(4-chlorophenyl)-3-(napthalen-2-ylmethyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5q). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 2-bromonapthanlene (62 mg, 0.3 mmol), using a catalyst composed of Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 66 mg (77%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by $^1$H NMR analysis: $[\alpha]^{23}_D-77.9$ (c 4.6, CH$_2$Cl$_2$). Data are for the major isomer. Mp = 63–65 °C. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.80 (d, $J = 7.7$ Hz, 1 H), 7.75 (t, $J = 7.7$ Hz, 2 H), 7.47–7.44 (m, 3 H), 7.38 (d, $J = 9.1$ Hz, 2 H), 7.31 (d, $J = 8.4$ Hz, 2 H), 7.07 (dd, $J = 0.7$, 8.4 Hz, 1 H), 5.78–5.72 (m, 1 H), 5.04 (d, $J = 16.8$ Hz, 1 H), 5.02 (d, $J = 9.8$ Hz, 1 H), 4.25 (dt, $J = 4.2$, 11.2 Hz, 1 H), 4.06 (dt, $J = 2.1$, 9.8 Hz, 1 H), 3.84 (ddt, $J = 2.1$, 4.9, 11.2 Hz, 1 H), 3.11 (dd, $J = 3.5$, 14.0 Hz, 1 H), 2.81 (dd, $J = 5.6$, 13.3 Hz, 1 H), 2.74 (dd, $J = 11.9$, 14.0, Hz, 1 H), 2.11–2.05 (m, 2 H), 2.04–1.94 (m, 2 H), 1.86 (dd, $J = 7.0$, 12.6 Hz, 1 H), 1.65–1.56 (m, 2 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 153.6, 140.8, 135.6, 135.1, 133.4, 132.2, 131.4, 130.4, 129.4, 129.1, 128.4, 127.7, 127.3, 127.1, 126.3, 125.7, 117.0, 59.6, 57.5, 52.7, 37.6, 30.8, 31.0, 30.2, 27.8; IR (film) 1646 cm$^{-1}$. MS (ESI) 431.1886 (431.1885 calcd for C$_{27}$H$_{27}$ClN$_2$O, M + H$^+$). The enantiopurity was determined to be 88:12 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, $\lambda$ 215 nm, RT= 24.4 and 28.2 min).
(−)-(3S,4aS,7R)-7-allyl-2-(4-chlorophenyl)-3-(2-methylbenzyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-5r). The general procedure was employed for the coupling of 3-4c (61 mg, 0.2 mmol) and 2-bromotoluene (36 µL, 0.3 mmol), using a catalyst composed of Pd(db)3 (3.7 mg, 0.004 mmol), and (S)-Siphos-PE (8 mg, 0.016 mmol). This procedure afforded 65 mg (82%) of the title compound as a pale brown oil and as a 5:1 mixture of diastereomers as determined by 1H NMR analysis: [α]23D −30.1 (c 5.7, CH2Cl2). Data are for the major isomer. 1H NMR (700 MHz, CDCl3) δ 7.36 (d, J = 9.1 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.11–7.08 (m, 3 H), 6.93–6.92 (m, 1 H), 5.78–5.71 (m, 1 H), 5.04 (dd, J = 1.4, 17.5 Hz, 1 H), 5.01 (dd, J = 1.4, 10.5 Hz, 1 H), 4.09 (dt, J = 4.2, 12.6 Hz, 1 H), 4.04 (dt, J = 2.8, 9.1 Hz, 1 H), 3.86 (ddt, J = 2.8, 5.6, 11.2 Hz, 1 H), 2.93 (dd, J = 3.5, 14.0 Hz, 1 H), 2.80 (dd, J = 5.6, 12.6 Hz, 1 H), 2.62 (dd, J = 11.2, 14.0 Hz, 1 H), 2.11–2.02 (m, 3 H), 2.01 (s, 3 H), 1.99–1.94 (m, 1 H), 1.87 (dd, J = 6.3, 12.6 Hz, 1 H), 1.65 (ddd, J = 6.3, 11.2, 17.5 Hz, 1 H), 1.58 (dt, J = 5.6, 12.6 Hz, 1 H); 13C NMR (175 MHz, CDCl3) δ 153.6, 140.7, 136.3, 135.7, 135.6, 131.5, 130.6, 130.3, 129.6, 129.0, 126.8, 126.0, 117.0, 58.4, 57.5, 52.9, 37.7, 36.8, 30.8, 30.1, 27.8, 19.2; IR (film) 1642 cm⁻¹. MS (ESI) 395.1885 (395.1885 calcd for C24H27ClN3O, M + H⁺). The enantiopurity was determined to be 71:29 er by chiral HPLC analysis (chiralcel ADH, 25 cm × 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, λ 215 nm, RT= 20.1 and 24.3 min).

Deprotection of Bicyclic Urea Product 3-5c
(--)-(Z,3S,4aS,7R)-N-(4-[7- Allyl-1-oxo-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-2(1H)-yl]phenyl)acetamide (3-8). A flame-dried screwtop flask was cooled under vacuum and charged with Pd\textsubscript{2}(dba)\textsubscript{3} (5.2 mg, 0.006 mmol), 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2’,4’,6’-triisopropyl-1,1’-biphenyl (13.7 mg, 0.03 mmol), K\textsubscript{3}PO\textsubscript{4} (182 mg, 0.86 mmol) and acetamide (50.8 mg, 0.86 mmol). The flask was evacuated and backfilled with N\textsubscript{2}, and then a solution of 3-5c (206 mg, 0.57 mmol) in tert-butanol (3 mL) was added via syringe. The flask was sealed, heated to 110 °C and stirred overnight (14 h). The mixture was cooled to room temperature and the mixture was filtered through a plug of celite, eluted with EtOAc (10 mL), and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 191 mg (88%) of the title compound as a foamy brown solid: mp = 38–42 °C. [\alpha]\textsuperscript{23}D = –25.2 (c 5.3, CH\textsubscript{2}Cl\textsubscript{2}). \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) \(\delta\) 8.93 (s, 1 H), 7.21 (d, \(J = 8.4\) Hz, 2 H), 6.98 (d, \(J = 8.4\) Hz, 2 H), 6.98–5.72 (m, 1 H), 5.49–5.40 (m, 1 H), 5.07–5.03 (m, 3 H), 4.03 (dt, \(J = 2.8, 9.1\) Hz, 1 H), 3.77 (dt, \(J = 4.2, 10.5\) Hz, 1 H), 3.67 (ddt, \(J = 2.8, 4.9, 8.4\) Hz, 1 H), 2.80 (dd, \(J = 4.9, 12.6\) Hz, 1 H), 2.25–2.08 (m, 4 H), 2.05 (s, 3 H) 2.02–1.98 (m, 1 H), 1.95–1.85 (m, 4 H), 1.70–1.64 (m, 3 H), 0.88 (t, \(J = 7.7\) Hz, 3 H); \textsuperscript{13}C NMR (175 MHz, CDCl\textsubscript{3}) \(\delta\) 168.8, 154.5, 137.3, 136.6, 135.5, 134.8, 128.3, 124.0, 121.3, 117.1, 58.5, 57.3, 52.8, 37.8, 31.2, 31.0, 30.8, 27.7, 24.0, 20.8, 14.1; IR (film) 3263, 1687, 1624 cm\textsuperscript{-1}. MS (ESI) 382.2493 (382.2489 calcd for C\textsubscript{23}H\textsubscript{31}N\textsubscript{3}O\textsubscript{2}, M + H\textsuperscript{+}).

![Chemical structure](image-url)
(−)-(Z,3S,4aS,7R)-7-Allyl-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (3-9). A Schlenk tube was charged with a stirbar, 3-8 (39 mg, 0.1 mmol) and CH$_3$CN (1 mL). A solution of ceric ammonium nitrate (164 mg, 0.3 mmol) in H$_2$O (1 mL) was added to the reaction flask and the mixture was stirred at rt for 5 min. The mixture was then heated at 50 °C for 15 min before being cooled to rt, at which time EtOAc (5 mL) was added. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous Na$_2$SO$_3$ (5 mL), saturated aqueous NaHCO$_3$ (5 mL), and brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (2% MeOH in CH$_2$Cl$_2$) on silica gel to afford 19 mg (77%) of the title compound as a yellow brown solid: [α]$_D^{23}$ −63.2 (c 0.5, CH$_2$Cl$_2$).

1H NMR (500 MHz, CDCl$_3$) δ 5.80–5.72 (m, 1 H), 5.57–5.51 (m, 1 H), 5.30–5.25 (m, 1 H), 5.06–5.02 (m, 2 H), 4.73 (s, 1 H), 4.00 (dt, $J$ = 3.0, 8.5 Hz, 1 H), 3.49 (ddt, $J$ = 3.0, 5.5, 11.5 Hz, 1 H), 3.46–3.41 (m, 1 H), 2.72 (d, $J$ = 14.5 Hz, 1 H), 2.26–2.20 (m, 1 H), 2.13–1.93 (m, 6 H), 1.88–1.77 (m, 2 H), 1.61–1.52 (m, 2 H), 0.96 (t, $J$ = 7.5 Hz, 3 H); 13C NMR (175 MHz, CDCl$_3$) δ 155.1, 135.6, 135.2, 124.0, 117.0, 56.2, 52.9, 50.0, 38.1, 35.7, 32.3, 30.7, 27.4, 20.8, 14.1; IR (film) 3207, 1652 cm$^{-1}$. MS (ESI) 249.1963 (249.1961 calcd for C$_{15}$H$_{24}$N$_2$O, M + H$^+$).

Conversion of Bicyclic Urea Product 3-5c to Tricyclic Guanidine 3-10

(−)-(Z,3S,4aS,7R)-7-Allyl-2-(4-chlorophenyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-imine hydrochloride (3-11). A flame-dried flask was cooled under a stream of N$_2$ and charged with 3-5c (177 mg, 0.49 mmol) and toluene (5 mL). Freshly distilled POCl$_3$ (2.5 mL, 27 mmol) was added and the mixture was stirred at rt until the starting material had been consumed as judged by ESI* MS analysis (ca. 3 hr). The reaction mixture was cooled to rt and concentrated in vacuo. The crude product was dissolved in acetonitrile (5 mL) and a solution
of ammonia (20 mL, 2 M in ethanol) was added. The mixture was stirred at rt until the starting material had been consumed as judged by ESI$^+$ MS analysis (ca. 1 hr). The reaction mixture was concentrated and dissolved in methylene chloride (5 mL). Water (5 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer was washed with saturated aqueous NaCl (3 x 10 mL). The combined aqueous layers were extracted with methylene chloride (3 x 10 mL). The combined organics layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 146 mg (75%) of the title compound as a pale white-yellow foam: $[\alpha]^{23}_D$ –45.5 (c 1.1, CH$_2$Cl$_2$). $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J$ = 7.7 Hz, 1 H), 7.40 (d, $J$ = 7.7 Hz, 1 H), 7.29 (d, $J$ = 7.0 Hz, 1 H), 7.14 (d, $J$ = 8.4 Hz, 1 H), 5.96–5.90 (m, 1 H), 5.45 (dt, $J$ = 7.0, 10.5 Hz, 1 H), 5.00–4.93 (m, 4 H), 3.75–3.72 (m, 1 H), 3.62–3.58 (m, 1 H), 2.67 (d, $J$ = 13.3 Hz, 1 H), 2.25 (dd, $J$ = 2.1, 14.0 Hz, 1 H), 2.18–2.16 (m, 1 H) 2.12–2.06 (m, 3 H), 2.03–1.93 (m, 2 H), 1.81–1.68 (m, 4 H), 0.82 (t, $J$ = 7.7 Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 151.3, 136.6, 136.1, 135.8, 134.5, 131.5, 131.4, 130.8, 128.9, 121.7, 118.3, 59.5, 59.1, 53.1, 36.2, 30.8, 30.4, 29.6, 28.1, 20.8, 13.9; IR (film) 3457, 3275, 1636 cm$^{-1}$. MS (ESI) 358.2048 (358.2045 calcd for C$_{21}$H$_{29}$ClN$_3$, M$^+$).

\begin{center}
\includegraphics[width=0.3\textwidth]{structure.png}
\end{center}

(–)-(Z,2aS,4S,7S,8aR)-5-(4-Chlorophenyl)-7-methyl-4-(pent-2-en-1-yl)-1,2,2a,3,4,5,6,7,8,8a-decahydro-2a$^1$,5,6-triazaacenaphthylene-2a$^1$-ium chloride (3-10). A test tube was charged with 3-11 (39.4 mg, 0.1 mmol), PdCl$_2$ (3.5 mg, 0.02 mmol), and CuCl (14.8 mg, 0.15 mmol). The tube was capped with a rubber septum, was briefly flushed with oxygen and then an oxygen-filled balloon attached to a needle (via an adaptor) was connected to the tube through the septum. A solution of THF and H$_2$O (7:1, 1.0 mL) was added to the test tube and the mixture was stirred at rt until the starting material had been consumed as judged by ESI$^+$ MS analysis (ca. 4 hr). Methanol (1 mL) and NaCNBH$_3$ (62.8 mg, 1.0 mmol) was added and the mixture was heated to
50 °C until the starting material had been consumed as judged by ESI+ MS analysis (ca. 3 hr). The reaction mixture was cooled to rt and concentrated in vacuo. The crude product was dissolved in methylene chloride (20 mL), the mixture was transferred to a separatory funnel and 2 M HCl (10 mL) was added. The layers were separated and the organic layer was washed with NH₄OH (10 mL) to potentially remove any excess copper. The layers were separated and the organic layer was washed with 2 M HCl (10 mL). The organics layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 31 mg (79%) of the title compound as a pale white-tan oil and as a 5:1 mixture of diastereomers as determined by ¹H NMR analysis: [α]²⁻³⁸.1 (c 0.6, CH₂Cl₂). Data are for the major isomer. ¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, J = 7.5 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 5.57–5.52 (m, 1 H), 5.10–5.05 (m, 1 H), 4.64 (s, 1 H), 3.99–3.90 (m, 2 H), 3.77–3.73 (m, 1 H), 3.69–3.65 (m, 1 H), 2.46–2.32 (m, 5 H), 2.28 (dt, J = 3.5, 13.0 Hz, 1 H), 1.99–1.93 (m, 3 H), 1.88–1.80 (m, 2 H), 1.51–1.44 (m, 1 H), 1.22 (d, J = 6.5 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 148.6, 136.6, 136.5, 135.2, 132.0–129.0 (br, 2 C), 121.9, 59.8, 57.7, 52.1, 47.4, 34.8, 30.0, 29.9, 29.6, 29.4, 20.9, 20.6, 14.0; IR (film) 3276, 1607 cm⁻¹. MS (ESI) 358.2047 (358.2045 calcd for C₂₁H₂₉ClN₃, M⁺).

**Conversion of Bicyclic Urea Product 3-5c to 9-epi-Batzelladine K 3-13**

\[-(Z,3S,4aS,7R)-N\{4-[1-Oxo-7-(2-oxopropyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-2(1H)-yl]phenyl\}acetamide (3-14)\]. A test tube was charged with 3-5c (300 mg, 0.79 mmol), PdCl₂ (28 mg, 0.16 mmol), and CuCl (117 mg, 1.18 mmol). The tube was capped with a rubber septum, was briefly flushed with oxygen and then an oxygen-filled balloon attached to a needle (via an adaptor) was connected to the tube through the septum. A solution
of DMF and H₂O (7:1, 8.0 mL) was added to the test tube and the mixture was stirred at rt until the starting material had been consumed as judged by ESI⁺ MS analysis (ca. 4 hr). EtOAc (20 mL) and brine (20 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer was washed with NH₄OH (5 mL) to potentially remove any excess copper. The combined aqueous layers were than extracted with EtOAc (20 mL). The organics layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 230 mg (74%) of the title compound as a pale yellow-pink solid: mp = 68–72 °C. [α]²³ D –38.8 (c 0.8, CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃) δ 8.66 (s, 1 H), 7.25 (d, J = 8.4 Hz, 2 H), 7.01 (d, J = 9.1 Hz, 2 H), 5.44–5.41 (m, 1 H), 5.06–5.03 (m, 1 H), 4.37–4.34 (m, 1 H), 3.80–3.77 (m, 1 H), 3.66 (ddd, J = 2.8, 4.9, 11.2 Hz, 1 H), 3.44 (dd, J = 2.8, 9.8 Hz, 1 H), 2.31 (dd, J = 9.8, 16.8 Hz, 1 H), 2.26–2.13 (m, 3 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 2.09–2.03 (m, 2 H), 1.91–1.86 (m, 2 H), 1.77 (dd, J = 7.0, 13.3 Hz, 1 H), 1.65–1.58 (m, 2 H), 0.88 (t, J = 7.0 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 207.5, 168.7, 154.2, 137.2, 136.7, 134.9, 128.3, 123.8, 121.1, 58.5, 53.7, 52.8, 47.6, 31.1, 30.8, 30.2, 29.4, 24.0, 20.8, 14.0 (one carbon signal is absent due to incidental equivalence); IR (film) 3261, 1711, 1687, 1621 cm⁻¹. MS (ESI) 398.2439 (398.2438 calcd for C₂₃H₃₁N₃O₃, M + H⁺).

A flame-dried flask was cooled under vacuum and charged with 3-14 (100 mg, 0.25 mmol) and Pd/C (10 mg). The flask was capped with a rubber septum, was briefly flushed with hydrogen and then a hydrogen-filled balloon attached to a needle (via an adaptor) was connected to the flask through the septum. Methanol (2.5 mL) was added to the flask and the mixture was stirred at rt until the starting material had been consumed as judged by ESI⁺ MS analysis (ca. 45 min). The crude product was then filtered through a plug of celite to remove the Pd/C and washed with methanol (5 mL). The crude material was concentrated in vacuo and carried on to the next step.
without further purification. The crude product was dissolved in CH$_3$CN (10 mL) and transferred to a round-bottom flask charged with a stirbar. A solution of ceric ammonium nitrate (123 mg, 0.75 mmol) in H$_2$O (30 mL) was added to the reaction flask and the mixture was stirred at rt for 5 min. The mixture was then heated at 50 °C for 4 hr before being cooled to rt, at which time EtOAc (25 mL) was added. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous Na$_2$SO$_3$ (15 mL), saturated aqueous NaHCO$_3$ (15 mL), and brine (15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 34 mg (51%) of the title compound as a white solid: mp = 84–88 °C. [α]$^2_3$D $-11.7$ (c 2.5, CH$_2$Cl$_2$). $^1$H NMR (700 MHz, CDCl$_3$) δ 4.79 (s, 1 H), 4.30–4.28 (m, 1 H), 3.48–3.45 (m, 1 H), 3.43–3.39 (m, 2 H), 2.29 (dd, $J = 9.8, 16.8$ Hz, 1 H), 2.10 (s, 3 H), 2.03–1.98 (m, 2 H), 1.95–1.94 (m, 1 H), 1.72 (dd, $J = 7.7, 12.6$ Hz, 1 H), 1.54–1.46 (m, 3 H), 1.38–1.25 (m, 7 H), 0.88 (t, $J = 7.0$ Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 207.7, 155.0, 52.8, 52.8, 50.0, 47.6, 37.8, 32.9, 31.6, 30.6, 30.3, 29.0, 25.5, 22.6, 14.0; IR (film) 3207, 1709, 1649 cm$^{-1}$. MS (ESI) 267.2065 (267.2067 calcd for C$_{15}$H$_{26}$N$_2$O$_2$, M + H$^+$).

(-)-9-epi-Batzelladine K (3-13). A flame-dried flask was cooled under vacuum and charged with 3-15 (25 mg, 0.09 mmol) and dichloromethane (0.9 mL). 2,6-di-tert-butylpyridine (203 µL, 0.94 mmol) and MeOTf (103 µL, 0.94 mmol) were added and the mixture was stirred at rt until the starting material had been consumed as judged by ESI$^+$ MS analysis (ca. 1 hr). The solvent was then removed in a hood by blowing a constant stream of N$_2$ over the stirring mixture. The solution was then poured in diethyl ether (20 ml) and washed with 1 M NaOH (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was used without further purification. The crude O-methylisourea was dissolved in methanol (2 mL) and transferred to a thick walled glass vial at which time ammonium chloride (10.1mg, 0.19 mmol) was added to this solution. Anhydrous ammonia was bubbled through this solution for ~15 min before the reaction vessel was sealed and heated to 60
overnight (14 hr). The reaction was cooled to rt and concentrated in vacuo. The crude guanidine product 3-16 was used without further purification. Crude product 3-16 was dissolved in methanol (3 mL), NaCNBH$_3$ (59 mg, 0.94 mmol) was added and the mixture was heated to 50 °C until the starting material had been consumed as judged by ESI$^+$ MS analysis (ca. 12 hr). The reaction mixture was cooled to rt and concentrated in vacuo. The crude product was dissolved in methylene chloride (20 mL), the mixture was transferred to a separatory funnel and washed with 2 M HCl (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in methanol (3 mL), NaCNBH$_3$ (59 mg, 0.94 mmol) was added and the mixture was heated to 50 °C until the starting material had been consumed as judged by ESI$^+$ MS analysis (ca. 12 hr). The reaction mixture was cooled to rt and concentrated in vacuo. The crude product was dissolved in methylene chloride (20 mL), the mixture was transferred to a separatory funnel and washed with 2 M HCl (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was determined to be a 3:1 mixture of diastereomers by $^1$H NMR analysis. The crude material was purified by flash chromatography on silica gel to afford 13 mg (48%) of the title compound as a pale yellow oil. The following data is for the pure isolated major diastereomer. [α]$^2$$_D$ –43.8 (c 0.5, CH$_2$Cl$_2$). $^1$H NMR (700 MHz, CDCl$_3$) δ 3.80–3.73 (m, 2 H), 3.58–3.53 (m, 1 H), 3.52–3.49 (m, 1 H), 2.26–2.21 (m, 3 H), 2.19 (dd, J = 4.2, 13.3 Hz, 1 H), 1.73–1.64 (m, 2 H), 1.60–1.56 (m, 2 H), 1.52–1.47 (m, 1 H), 1.44–1.27 (m, 7 H), 1.27 (d, J = 6.3 Hz, 3 H), 0.93 (t, J = 7.0 Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 149.4, 56.3, 51.6, 48.4, 45.8, 36.2, 35.5, 31.5, 31.2, 30.5, 30.2, 25.5, 22.4, 20.5, 14.0; $^1$H NMR (700 MHz, CD$_3$OD) δ 7.56 (d, J = 7.5 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 5.57–5.52 (m, 1 H), 5.10–5.05 (m, 1 H), 4.64 (s, 1 H), 3.99–3.90 (m, 2 H), 3.77–3.73 (m, 1 H), 3.69–3.65 (m, 1 H), 2.46–2.32 (m, 5 H), 2.28 (dt, J = 3.5, 13.0 Hz, 1 H), 1.99–1.93 (m, 3 H), 1.88–1.80 (m, 2 H), 1.51–1.44 (m, 1 H), 1.22 (d, J = 6.5 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H); $^{13}$C NMR (175 MHz, CD$_3$OD) δ 150.4, 57.5, 53.5, 50.2, 47.3, 36.8, 36.1, 32.7, 31.9, 31.3, 30.7, 26.8, 23.6, 20.8 14.3; IR (film) 3284, 3202, 1637 cm$^{-1}$. MS (ESI) 250.2278 (250.2278 calcd for C$_{15}$H$_{28}$N$_3$, M$^+$).

**Assignment of Stereochemistry**

The relative stereochemistry of compound 3-5k was assigned on the basis of observed $^1$H NMR nOe experiments. Significant nOe relationships are shown below. The stereochemistry of all other bicyclic urea products was assigned based on analogy to 3-5k.
The relative stereochemistry of compounds 3-10 and 3-13 were assigned on the basis of observed \(^1\)H NMR nOe experiments. Significant nOe relationships are shown below.

The absolute stereochemistry of the urea products was assigned via the synthesis of compound \textit{ent}-3-5c from pent-4-enal via the route illustrated below in Scheme 3-6. The optical rotation of product \textit{ent}-3-5c prepared via this route was opposite that of the product 3-5c generated in the Pd-catalyzed carboamination reaction between 3-4c and Z-bromobutene. In addition, analysis of product \textit{ent}-3-5c by chiral HPLC indicated that \textit{ent}-3-5c was the enantiomer of product 3-5c formed in the catalytic reaction.
(-)-(R<sub>3</sub>)-2-Methyl-N-(pent-4-en-1-ylidene)propane-2-sulfinamide (3-S1). This compound was prepared according to the procedure reported by Ellman. A flame-dried flask was cooled under a stream of N<sub>2</sub> and charged with pent-4-enal (1.38 mL, 14 mmol) and THF (40 mL). Titanium ethoxide (4.2 mL, 20 mmol) was added and the reaction mixture was stirred at rt for 5 min. (R)-<i>tert</i>-<i>tert</i>-butanesulfinamide (1.21 g, 10 mmol) was added in one portion and the mixture was stirred overnight (ca. 14 h) at rt. The reaction mixture was poured into brine (40 mL) and stirred for 10 min. Ethyl acetate (20 mL) was added, the mixture was filtered through celite and the celite was washed with ethyl acetate (50 mL). The mixture was transferred to a separatory funnel, brine (20 mL) was added, and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 1.38 g (74%) of the title compound as a colorless oil. Spectroscopic properties are identical to those previously reported.<sup>60</sup> ¹H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.08 (t, <i>J</i> = 4.5 Hz, 1 H), 5.84 (ddt, <i>J</i> = 4.5, 10.0, 17.0 Hz, 1 H), 5.08 (dd, <i>J</i> = 1.5, 17.0 Hz, 1 H), 5.02 (dd, <i>J</i> = 1.5, 10.0 Hz, 1 H), 2.63 (td, <i>J</i> = 4.0, 7.5 Hz, 2 H), 2.40 (q, <i>J</i> = 7.0 Hz, 2 H), 1.19 (s, 9 H).
(R<sub>s</sub>, 4R)-2-Methyl-N-(octa-1,7-dien-4-yl)propane-2-sulfinamide (3-S2). A flame-dried flask was cooled under a stream of \( \text{N}_2 \) and charged with freshly ground magnesium turnings (720 mg, 4 equiv). The magnesium was suspended in ether (14.8 mL, 1 M), cooled to 0 °C in an ice/water bath and allyl bromide (1.28 mL, 14.8 mmol) was added dropwise. After addition, the ice bath was removed, and the reaction mixture was stirred at rt for 30 min. Stirring was stopped and the solution was filtered through glass wool prior to addition to 3-S1. A flame-dried flask was cooled under a stream of \( \text{N}_2 \) and charged with 3-S1 (1.38 g, 7.4 mmol) and THF (37 mL, 0.2 M). The sulfinyl imine solution was cooled to 0 °C in an ice/water bath before the filtered Grignard reagent solution was added dropwise. The reaction mixture was stirred at 0 °C until the starting material had been completely consumed as judged by TLC analysis (1 h). Water was then added dropwise until precipitation of magnesium salts occurred and the resulting solution was decanted into a separate flask. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated \textit{in vacuo}. Analysis of the crude product by \( ^1 \text{H} \) NMR indicated that a 10:1 mixture of diastereomers had formed. The crude material was purified by flash chromatography on silica gel to afford 1.02 g (60%) of the title compound as a 10:1 mixture of diastereomers as a clear colorless oil. Data are for the major isomer. \( ^1 \text{H} \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.83–5.74 (m, 2 H), 5.18–4.97 (m, 4 H), 3.36–3.32 (m, 1 H), 3.21 (d, \( J = 6.5 \) Hz, 1 H), 2.45–2.40 (m, 1 H), 2.37–2.32 (m, 1 H), 2.18–2.08 (m, 2 H), 1.62–1.58 (m, 2 H), 1.21 (s, 9 H).

(R)-tert-Butyl octa-1,7-dien-4-ylcarbamate ([R]-3-6). A flame-dried flask was cooled under a stream of \( \text{N}_2 \) and charged with 3-S2 (1.02 g, 4.4 mmol) and methanol (22 mL). A solution of anhydrous hydrochloric acid (4.4 mL, 17.7 mmol, 4 M in dioxane) was added and the mixture was stirred at rt for 1 h, at which time TLC analysis indicated that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and CH\(_2\)Cl\(_2\) (10 mL), basified with NH\(_2\)OH to pH > 12, and transferred to a separatory funnel. The layers were
separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in THF (44 mL, 0.1 M), solid di-tert-butyl dicarbonate (1.2 g, 5.3 mmol) was added and the reaction mixture was stirred at rt for 3 h. 1 M NaOH (5 mL) was added and the resulting biphasic mixture was stirred for 1 h at rt. The mixture was transferred to a separatory funnel, 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. The crude material was purified by flash chromatography on silica gel to afford 941 mg (94%) of the title compound as a clear colorless oil. The spectroscopic properties of this compound were identical to that of compound (±)-3-6 described above.

(E,2R,5S)-tert-Butyl 2-allyl-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate [(E,2R,5S)3-7]. A flame-dried Schlenk flask was cooled under a stream of N$_2$ and charged with Pd$_2$(dba)$_3$ (77 mg, 0.084 mmol), tri(2-furyl)phosphine (77 mg, 0.33 mmol) and NaOtBu (802 mg, 8.4 mmol). The flask was purged with N$_2$, then a solution of (R)-3-6 (941 mg, 4.2 mmol) in freshly distilled xylene (21 mL) was added via syringe and the resulting mixture was stirred at rt for 2 min. (E)-(2-bromovinyl)trimethylsilane (1.28 mL, 8.4 mmol) was added and the flask was heated to 140 °C and stirred for 3 h. The mixture was cooled to room temperature and saturated aqueous NH$_4$Cl (10 mL) and ethyl acetate (10 mL) were added. The layers were separated, the organic layer was filtered through a plug of silica gel, and the silica gel was washed with ethyl acetate (20 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 647 g (48%) of the title compound as a dark brown oil. The spectroscopic properties of this compound were identical to that of compound (±)-3-7 described above.
(\textit{E,2R,5S})-2-\textit{Allyl}-\textit{N}(4-\textit{chlorophenyl})-5-[3-(\textit{trimethylsilyl})\textit{allyl}]\textit{pyrrolidine}-1-\textit{carboxamide} (3-S3). A round-bottom flask equipped with a stirbar was charged with (\textit{E,2R,5S})-3-7 (647 mg, 2.0 mmol) and dichloromethane (20 mL, 0.1 M). Trifluoroacetic acid (2.0 mL, 1.0 M) was added to the flask and the mixture was stirred for 20 min at rt. The solution was diluted with water, basified with NH\textsubscript{4}OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated \textit{in vacuo}. The crude product was dissolved in dichloromethane (20 mL, 0.1 M) and 4-\textit{chlorophenyl isocyanate} (369 mg, 1.2 equiv) was added. The reaction mixture was stirred at rt for 1 h until starting material had been completely consumed as judged by TLC analysis. The crude reaction mixture was concentrated \textit{in vacuo}, and purified by flash chromatography on silica gel to afford 244 mg (32\%) of the title compound as a orange brown oil. \textit{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \textdelta 7.31 (d, \textit{J} = 9.0 Hz, 2 H), 7.22 (d, \textit{J} = 9.0 Hz, 2 H), 6.41 (s, 1 H), 6.04 (dt, \textit{J} = 7.0, 18.5 Hz, 1 H), 5.93–5.84 (m, 1 H), 5.82 (d, \textit{J} = 18.5 Hz, 1 H), 5.22–5.17 (m, 2 H), 4.02–3.95 (m, 2 H), 2.61–2.52 (m, 2 H), 2.35 (dt, \textit{J} = 7.0, 13.5 Hz, 1 H), 2.24 (dt, \textit{J} = 7.5, 14.0 Hz, 1 H), 2.02–1.96 (m, 2 H), 1.80–1.74 (m, 2 H), 0.05 (s, 9 H).

\includegraphics{image}

\textit{\textit{E,Z,3R,4aR,7S})-2-(4-\textit{Chlorophenyl})-3-(pent-2-en-1-\textit{yl})-7-[3-(\textit{trimethylsilyl})\textit{allyl}]hexahydropyrrolo[1,2-c]pyrimidin-1(2\textit{H})-\textit{one} (3-S4). A flame-dried Schlenk tube was cooled under vacuum and charged with Pd\textsubscript{2}(dba)\textsubscript{3} (3.1 mg, 0.003 mmol),
PCy₃HBF₄ (5.0 mg, 0.014 mmol) and NaOtBu (25 mg, 0.26 mmol). The flask was evacuated and purged with N₂. A solution of 3-S3 (65 mg, 0.17 mmol) in toluene (0.85 mL) was added via syringe and the resulting mixture was stirred at rt for 2 min. (Z)-1-bromobut-1-ene (130 µL, 0.26 mmol, 2.0 M solution in toluene) was added and the tube was heated to 100 °C and stirred until the starting material was completely consumed as judged by TLC analysis (1 h). The mixture was cooled to room temperature and saturated aqueous NH₄Cl (1 mL) and ethyl acetate (1 mL) were added. The layers were separated, the organic layer was filtered through a plug of silica gel, and the silica gel was washed with ethyl acetate (1 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 53 mg (71%) of the title compound as a yellow oil. 

**¹H NMR** (500 MHz, CDCl₃) δ 7.31 (d, J = 9.0 Hz, 2 H), 7.19 (d, J = 9.0 Hz, 2 H), 5.94 (ddd, J = 6.0, 7.5, 18.5 Hz, 1 H), 5.68 (d, J = 18.5 Hz, 1 H), 5.47–5.42 (m, 1 H), 5.12–5.07 (m, 1 H), 4.03 (dt, J = 2.5, 8.5 Hz, 1 H), 3.90 (dt, J = 4.5, 9.5 Hz, 1 H), 3.66 (ddt, J = 2.5, 5.0, 11.5 Hz, 1 H), 2.73 (dd, J = 5.5, 12.5 Hz, 1 H), 2.27–2.16 (m, 4 H), 2.01–1.89 (m, 4 H), 1.84–1.81 (m, 1 H), 1.69–1.61 (m, 2 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.03 (s, 9 H).

(+)-(Z,3R,4aR,7S)-7- Allyl-2-(4-chlorophenyl)-3-(pent-2-en-1-yl) hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (ent-3-5c). A Schlenk tube was charged with 3-S4 (53 mg, 0.12 mmol) and CH₂Cl₂ (1.2 mL). TFA (0.6 mL) was added and the reaction mixture was stirred overnight at 40 °C. The reaction mixture was then cooled to rt, diluted with water (1 mL), and basified with NH₄OH to pH > 12. The reaction mixture was transferred to a separatory funnel and the layers were separated. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel. This procedure afforded 29 mg (67%) of the title compound as a yellow oil: [α]³⁵D +17.7 (c 2.9, CH₂Cl₂). The spectroscopic properties of this compound were identical to that of compound 3-5c.
The enantiopurity was determined to be 10:90 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 0.75 mL/min, \( \lambda \) 190 nm, RT= 13.4 and 17.8 min).
Chapter 4
Stereocontrolled Synthesis of trans-Bicyclic Sulfamides via Pd-Catalyzed Carboamination Reactions

4.1 Introduction

As detailed in chapter 1, polycyclic guanidine natural products comprise a class of marine alkaloids that exhibit remarkable biological properties.1–5 Due to their therapeutic potential,6 these alkaloids have been the subject of a number of elegant syntheses.15,16,20,30,33,35,38 However, these compounds remain challenging synthetic targets due to their structural and stereochemical complexity. Further complicating the synthesis of these compounds is the stereochemical diversity displayed within this particular family of alkaloids. For example, merobatzelladine B features a cis-relationship between the C-6 proton and the C-8 alkyl chain,12,14 where as batzelladine K contains a trans-relationship between these groups (Figure 4.1).70 As such, a general method that allows for the preparation of both stereoisomeric bicyclic cores ("cis" and "trans") from a single intermediate is of tremendous interest. However, despite all of the work that has been directed towards the synthesis of these alkaloids, no single method allows for the highly stereoselective construction of both stereoisomeric cores.20

Figure 4.1 Biologically active tricyclic guanidine natural products.

As described in chapters 2 and 3, bicyclic ureas with the cis-stereochemical configuration (4-1) were synthesized with excellent control of selectivity through the development of Pd-catalyzed carboamination reactions between 2-allylpyrrolidinyl ureas 4-2 and alkenyl bromides (Scheme 4.1).60,88 While this method was the first to provide access to the cis-stereoisomer of the batzelladine alkaloids, this methodology could not be employed for the synthesis of natural
products that feature the trans-core, such as batzelladine K. This limitation is intrinsic to carboamination reactions that proceed via a syn-aminopalladation mechanism because the stereochemical outcome is substrate-controlled.\textsuperscript{40–42}

**Scheme 4.1** Synthesis of bicyclic ureas via syn-aminopalladation.

In contrast to this work, our group recently described the synthesis of cyclic sulfamides and ureas via Pd-catalyzed carboamination reactions that proceed via anti-aminopalladation.\textsuperscript{50} As shown in Scheme 4.2, the nitrogen nucleophile and carbon electrophile are added across opposite faces of the olefin leading to carboamination product 4-3. In light of this work, we speculated that similar reaction conditions might also facilitate the transformation of allylpyrrolidinyl urea 4-4 into bicyclic urea 4-5. It was anticipated an anti-aminopalladation mechanism might lead to a reversal in the stereochemical outcome previously observed and generate bicyclic ureas with the trans-core. Concurrent studies in our laboratory have demonstrated that the selectivity of carboamination reactions involving substrates bearing allylic substituents can be controlled by influencing the aminopalladation mechanistic pathways of the catalytic cycle through choice of catalyst and reaction conditions.\textsuperscript{50} Herein we report our initial findings on the synthesis of bicyclic ureas and sulfamides via Pd-catalyzed carboamination reactions that are believed to proceed via anti-aminopalladation.

**Scheme 4.2** Synthesis of cyclic ureas via anti-aminopalladation.

### 4.2 Optimization of Reaction Conditions

We initially elected to examine the Pd-catalyzed carboamination between 2-allylpyrrolidinyl urea 4-6 and phenyl triflate using the optimized anti-aminopalladation conditions described for the synthesis of cyclic ureas (Scheme 4.3). Gratifyingly, the desired product 4-7 was generated in
excellent yield (92%) and with the desired reversal in selectivity (2:1 dr \textit{trans}: \textit{cis}). However, efforts to improve the selectivity of the transformation through the use of other protecting groups, ligands, solvents, and reaction temperatures were largely ineffective. However, it should be noted that employing the ligand Trixiephos did lead to some improvement in diastereoselectivity (2.6:1 dr) without compromising the chemical yield of the reaction (91% NMR yield).

We postulated that two factors might be the cause of the modest diastereoselectivity observed for the cross coupling of 4-6 and phenyl triflate: (1) the rates of \textit{syn}- and \textit{anti}-aminopalladation are comparable; and/or (2) the transition states/intermediates leading to the two possible stereoisomers are energetically similar. Both factors can be heavily influenced by the structural and electronic nature of the substrate. Numerous publications, including the Wolfe group’s original report on \textit{anti}-aminopalladation,\textsuperscript{50} have demonstrated that slight changes to the substrate can dramatically influence the mechanism of aminopalladation reactions and in turn, the ratio of products resulting from \textit{syn}- or \textit{anti}-addition.\textsuperscript{90,91} We reasoned that employing a less nucleophilic substrate might favor \textit{anti}-aminopalladation by decreasing the likelihood that the substrate would form the Pd-N bond required to undergo \textit{syn}-migratory insertion. Additionally, we expected that changing the hybridization of the substrate would influence the stereodetermining transition states/intermediates leading to the two possible stereoisomers and consequently the selectivity of the desired transformation could be potentially improved.

In an effort to test the hypothesis outlined above, 2-allylpyrrolidinyl sulfamide substrate 4-8a was synthesized and subjected to various catalysts (Table 4.1). The coupling of PMP-protected sulfamide 4-8a and phenyl triflate under the previously optimized conditions led to an improvement in selectivity (6:1 dr \textit{trans}: \textit{cis}). Unfortunately, several of the ligands screened led to low formation of desired product 4-9a and generated significant amounts of side products resulting from Heck-arylation of the alkene (4-10) and/or \(\beta\)-hydride elimination (4-11). CPhos provided the best results but side products 4-10 and 4-11 were still formed in substantial
quantities (entry 5). Moreover, the coupling of 4-8a with phenyl triflate proved to be highly variable, making it difficult to obtain consistently high and reproducible yields. After some experimentation, it was discovered that changing the solvent from benzo trifluoride to tert-butanol led to significantly improved and reproducible yields, and just as importantly, side products 4-10 and 4-11 were generated in only trace amounts (entry 6). 87,92–94

Table 4.1 Ligand screen and solvent optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ligand</th>
<th>NMR Yield (isolated)</th>
<th>NMR Yield 4-10</th>
<th>NMR Yield 4-11</th>
<th>dr (trans:cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCF₃</td>
<td>RuPhos</td>
<td>50</td>
<td>5</td>
<td>&lt;5</td>
<td>6:1</td>
</tr>
<tr>
<td>2</td>
<td>PhCF₃</td>
<td>DavePhos</td>
<td>30</td>
<td>10</td>
<td>&lt;5</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>PhCF₃</td>
<td>BrettPhos</td>
<td>40</td>
<td>&lt;5</td>
<td>30</td>
<td>6:1</td>
</tr>
<tr>
<td>4</td>
<td>PhCF₃</td>
<td>tBuXPhos</td>
<td>30</td>
<td>5</td>
<td>40</td>
<td>6:1</td>
</tr>
<tr>
<td>5</td>
<td>PhCF₃</td>
<td>CPhos</td>
<td>80</td>
<td>5</td>
<td>10</td>
<td>6:1</td>
</tr>
<tr>
<td>6</td>
<td>tBuOH[ b]</td>
<td>CPhos</td>
<td>90 (72)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>7:1</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: 1.0 equiv 4-8a, 2.0 equiv Ph-OTf, 2.0 equiv LiO-tBu, 4 mol % Pd(OAc)₂, 10 mol % ligand, solvent (0.1 M), 100 °C. [b] Reaction was conducted at 82 °C.

In light of the work described in chapter 3, in which the protecting group on the cyclizing nitrogen significantly influenced the selectivity of the carboamination reactions, 79,88 several different N-protected sulfamide substrates 4-8 were prepared. As shown in Table 4.2, the coupling of substrates 4-8 with phenyl triflate was explored using the optimized catalyst system and reaction conditions. Substrate 4-8b bearing a p-chlorophenyl N-aryl group underwent the desired transformation in comparable yield and selectivity to that of substrate 4-9a (entry 2). Disappointingly, N-Benzyl and N-PMB protected substrates were converted to products 4-9c and 4-9d respectively, with significantly lower selectivities than 4-9a or 4-9b (entries 3 and 4).
Table 4.2 N-Protecting group effects.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>PG</th>
<th>Product</th>
<th>Yield (%)[b]</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-8a</td>
<td>PMP</td>
<td>4-9a</td>
<td>72</td>
<td>7:1</td>
</tr>
<tr>
<td>2</td>
<td>4-8b</td>
<td>p-Cl-C₆H₄</td>
<td>4-9b</td>
<td>58</td>
<td>7:1</td>
</tr>
<tr>
<td>3</td>
<td>4-8c</td>
<td>Bn</td>
<td>4-9c</td>
<td>86[c]</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>4-8d</td>
<td>PMB</td>
<td>4-9d</td>
<td>82[c]</td>
<td>3:1</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: 1.0 equiv 4-8, 2.0 equiv Ph-OTf, 2.0 equiv LiOrBu, 4 mol % Pd(OAc)₂, 10 mol % C-Phos, tBuOH (0.1 M), 82 °C. [b] Isolated yield. [c] Reaction was conducted in PhCF₃ at 100 °C.

4.3 Synthesis of Bicyclic Sulfamides via Pd-Catalyzed Carboamination Reactions

After exploring the impact of catalyst structure and protecting group on the reaction outcome, the scope of the Pd-catalyzed carboamination reactions was examined by coupling N-PMP-protected pyrrolidinyl sulfamide substrates 4-8a and 4-8e with a variety of different aryl triflates (Table 4.3). Aryl triflates bearing either electron-donating or electron-withdrawing groups afforded bicyclic sulfamide products 4-9 in good yields and selectivities (entries 2–4 and 8). Additionally, the reaction of an ortho-substituted aryl triflate also proceeded in good yield and with similar diastereoselectivity (entry 5). 1-Cyclohexenyl triflate also proved to be a viable substrate, providing the desired bicyclic product in good yield (entry 6). Improved selectivities were observed for the cross-coupling reactions involving PMP-protected meso-2,5-diallylpyrrolidinyl sulfamide substrate 4-8e (entries 7 and 8), although shorter reaction times were required to minimize undesired isomerization of the remaining terminal olefin. In most cases the Pd-catalyzed carboamination reactions did not lead to significant amounts of undesired side products, however Heck arylation (4-10) and β-hydride elimination (4-11) side products were observed occasionally. In contrast, when benzotrifluoride was employed as the solvent, substantial quantities of 4-10 and 4-11 were generated. For example, when the carboamination reaction of 4-8e and phenyl triflate was conducted in benzotrifluoride, the yield of the desired product (4-9j) was modest (57%) and was not separable from β-hydride elimination side products 4-11 (~25%) via flash chromatography.
Table 4.3 Synthesis of 5-6 trans-bicyclic sulfamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr (crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-8a</td>
<td>H</td>
<td>Ph</td>
<td>4-9a</td>
<td>72</td>
<td>7:1</td>
</tr>
<tr>
<td>2</td>
<td>4-8a</td>
<td>H</td>
<td>p-tBu-C₆H₄</td>
<td>4-9e</td>
<td>72</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>4-8a</td>
<td>H</td>
<td>p-MeO-C₆H₄</td>
<td>4-9f</td>
<td>65</td>
<td>7:1 (6:1)</td>
</tr>
<tr>
<td>4</td>
<td>4-8a</td>
<td>H</td>
<td>benzoylphenyl</td>
<td>4-9g</td>
<td>65</td>
<td>8:1 (5:1)</td>
</tr>
<tr>
<td>5</td>
<td>4-8a</td>
<td>H</td>
<td>o-Me-C₆H₄</td>
<td>4-9h</td>
<td>84</td>
<td>5:1</td>
</tr>
<tr>
<td>6</td>
<td>4-8a</td>
<td>H</td>
<td>cyclohexenyl</td>
<td>4-9i</td>
<td>73[c]</td>
<td>6:1</td>
</tr>
<tr>
<td>7</td>
<td>4-8e</td>
<td>allyl</td>
<td>Ph</td>
<td>4-9j</td>
<td>62[d]</td>
<td>20:1 (12:1)</td>
</tr>
<tr>
<td>8</td>
<td>4-8e</td>
<td>allyl</td>
<td>p-MeO-C₆H₄</td>
<td>4-9k</td>
<td>64[d]</td>
<td>&gt;20:1 (&gt;10:1)</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: 1.0 equiv 4-8a or 4-8e, 2.0 equiv R-OTf, 2.0 equiv LiOtBu, 4 mol % Pd(OAc)₂, 10 mol % C-Phos, tBuOH (0.1 M), 82 °C, 16 h. [b] Isolated yield. [c] Reaction was conducted with 3.0 equiv of LiOtBu and 3.0 equiv R-OTf. [d] Reaction time was 2 h.

Inspired by tetraponerine alkaloids T-4 and T-8,⁹⁵ which feature a trans-6-6 fused bicyclic ring system, 2-allylpiperidinyl sulfamide substrate 4-12 was prepared and subjected to the optimized reaction conditions with tert-butanol as the solvent (Scheme 4.4). As expected, the coupling of 4-12 and phenyl triflate proceeded in good chemical yield (84%) and with good stereocontrol (5:1 dr). Future work in the group is focused on exploring the scope of this transformation and its application to the total synthesis of tetraponerines T-4 and T-8.

Scheme 4.4 Synthesis of 6-6 bicyclic sulfamides.

Having successfully developed reaction conditions that afford trans-bicyclic sulfamides via an achiral Pd-catalyst, efforts to render the reactions asymmetric were undertaken. The successful development of an asymmetric desymmetrization reaction of meso-2,5-diallylpyrroldinyl sulfamides would provide bicyclic compounds that could potentially serve as
an intermediate in the asymmetric synthesis of batzelladine K, or analogs thereof, in as few as ten steps (Nagasawa accomplished the only asymmetric synthesis of the alkaloid in 18 steps). The previously prepared sulfamide substrate 4-8e was subjected to a variety of chiral Pd-catalysts for the coupling with phenyl triflate (Table 4.4). Unfortunately, not a single catalyst system that was screened led to formation of desired product 4-9j. Despite the lack of success involving the initial screen of chiral ligands, further studies in this area are warranted given the excellent stereocontrol observed for the formation of 4-9j using a racemic catalyst and the potential utility of this reaction in total synthesis.

Table 4.4 Asymmetric desymmetrization of meso-2,5-diallylpyrroldinyl sulfamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ligand</th>
<th>Conversion[b]</th>
<th>Major Product</th>
<th>Yield (%)</th>
<th>dr (crude)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCF₃</td>
<td>(S)-Siphos-PE</td>
<td>&lt;10</td>
<td>–</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>tBuOH</td>
<td>(S)-Siphos-PE</td>
<td>&lt;10</td>
<td>–</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>PhCF₃</td>
<td>(R)-Siphos-PE</td>
<td>&lt;10</td>
<td>–</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>tBuOH</td>
<td>(R)-Siphos-PE</td>
<td>&lt;10</td>
<td>–</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>tBuOH</td>
<td>(R)-MOP</td>
<td>~50</td>
<td>heck</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>tBuOH</td>
<td>(R)-SDP</td>
<td>~75</td>
<td>heck</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>tBuOH</td>
<td>(S)-NMDPP</td>
<td>&lt;10</td>
<td>–</td>
<td>ND</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: 1.0 equiv 4-8e, 2.0 equiv Ph-OTf, 2.0 equiv LiOttBu, 4 mol % Pd(OAc)$_2$, 10 mol % Ligand, PhCF$_3$ (0.1 M) at 100 °C or tBuOH (0.1 M) at 82 °C. [b] Conversion = percentage of starting material 4-8e consumed.
4.4 Plausible Mechanism and Stereochemical Rationale

The mechanism of the Pd-catalyzed reactions described in this chapter for the formation of bicyclic sulfamides likely proceeds as depicted in Scheme 4.5. The catalytic cycle is initiated by oxidative addition of the aryl triflate to palladium (0). The non-coordinating nature of the triflate counterion likely leads to cationic palladium complex 4-14. Activation of the olefin through coordination of the Pd-catalyst leads to outer-sphere nucleophilic attack of the sulfamide group onto the alkene, resulting in anti-aminopalladation. Reductive elimination from Pd-alkyl intermediate 4-15 affords the desired sulfamide product (4-9) and regenerates the palladium catalyst.

Scheme 4.5 Plausible catalytic cycle.

The stereochemical outcome of the Pd-catalyzed reactions for the synthesis of trans-bicyclic sulfamides is particularly interesting given the work described in chapters 2 and 3 of this thesis. Despite seemingly minor changes to the substrate, catalyst and reaction conditions, the stereoselectivity of the reaction is dramatically altered, reversing a preference for the cis-stereoisomer (drs as high as 20:1) to form the trans-bicycle as the major product with good levels of stereocontrol (up to 12:1 crude dr). While a change in selectivity was anticipated due to the mechanistic change involving the aminopalladation step of the catalytic cycle, the high
selectivity for the trans-isomer is more surprising given the low selectivity generally observed for transformations involving anti-aminopalladation.\textsuperscript{40,97}

While a number of mechanistic details remain unclear, the stereochemical outcome of the carboamination reactions can be rationalized by taking a closer look at the mechanism and the possible intermediates leading to the two stereoisomeric products (Scheme 4.6). Although the new stereocenter is formed during the aminopalladation step, the stereodetermining step can be either insertion or reductive elimination. For related aminopalladation transformations, it is known that electron-poor $N$-substituents decrease the rate of C-C bond-forming reductive elimination.\textsuperscript{47,48} Furthermore, Stahl has demonstrated that the more electron-deficient the nitrogen nucleophile, the more readily it undergoes $\beta$-amidate elimination (retro-aminopalladation).\textsuperscript{98} Thus, given the electron-deficient nature of the sulfamide group, insertion is likely to be reversible and reductive elimination is most likely the stereodetermining step.

Scheme 4.6 Stereochemical rationale for the synthesis of bicyclic sulfamides.

As mentioned earlier, the diastereoselectivity observed for these transformations is unusually high for reactions proceeding via an anti-aminopalladation mechanism.\textsuperscript{40,97} However, rationalizing the observed stereochemical outcome of the carboamination reactions is not straightforward. One possibility is that the observed selectivity is thermodynamically controlled and arises due to differences in the stability of intermediates 4-16 and 4-17. It appears that there are unfavorable 1,3-diaxial interactions involving Pd-alkyl intermediate 4-17, which is formed following insertion of 4-18, where the olefin occupies a pseudo-axial position. The steric repulsions present in intermediate 4-17 likely forces the equilibrium to favor Pd-alkyl intermediate 4-16, which is generated via aminopalladation of intermediate 4-19. This model appears to be consistent with the observed stereochemical outcome as reductive elimination from
thermodynamically favored intermediate 4-16 leads to the major stereoisomer, whereas reductive elimination from 4-17 generates the minor diastereomer.

Scheme 4.7 Possible boat-like intermediates.

The rationale outlined in Scheme 4.6 deviates substantially from the work described in chapters 2 and 3, in which the stereochemical outcome is likely kinetically controlled and is proposed to arise from differences in boat-like transition states 2-7 and 2-8 (Scheme 2.2).\textsuperscript{80,88} The possibility that these transformations are actually under kinetic control and/or that the selectivity arises from boat-like transition states/intermediates similar to those described in chapters 2 and 3 cannot be ruled out. However, boat-like intermediates 4-20 and 4-21 as depicted in Scheme 4.7, appear to be much higher in energy than the analogous chair-like intermediates 4-16 and 4-17 due to increased ring strain. Moreover, chair-like intermediates, not boat-like intermediates, have been proposed in related anti-aminopalladation reactions for the formation of 6-membered N-containing heterocycles.\textsuperscript{99} Furthermore, this type of model does not seem consistent with the selective formation of trans-bicyclic sulfamides, as the boat-like transition state leading to the observed major isomer appears to suffer from unfavorable steric interactions. In all, these transformations are most likely under thermodynamic control and the observed selectivity for the formation of isomer 4-9-major likely arises from the energy differences between chair-like intermediates 4-16 and 4-17 as depicted in Scheme 4.6. Future work in this area is aimed at better understanding the stereochemical outcome through the computations and exploration of the relative stabilities of the proposed intermediates and final products. A better understanding of the mechanism and origin of the stereoselectivity may facilitate the further optimization of these transformations and the development of an asymmetric variant of this chemistry.

4.5 Conclusions

In conclusion, we have developed a new method for the synthesis of bicyclic sulfamides via the Pd-catalyzed alkene carboamination of 2-allylpyrrolidinyl sulfamides. The reactions proceed in good yields (58-92%) and with good control of stereoselectivity (up to 12:1 dr). Importantly,
by employing reaction conditions that favor an *anti*-aminopalladation mechanism, the stereochemical outcome of the reactions is reversed relative to the Pd-catalyzed carboamination reactions that proceed via *syn*-aminopalladation. Future studies on the development of an asymmetric variant of this chemistry and application of this chemistry towards the total synthesis polycyclic guanidine alkaloids that feature the *trans*-core such as batzelladine K is warranted.

*Part of the work described in this chapter was carried out by Grace McKenna including the synthesis of 4-12.

4.6 Experimental

**General:** All reactions were carried out under a nitrogen atmosphere unless otherwise noted. Palladium acetate was purchased from Strem Chemical Co. and used without purification. All phosphine ligands were obtained from commercial sources and were used without further purification. All other reagents were obtained from commercial sources and were used as obtained unless otherwise noted. (Z)-1-bromobutene\(^63\) was prepared according to a slight modification of a literature procedure; the preparation was conducted at rt instead of using microwave heating as detailed in chapter 2. *tert*-Butyl 2-allylpyrrolidine-1-carboxylate,\(^{100}\) *tert*-butyl 2-allylpiperidine-1-carboxylate,\(^{100}\) \((\pm)-(E,2R^*,5S^*)-\) *tert*-butyl 2-allyl-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate,\(^{88}\) \(N\)-(4-methoxyphenyl)-2-oxooxazolidine-3-sulfonamide,\(^{50}\) \(N\)-(4-chlorophenyl)-2-oxooxazolidine-3-sulfonamide,\(^{101}\) \(N\)-benzyl-2-oxooxazolidine-3-sulfonamide,\(^{50}\) and \(N\)-(4-methoxybenzyl)-2-oxooxazolidine-3-sulfonamide\(^{50}\) were prepared according to published procedures. Lithium *tert*-butoxide was stored in a glovebox and removed only prior to use. Toluene, THF, diethyl ether and dichloromethane were purified using a GlassContour solvent purification system. Benzo trifluoride was purified by distillation under N\(_2\) prior to use. *tert*-Butanol was used without any purification. Yields refer to isolated yields of compounds estimated to be \(\geq 95\%\) pure as determined by \(^1\)H NMR analysis unless otherwise noted. The yields reported in chapter 4 and the experimental section describe the result of a single experiment. Structural and stereochemical assignments were made on the basis of 2-D COSY, and NOESY experiments. Ratios of diastereomers were determined by \(^1\)H NMR analysis.
Preparation and Characterization of Substrates

(±)-2-Allyl-N-(4-nitrophenyl)pyrrolidine-1-carboxamide (4-6). A round-bottom flask equipped with a stirbar was charged with tert-butyl 2-allylpyrrolidine-1-carboxylate (887 mg, 4.2 mmol) and dichloromethane (21 mL, 0.2 M). Trifluoroacetic acid (4.2 mL, 1.0 M) was added to the flask and the mixture was stirred until the starting material had been completely consumed as judged by TLC analysis (ca. 30 min). The solution was diluted with water, basified with NH₄OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in dichloromethane (21 mL, 0.2 M) and 4-nitrophenyl isocyanate (1.0 g, 6.3 mmol) was added. The reaction mixture was stirred at rt until starting material had been completely consumed as judged by TLC analysis (ca. 1 h). The crude reaction mixture was concentrated in vacuo, and purified by flash chromatography on silica gel. The chromatographed product material was diluted with dichloromethane (35 mL) and washed with 1M HCl (2 x 15 mL) to remove any remaining 4-nitroaniline. This procedure afforded 290 mg (25%) of the title compound as a yellow solid: mp = 104–106 °C. ¹H NMR (700 MHz, CDCl₃) δ 8.15 (d, J = 9.1 Hz, 2 H), 7.58 (d, J = 9.1 Hz, 2 H), 6.64 (s, 1 H), 5.84–5.78 (m, 1 H), 5.17–5.09 (m, 2 H), 4.09 (s, br, 1 H), 3.53–3.46 (m, 2 H), 2.56 (dt, J = 12.4, 5.3 Hz, 1 H), 2.25–2.18 (m, 1 H), 2.09–2.02 (m, 1 H), 2.04–1.94 (m, 2 H), 1.85 (m, 1 H); ¹³C NMR (175 MHz, CDCl₃) δ 152.7, 145.4, 142.3, 134.7, 125.1, 118.0, 117.9, 57.5, 46.5, 38.5, 29.6, 23.7; IR (film) 3314, 1652, 1501, 1329 cm⁻¹. MS (ESI) 276.1344 (276.1343 calcd for C_{14}H_{17}N_{3}O₃, M + H⁺).

General Procedure for the Synthesis of Sulfamide Substrates 4-8 and 4-12.

A round-bottom flask equipped with a stirbar was charged with the appropriate N-Boc-protected amine (1.2 equiv) and dichloromethane (0.2 M). Trifluoroacetic acid (1.0 M) was
added to the flask and the mixture was stirred until the starting material had been completely consumed as judged by TLC analysis (ca. 30 min). The solution was then concentrated in vacuo. Toluene was added and the reaction flask was concentrated in vacuo to remove any excess TFA. The crude amine (TFA salt) was used without any additional purification.

A separate flame dried flask was charged with the appropriate oxazolidinone substrate (1.0 equiv), 4-dimethylaminopyridine (0.2 equiv), and a stirbar, then was evacuated and backfilled with N₂. Acetonitrile was added, followed by Et₃N (3.0 equiv), and then the reaction vessel was placed in an oil bath at 75 °C. The appropriate amine TFA salt (1.2 equiv) as prepared above was added and the resulting mixture was stirred at 75 °C overnight (approximately 16 hours). The mixture was cooled to rt, solvent was removed via rotary evaporation, and the residue was partitioned between CH₂Cl₂ and 3 M HCl. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Solvent was removed in vacuo and the resulting residue was purified by flash chromatography on silica gel.

(±)-2-Allyl-N-(4-methoxyphenyl)pyrrolidine-1-sulfonamide (4-8a). The title compound was prepared from N-(4-methoxyphenyl)-2-oxooxazolidine-3-sulfonamide (825 mg, 4.0 mmol) and tert-butyl 2-allylpyrrolidine-1-carboxylate (1.06 g, 5.0 mmol) in two steps via the general procedure described above. This procedure afforded 808 mg (68%) of the title compound as a pale yellow oil. ¹H NMR (700 MHz, CDCl₃) δ 7.18 (d, J = 9.1 Hz, 2 H), 6.85 (d, J = 9.1 Hz, 2 H), 6.30 (s, br, 1 H), 5.70–5.61 (m, 1 H), 5.05–4.99 (m, 2 H), 3.79 (s, 3 H), 3.79–3.77 (m, 1 H), 3.36–3.27 (m, 2 H), 2.46–2.41 (m, 1 H), 2.12 (dt, J = 13.9, 8.5 Hz, 1 H), 1.86–1.73 (m, 3 H), 1.70–1.66 (m, 1 H); ¹³C NMR (175 MHz, CDCl₃) δ 157.2, 134.5, 130.1, 123.7, 117.5, 114.4, 60.3, 55.5, 49.1, 39.9, 30.1, 24.2; IR (film) 3267, 1327, 1245, 1146 cm⁻¹. MS (ESI) 297.1274 (297.1267 calcd for C₁₄H₂₆N₂O₃S, M + H⁺).
(±)-2-Allyl-N-(4-chlorophenyl)pyrroline-1-sulfonamide (4-8b). The title compound was prepared from N-(4-chlorophenyl)-2-oxooxazolidine-3-sulfonamide (4.1 g, 15.0 mmol) and tert-butyl 2-allylpyrroline-1-carboxylate (3.8 g, 18.0 mmol) in two steps via the general procedure described above. This procedure afforded 1.74 g (39%) of the title compound as a pale yellow solid: mp = 46–49 ºC. ¹H NMR (500 MHz, CDCl₃) δ 7.27 (d, J = 9.0 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H), 7.02 (s, 1 H), 5.71–5.63 (m, 1 H), 5.06–5.02 (m, 2 H), 3.88–3.84 (m, 1 H), 3.40–3.35 (m, 1 H), 3.30–3.25 (m, 1 H), 2.48–2.44 (m, 1 H), 2.19–2.14 (m, 1 H), 1.85–1.70 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 136.0, 134.2, 129.8, 129.4, 121.4, 117.8, 60.4, 49.2, 39.7, 30.2, 24.2; IR (film) 3265, 1490, 1324, 1148 cm⁻¹. MS (ESI) 301.0774 (301.0772 calcd for C₁₃H₁₇ClN₂O₂S, M + H⁺).

(±)-2-Allyl-N-benzylpyrroline-1-sulfonamide (4-8c). The title compound was prepared from N-benzyl-2-oxooxazolidine-3-sulfonamide (2.1 g, 8.3 mmol) and tert-butyl 2-allylpyrroline-1-carboxylate (2.1 g, 10.0 mmol) in two steps via the general procedure described above. This procedure afforded 1.22 g (52%) of the title compound as a pale yellow solid: mp = 38–41 ºC. ¹H NMR (700 MHz, CDCl₃) δ 7.30–7.20 (m, 5 H), 5.72–5.64 (m, 1 H), 5.03–4.96 (m, 2 H), 4.68 (s, br, 1 H), 4.15 (s, 2 H), 3.76 (ddt, J = 9.0, 7.8, 3.9 Hz, 1 H), 3.31–3.24 (m, 1 H), 3.16 (ddd, J = 9.5, 6.6, 4.9 Hz, 1 H), 2.46 (dddt, J = 13.7, 6.8, 4.0, 1.4 Hz, 1 H), 2.18–2.10 (m, 1 H), 1.84–1.69 (m, 3 H), 1.68–1.61 (m, 1 H); ¹³C NMR (175 MHz, CDCl₃) δ 137.0, 134.6, 128.7, 127.9, 127.9, 117.5, 59.6, 49.0, 47.4, 40.1, 30.3, 24.3; IR (film) 3282, 1312, 1143 cm⁻¹. MS (ESI) 281.1325 (281.1318 calcd for C₁₄H₂₀N₂O₂S, M + H⁺).
(±)-2-Allyl-\(N\)-(4-methoxybenzyl)pyrrolidine-1-sulfonamide (4-8d). The title compound was prepared from \(N\)-(4-methoxybenzyl)-2-oxooxazolidine-3-sulfonamide (2.4 g, 8.3 mmol) and tert-butyl 2-allylpyrrolidine-1-carboxylate (2.1 g, 10.0 mmol) in two steps via the general procedure described above. This procedure afforded 1.10 g (43%) of the title compound as a yellow solid: mp = 39–42 °C. \(^{1}\)H NMR (700 MHz, CDCl\(_3\)) δ 7.25 (d, \(J = 9.1\) Hz, 2 H), 6.88 (d, \(J = 8.4\) Hz, 2 H), 5.77 (ddt, \(J = 17.2, 10.2, 7.1\) Hz, 1 H), 5.12–5.04 (m, 2 H), 4.16 (s, 2 H), 3.88–3.79 (m, 1 H), 3.80 (s, 3 H), 3.37 (dt, \(J = 9.9, 7.3\) Hz, 1 H), 3.25 (ddd, \(J = 9.7, 6.7, 5.1\) Hz, 1 H), 2.56–2.53 (m, 1 H), 2.27–2.19 (m, 1 H), 1.95–1.79 (m, 3 H), 1.75–1.69 (m, 1 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) δ 159.3, 134.7, 129.3, 129.0, 117.5, 114.1, 59.6, 55.3, 49.1, 47.0, 40.1, 30.3, 24.3; IR (film) 3289, 1302, 1144 cm\(^{-1}\). MS (ESI) 311.1416 (311.1424 calcd for C\(_{15}\)H\(_{22}\)N\(_2\)O\(_3\)S, M + H\(^+\)).

(2S,5R)-2,5-Diallyl-\(N\)-(4-methoxyphenyl)pyrrolidine-1-sulfonamide (4-8e). The title compound was prepared from \(N\)-(4-methoxyphenyl)-2-oxooxazolidine-3-sulfonamide (1.6 g, 5.9 mmol) and (±)-(\(E,2R^{*},5S^{*}\))-tert-butyl 2-allyl-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate (2.3 g, 7.1 mmol) in two steps via the general procedure described above. This procedure afforded 1.46 g (73%) of the title compound as a off-white solid: mp = 57–60 °C. \(^{1}\)H NMR (700 MHz, CDCl\(_3\)) δ 7.19 (d, \(J = 8.4\) Hz, 2 H), 6.85 (d, \(J = 8.4\) Hz, 2 H), 5.75–5.67 (m, 2 H), 5.07–5.02 (m, 4 H), 3.79 (s, 3 H), 3.79–3.74 (m, 2 H), 2.50 (dt, \(J = 12.0, 5.5\) Hz, 2 H), 2.16 (dt, \(J = 14.8, 8.3\) Hz, 2 H), 1.77–1.71 (m, 2 H), 1.68–1.62 (m, 2 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) δ 157.2, 134.6, 130.0, 123.7, 117.5, 114.4, 61.6, 55.4, 40.4, 29.0; IR (film) 3268, 1508, 1247, 1151 cm\(^{-1}\). MS (ESI) 337.1580 (337.1580 calcd for C\(_{17}\)H\(_{24}\)N\(_2\)O\(_3\)S, M + H\(^+\)).
(±)-2-Allyl-N-(4-methoxyphenyl)piperidine-1-sulfonamide (4-12). The title compound was prepared from N-(4-methoxyphenyl)-2-oxooxazolidine-3-sulfonamide (1.6 g, 6.0 mmol) and tert-butyl 2-allylpiperidine-1-carboxylate (1.6 g, 7.2 mmol) in two steps via the general procedure described above with one change. Instead of employing 2-allyl piperidine as the TFA salt, it was basified with NH₄OH and used as the free base. This procedure afforded 521 mg (28%) of the title compound as a yellow oil. ¹H NMR (700 MHz, CDCl₃) δ 7.11 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.16 (s, 1 H), 5.68 (ddt, J = 17.2, 10.1, 7.1 Hz, 1 H), 5.09–5.01 (m, 2 H), 3.97–3.93 (m, 1 H), 3.79 (s, 3 H), 3.63–3.58 (m, 1 H), 2.99 (td, J = 13.3, 2.8 Hz, 1 H), 2.42–2.31 (m, 2 H), 1.61–1.39 (m, 5 H), 1.35–1.23 (m, 1 H); ¹³C NMR (175 MHz, CDCl₃) δ 157.1, 135.0, 130.1, 123.3, 117.3, 114.4, 55.5, 55.3, 41.4, 34.1, 26.7, 24.8, 18.0; IR (film) 3272, 1509, 1246, 1142 cm⁻¹. MS (ESI) 311.1422 (311.1424 calcd for C₁₅H₂₂N₂O₃S, M + H⁺).

Preparation and Characterization of Bicyclic Products

General Procedure for Synthesis of Bicyclic Ureas and Sulfamides

General Procedure A (for reactions run in benzotrifluoride): A test tube was charged with Pd(OAc)₂ (0.04 equiv), a phosphine ligand (0.1 equiv), and LiOrBu (2.0 equiv). The test tube was purged with N₂ then the appropriate aryl triflate (2.0 equiv) was added, followed by the appropriate substrate (1.0 equiv) in benzotrifluoride (0.2 M). The tube was heated to 100 ºC and stirred overnight or until the starting material was completely consumed as judged by TLC or ¹H NMR analysis. The mixture was cooled to room temperature and saturated aqueous NH₄Cl (5 mL/mmol substrate) and dichloromethane (5 mL/mmol substrate) were added. The layers were separated and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

General Procedure B (for reactions run in tert-butanol): A test tube was charged with Pd(OAc)₂ (0.04 equiv), a phosphine ligand (0.1 equiv), and LiOrBu (2.0 equiv). The test tube was
purged with N₂ then the appropriate aryl triflate (2.0 equiv) was added, followed by the appropriate substrate (1.0 equiv) in tert-butanol (0.2 M). The tube was heated to 82 °C and stirred overnight or until the starting material was completely consumed as judged by TLC or ¹H NMR analysis. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

\[(\pm)-3S*,4aR*)-3-Benzyl-2-(4-nitrophenyl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (4-7).\] General procedure A was employed for the coupling of 4-6 (55 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)₂ (1.8 mg, 0.008 mmol), and RuPhos (9.3 mg, 0.02 mmol). This procedure afforded 66 mg (94%) of the title compound as a yellow solid and as a 2:1 mixture of diastereomers as determined by ¹H NMR analysis: mp = 51–55 °C. Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 8.26 (d, J = 9.1 Hz, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.29–7.23 (m, 3 H), 7.04 (d, J = 7.0 Hz, 2 H), 4.14 (tt, J = 10.6, 3.9 Hz, 1 H), 3.58–3.47 (m, 3 H), 2.85 (dd, J = 13.5, 3.8 Hz, 1 H), 2.32 (dd, J = 13.4, 10.1 Hz, 1 H), 2.26–1.46 (m, 6 H); ¹³C NMR (175 MHz, CDCl₃) δ 153.5, 147.5, 145.2, 137.0, 129.0, 128.7, 128.6, 126.7, 124.0, 58.2, 54.7, 46.0, 41.6, 35.0, 33.5, 23.0; IR (film) 1639, 1515, 1339 cm⁻¹. MS (ESI) 352.1656 (352.1656 calcd for C₂₀H₂₁N₃O₃, M + H⁺).

\[(\pm)-3S*,4aR*)-3-Benzyl-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9a).\] General procedure B was employed for the coupling of 4-8a (59 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)₂ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 54
mg (72%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 45–48 °C. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.39 (d, $J$ = 8.4 Hz, 2 H), 7.29–7.20 (m, 3 H), 7.06 (d, $J$ = 7.7 Hz, 2 H), 6.91 (d, $J$ = 9.1 Hz, 2 H), 4.26–4.19 (m, 1 H), 3.80 (s, 3 H), 3.53 (td, $J$ = 9.5, 5.7 Hz, 1 H), 3.38 (td, $J$ = 9.5, 5.8 Hz, 1 H), 2.81 (dd, $J$ = 13.6, 4.4 Hz, 1 H), 2.21–2.08 (m, 2 H), 2.07–1.91 (m, 3 H), 1.68–1.53 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 159.4, 137.4, 130.9, 130.4, 129.1, 128.6, 126.6, 114.3, 61.8, 60.2, 55.4, 46.5, 40.4, 32.6, 31.3, 21.3; IR (film) 1506, 1337, 1248, 1158 cm$^{-1}$. MS (ESI) 373.1589 (373.1580 calcd for C$_{20}$H$_{24}$N$_2$O$_3$S, M + H$^+$).

(±)-(3$^S$,4$^a$R$^*$)-3-Benzyl-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9b). General procedure B was employed for the coupling of 4-8b (60 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 44 mg (58%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 50–53 °C. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.41 (d, $J$ = 9.1 Hz, 2 H), 7.37 (d, $J$ = 8.4 Hz, 2 H), 7.29–7.22 (m, 3 H), 7.05 (d, $J$ = 7.7 Hz, 2 H), 4.25 (m, 1 H), 3.81 (ddt, $J$ = 11.2, 6.6, 4.2 Hz, 1 H), 3.53 (td, $J$ = 9.5, 5.8 Hz, 1 H), 3.43–3.35 (m, 1 H), 2.78 (dd, $J$ = 13.6, 4.5 Hz, 1 H), 2.21 (dd, $J$ = 13.3, 9.8 Hz, 1 H), 2.18–2.10 (m, 1 H), 2.08–1.87 (m, 2 H), 1.69–1.52 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 136.9, 136.6, 134.3, 131.2, 129.4, 129.0, 128.6, 126.8, 61.8, 60.2, 46.6, 40.4, 32.6, 31.3, 21.4; IR (film) 1486, 1338, 1159 cm$^{-1}$. MS (ESI) 377.1089 (377.1085 calcd for C$_{19}$H$_{21}$ClN$_2$O$_3$S, M + H$^+$).
(±)-(3S*,4aR*)-2,3-Dibenzylhexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9c). General procedure A was employed for the coupling of 4-8c (56 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 61 mg (86%) of the title compound as a white solid and as a 3:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 113–116 °C. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.42 (d, $J = 7.0$ Hz, 2 H), 7.34–7.18 (m, 6 H), 7.07 (d, $J = 7.0$ Hz, 2 H), 4.59 (d, $J = 16.2$ Hz, 1 H), 4.15 (d, $J = 16.1$ Hz, 1 H), 4.15–4.09 (m, 1 H), 3.48 (m, 1 H), 3.26 (m, 2 H), 2.92 (dd, $J = 13.4, 4.6$ Hz, 1 H), 2.54 (dd, $J = 13.4, 10.5$ Hz, 1 H), 2.07–2.01 (m, 1 H), 1.98–1.90 (m, 1 H), 1.82 (m, 1 H), 1.71–1.49 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 138.5, 137.4, 129.2, 128.5, 127.7, 127.2, 126.7, 61.6, 60.8, 49.6, 45.8, 40.6, 31.6, 30.7, 21.1; IR (film) 1333, 1155 cm$^{-1}$. MS (ESI) 357.1632 (357.1631 calcd for C$_{20}$H$_{24}$N$_2$O$_2$S, M + H$^+$).

(±)-(3S*,4aR*)-3-Benzyl-2-(4-methoxybenzyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9d). General procedure A was employed for the coupling of 4-8d (62 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 63 mg (82%) of the title compound as a red-brown oil and as a 3:1 mixture of diastereomers as determined by $^1$H NMR analysis. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.32 (d, $J = 8.4$ Hz, 2 H), 7.26–7.15 (m, 3 H), 7.08 (d, $J = 7.0$ Hz, 2 H), 6.85 (d, $J = 8.4$ Hz, 2 H), 4.51 (d, $J = 15.9$ Hz, 1 H), 4.08 (d, $J = 16.1$ Hz, 1 H), 4.11–4.03 (m, 1 H), 3.80 (s, 3 H), 3.48–3.42 (m, 1 H), 3.27–3.21 (m, 2 H), 2.92 (dd, $J = 13.3, 4.9$ Hz, 1 H), 2.55 (dd, $J = 13.4, 10.3$ Hz, 1 H), 2.06–1.98 (m, 1 H), 1.96–1.85 (m, 1 H), 1.82–1.76 (m, 1 H), 1.70–1.46 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 158.8, 137.5, 130.4, 129.1, 129.1, 128.5, 126.6, 113.7, 61.3, 60.7, 55.2, 49.3, 45.9, 40.7, 31.6, 30.9, 21.3; IR (film) 1332, 1245, 1155 cm$^{-1}$. MS (ESI) 387.1725 (387.1737 calcd for C$_{21}$H$_{26}$N$_2$O$_3$S, M + H$^+$).
(±)-(3S*,4aR*)-3-[4-(tert-Butyl)benzyl]-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9e). General procedure B was employed for the coupling of 4-8a (59 mg, 0.2 mmol) and 4-(tert-butyl)phenyl triflate (113 mg, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 62 mg (72%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 61–63 °C. Data are for the major isomer.

$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.39 (d, $J$ = 9.1 Hz, 2 H), 7.27 (d, $J$ = 7.7 Hz, 2 H), 6.98 (d, $J$ = 8.4 Hz, 2 H), 6.90 (d, $J$ = 9.1 Hz, 2 H), 4.25–4.19 (m, 1 H), 3.81 (s, 3 H), 3.80–3.76 (m, 1 H), 3.54–3.49 (m, 1 H), 3.41–3.34 (m, 1 H), 2.77 (dd, $J$ = 13.7, 4.3 Hz, 1 H), 2.14–2.09 (m, 2 H), 2.07–1.87 (m, 2 H), 1.70–1.52 (m, 3 H), 1.29 (s, 9 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 159.4, 149.5, 134.2, 130.9, 130.4, 128.7, 125.4, 114.3, 61.8, 60.2, 55.4, 46.5, 39.9, 37.4, 34.4, 32.6, 31.3, 21.3; IR (film) 1506, 1338, 1247, 1158 cm$^{-1}$. MS (ESI) 429.2215 (429.2215 calcd for C$_{24}$H$_{32}$N$_2$O$_3$S, M + H$^+$).

(±)-(3S*,4aR*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9f). General procedure B was employed for the coupling of 4-8a (59 mg, 0.2 mmol) and 4-methoxyphenyl triflate (72 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 52 mg (65%) of the title compound as a white solid and as a 7:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 48–51 °C. Data are for the major isomer.

$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.38 (d, $J$ = 8.4 Hz, 2 H), 6.97 (d, $J$ = 8.4 Hz, 2 H), 6.91 (d, $J$ = 9.1 Hz, 2 H), 6.80 (d, $J$ = 8.4 Hz, 2 H), 4.20–4.14 (m, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.80–3.73 (m, 1 H), 3.56–3.46 (m, 1 H), 3.37 (td, $J$ = 9.4, 5.7 Hz, 1 H), 2.74 (dd, $J$ = 13.7, 4.4 Hz, 1 H), 2.15–2.08 (m, 2 H), 2.04–1.91 (m, 2 H), 1.64–1.50 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$
(±)-(3S*,4aR*)-(4-[[2-(4-Methoxyphenyl)-1,1-dioxido-2H-pyrrolo[1,2-b][1,2,6]thiadiazin-3-yl]methyl]phenyl)(phenyl)methanone (4-9g). General procedure B was employed for the coupling of 4-8a (59 mg, 0.2 mmol) and 4-benzoylephenyl triflate (132 mg, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The diastereoselectivity of the reaction was judged to be 5:1 dr as determined by $^1$H NMR analysis prior to flash chromatography. This procedure afforded 62 mg (65%) of the title compound as a white solid and as a 8:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 58–61 °C. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.78 (d, $J$ = 7.7 Hz, 2 H), 7.72 (d, $J$ = 8.4 Hz, 2 H), 7.59 (t, $J$ = 7.5 Hz, 1 H), 7.49 (t, $J$ = 7.6 Hz, 2 H), 7.38 (d, $J$ = 8.8 Hz, 2 H), 7.18 (d, $J$ = 7.9 Hz, 2 H), 6.91 (d, $J$ = 8.7 Hz, 2 H), 4.33–4.28 (m, 1 H), 3.79 (s, 3 H), 3.54 (td, $J$ = 9.4, 5.7 Hz, 1 H), 3.39 (td, $J$ = 9.3, 5.8 Hz, 1 H), 2.87 (dd, $J$ = 13.7, 4.8 Hz, 1 H), 2.33 (dd, $J$ = 13.7, 9.8 Hz, 1 H), 2.19–2.12 (m, 1 H), 2.01–1.95 (m, 2 H), 1.68–1.62 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 196.2, 159.5, 142.4, 137.5, 136.1, 132.5, 130.9, 130.4, 130.2, 130.0, 129.0, 128.3, 114.4, 61.5, 60.1, 55.4, 46.5, 40.4, 32.9, 31.4, 21.3; IR (film) 1654, 1605, 1506, 1339, 1278, 1249, 1157 cm$^{-1}$. MS (ESI) 477.1847 (477.1843 calcd for C$_{27}$H$_{28}$N$_2$O$_4$S, M + H$^+$).

(±)-(3S*,4aR*)-(2-(4-Methoxyphenyl)-3-(2-methylbenzyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9h). General procedure B was employed for the coupling of 4-8a (59 mg, 0.2 mmol) and 2-tolyl triflate (96 mg, 0.4 mmol), using a catalyst composed of
Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 65 mg (84%) of the title compound as a white solid and as a 5:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 39–43 ºC. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.41 (d, $J$ = 9.1 Hz, 2 H), 7.12–7.10 (m, 3 H), 7.05–7.02 (m, 1 H), 6.91 (d, $J$ = 9.1 Hz, 2 H), 4.24–4.17 (m, 1 H), 3.82 (s, 3 H), 3.81–3.74 (m, 1 H), 3.55 (td, $J$ = 9.4, 5.7 Hz, 1 H), 3.43–3.36 (m, 1 H), 2.75 (dd, $J$ = 13.8, 4.4 Hz, 1 H), 2.22 (dd, $J$ = 13.8, 10.5 Hz, 1 H), 2.18 (s, 3 H), 2.13 (ddt, $J$ = 12.6, 9.6, 6.5 Hz, 1 H), 2.09–1.95 (m, 2 H), 1.67–1.60 (m, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 159.4, 136.3, 135.5, 130.9, 130.5, 130.4, 130.1, 126.8, 125.9, 114.3, 60.4, 60.2, 55.4, 46.5, 37.9, 32.7, 31.3, 21.3, 19.6; IR (film) 1506, 1338, 1248, 1157 cm$^{-1}$. MS (ESI) 387.1745 (387.1737 calcd for C$_{21}$H$_{26}$N$_2$O$_3$S, M + H$^+$).

(±)-(3S*,4aR*)-3-(Cyclohex-1-en-1-ylmethyl)-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9i). A slight modification to general procedure B was employed for the coupling of 4-8a (59 mg, 0.2 mmol) and 1-cyclohexenyl triflate (63 µL, 0.6 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol) by adding more of the alkenyl triflate (3.0 equiv) and LiOtBu (48 mg, 0.6 mmol, 3.0 equiv) to the reaction. This procedure afforded 55 mg (73%) of the title compound as a pale yellow oil and as a 6:1 mixture of diastereomers as determined by $^1$H NMR analysis. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.32 (d, $J$ = 8.4 Hz, 2 H), 6.87 (d, $J$ = 9.1 Hz, 2 H), 5.33 (s, 1 H), 4.13–4.07 (m, 1 H), 3.87–3.82 (m, 1 H), 3.79 (m, 3 H), 3.51 (td, $J$ = 9.4, 5.6 Hz, 1 H), 3.36 (td, $J$ = 9.4, 5.8 Hz, 1 H), 2.20 (ddt, $J$ = 12.7, 9.7, 6.5 Hz, 1 H), 2.08–1.42 (m, 15 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 159.2, 133.1, 131.0, 130.4, 124.9, 114.0, 60.4, 58.5, 55.4, 46.4, 42.8, 33.0, 31.4, 28.2, 25.2, 22.8, 22.2, 21.3; IR (film) 1506, 1337, 1248, 1156 cm$^{-1}$. MS (ESI) 377.1903 (377.1893 calcd for C$_{20}$H$_{26}$N$_2$O$_3$S, M + H$^+$).
General procedure B was employed for the coupling of 4-8e (67 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The diastereoselectivity of the reaction was judged to be 12:1 dr as determined by $^1$H NMR analysis prior to flash chromatography. This procedure afforded 51 mg (62%) of the title compound as a pale yellow oil and as a 20:1 mixture of diastereomers as determined by $^1$H NMR analysis. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.40 (d, $J = 8.4$ Hz, 2 H), 7.26–7.19 (m, 3 H), 7.09 (d, $J = 7.0$ Hz, 2 H), 6.88 (d, $J = 9.1$ Hz, 2 H), 5.78 (ddt, $J = 15.8$, 11.2, 7.1 Hz, 1 H), 5.10–5.04 (m, 2 H), 4.41 (tdd, $J = 9.9$, 5.3, 2.6 Hz, 1 H), 3.82 (s, 3 H), 3.77–3.72 (m, 1 H), 3.44 (tdd, $J = 11.3$, 5.0, 3.0 Hz, 1 H), 2.82 (dd, $J = 13.8$, 5.3 Hz, 1 H), 2.64–2.58 (m, 1 H), 2.37 (dt, $J = 14.0$, 7.8 Hz, 1 H), 2.11 (dd, $J = 13.8$, 10.0 Hz, 1 H), 2.01–1.94 (m, 1 H), 1.90 (ddt, $J = 13.0$, 10.2, 8.9 Hz, 1 H), 1.78–1.68 (m, 2 H), 1.68–1.53 (m, 2 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 159.4, 137.3, 134.4, 131.4, 130.5, 129.1, 128.5, 126.7, 117.7, 114.0, 62.8, 61.7, 57.8, 55.4, 40.0, 39.8, 32.9, 30.5, 26.8; IR (film) 1506, 1344, 1249, 1155 cm$^{-1}$. MS (ESI) 413.1895 (413.1893 calcd for C$_{23}$H$_{28}$N$_2$O$_3$S, M + H$^+$).

(±)-(3$S^*$,4a$R^*$,7$S^*$)-7-Allyl-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-9k). General procedure B was employed for the coupling of 4-8e (67 mg, 0.2 mmol) and 4-methoxyphenyl triflate (72 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). The diastereoselectivity of the reaction was judged to be >10:1 dr as determined by $^1$H NMR analysis prior to flash chromatography. This procedure afforded 57 mg (64%) of the title compound as a
white solid and as a >20:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 44–46 °C. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.39 (d, $J = 8.6$ Hz, 2 H), 7.00 (d, $J = 8.6$ Hz, 2 H), 6.88 (d, $J = 9.1$ Hz, 2 H), 6.81 (d, $J = 8.4$ Hz, 2 H), 5.82–7.73 (m, 1 H), 5.10–5.04 (m, 2 H), 4.39–4.35 (m, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.77–3.72 (m, 1 H), 3.46–3.39 (m, 1 H), 2.76 (dd, $J = 13.9$, 5.3 Hz, 1 H), 2.61 (dd, $J = 14.4$, 6.0 Hz, 1 H), 2.37 (dt, $J = 15.0$, 7.9 Hz, 1 H), 2.04 (dd, $J = 13.9$, 10.0 Hz, 1 H), 2.01–1.88 (m, 2 H), 1.78–1.68 (m, 2 H), 1.62–1.53 (m, 2 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 159.5, 158.4, 134.4, 131.5, 130.6, 130.0, 129.3, 117.7, 114.0, 113.9, 62.9, 61.9, 57.9, 55.4, 55.2, 39.8, 39.1, 32.9, 30.5, 26.8; IR (film) 1507, 1345, 1247, 1156 cm$^{-1}$. MS (ESI) 443.1993 (443.1999 calcd for C$_{24}$H$_{30}$N$_2$O$_4$S, M + H$^+$).

(±)-(3S*,4aR*)-3-Benzyl-2-(4-methoxyphenyl)octahydropyrido[1,2-b][1,2,6]thiadiazine-1,1-dioxide (4-13). General procedure B was employed for the coupling of 4-12 (62 mg, 0.2 mmol) and phenyl triflate (65 µL, 0.4 mmol), using a catalyst composed of Pd(OAc)$_2$ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 65 mg (84%) of the title compound as a white solid and as a 5:1 mixture of diastereomers as determined by $^1$H NMR analysis: mp = 46–49 °C. Data are for the major isomer. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 (d, $J = 8.5$ Hz, 2 H), 7.28–7.20 (m, 3 H), 7.07 (d, $J = 7.5$ Hz, 2 H), 6.91 (d, $J = 9.0$ Hz, 2 H), 4.41–4.37 (m, 1 H), 3.82 (s, 3 H), 3.59–3.43 (m, 2 H), 2.97–2.88 (m, 1 H), 2.79 (dd, $J = 13.6$, 4.8 Hz, 1 H), 2.13 (dd, $J = 13.7$, 10.1 Hz, 1 H), 1.89–1.65 (m, 4 H), 1.58–1.36 (m, 4 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 159.4, 137.2, 131.2, 130.0, 129.1, 128.5, 126.7, 114.2, 60.4, 57.1, 55.4, 44.3, 40.3, 32.1, 31.9, 24.9, 21.9; IR (film) 1507, 1338, 1250, 1156 cm$^{-1}$. MS (ESI) 387.1737 (387.1737 calcd for C$_{21}$H$_{26}$N$_2$O$_3$S, M + H$^+$).

**Assignment of Stereochemistry**

The relative stereochemistry of compound 4-9a and 4-9j was assigned on the basis of 1D NOESY experiments. Significant nOe relationships are shown below. The stereochemistry of all other 5-6 bicyclic sulfamide products was assigned based on analogy to 4-9a and 4-9j.
The relative stereochemistry of compound 4-13 was assigned on the basis of observed 1D NOESY experiments. Significant nOe relationships are shown below. The stereochemistry of all other 6-6 bicyclic sulfamide products was assigned based on analogy to 4-13.
Chapter 5

Efforts Towards the Total Synthesis of the Tetraponerine Alkaloids

5.1 Introduction

The tetraponerine alkaloids are a group of eight natural products that were first isolated from the New Guinean ant *Tetraponera sp.* in 1987 by Braekman (Figure 5.1). Interestingly, these compounds are the primary toxic constituents found in the ant’s poisonous venom. Moreover, the tetraponerine alkaloids are known to be effective inhibitors of several different nicotinic acetylcholine receptors, as well as exhibit other biological properties including interesting insecticidal and cytotoxic activity.

![Figure 5.1 Tetraponerine natural products.](image)

We initially became interested in the tetraponerine alkaloids because of the structural and stereochemical similarities to the tricyclic guanidine natural products discussed in chapters 1-4. For instance, the tetraponerine alkaloids, much like the tricyclic guanidines, can be classified into two distinct subgroups based on their stereochemical configuration. Specifically, four of the eight alkaloids (T-1, T-3, T-5 and T-7) feature a *cis* relationship between the C7 proton and the C5 alkyl chain, whereas the other four alkaloids (T-2, T-4, T-6 and T-8) possess a *trans* relationship. Within each subclass, the molecules differ from one another in terms of C5 chain length (propyl or pentyl) and the size of the A ring (5 or 6).

A number of groups have undertaken the synthetic challenges posed by the structural and stereochemical complexity of this family of alkaloids, and developed elegant methods for their syntheses. However, general methods that provide access to both sets of stereoisomers...
are strikingly uncommon. In fact, the only asymmetric synthesis of all eight natural products in the tetraponerine family was accomplished by Royer via an iterative sequence of highly stereoselective amino nitrile alkylations (Scheme 5.1). Thus a synthetic strategy that allows for the facile synthesis of both stereoisomeric cores with high levels of stereoselectivity and is amenable to the rapid generation of analogs is still a worthwhile pursuit. As such, the research described in this chapter details our initial efforts to employ Pd-catalyzed carboamination reactions for the asymmetric total synthesis of the tetraponerine family of alkaloids.

Scheme 5.1 Total synthesis of tetraponerine alkaloids via amino nitrile alkylations.

5.2 Synthetic Strategy

Overall, we envisioned that all eight of the tetraponerine alkaloids could be synthesized by utilizing the Pd-catalyzed carboamination reactions developed in chapters 2-4. As shown in Scheme 5.2, we anticipated that we could access the core of the natural products featuring a cis-configuration (T-1, T-3, T-5 and T-7) by synthesizing bicyclic ureas 5-1 via the syn-aminopalladation chemistry described in chapter 2. Alternatively, the trans-configured alkaloids (T-2, T-4, T-6 and T-8) could be prepared from bicyclic sulfamides 5-2 constructed by employing the carboamination reactions detailed in chapter 4 that proceed via anti-aminopalladation. Furthermore, this carboamination strategy was particularly attractive for its potential to install different C-5 alkyl chains from a single intermediate (5-3). Specifically, the propyl or pentyl side chains could be prepared from a single precursor by simply changing the electrophile employed during the carboamination reaction. Similarly, the use of aryl or other alkenyl halide coupling partners would facilitate the synthesis of tetraponerine analogs. It should be noted that all of the substrates and products in this chapter could be synthesized asymmetrically via the enantioselective allylation of N-Boc-pyrrolidine (lit: 95:5 er) or N-Boc-piperidine (lit: 95:5 er). However, for purposes of exploratory methodology development we
elected to carry out the following optimization studies on inexpensive racemic material; thus, all substrates and products in chapter 5 are racemic.

**Scheme 5.2** Synthetic strategy towards the core of the tetraponerines via Pd-catalyzed carboamination reactions.

As depicted in Scheme 5.3, we expected that the carboamination products 5-1 and 5-2 could be easily transformed into the tetraponerine natural products in a few straightforward steps. Cleavage of the urea or sulfamide bridge (X), followed by hydrogenation of the olefin and concomitant deprotection of the N-protecting group, would provide diamines 5-4. Based on literature precedent, treatment of 5-4 with 4-bromobutanal in the presence of acid is expected to afford the tricyclic natural products with high stereocontrol.\[^{107}\]

**Scheme 5.3** Proposed synthesis of the tetraponerine alkaloids from bicyclic ureas and sulfamides.

**5.3 Pd-Catalyzed Carboamination Reactions**

We initially elected to investigate the Pd-catalyzed carboamination reaction of 2-allylpyrroolidinyl urea substrate 5-3a using the optimized conditions developed in chapter 2 (Table 5.1). As expected, the coupling of 5-3a with 1-bromobutene afforded bicyclic urea 5-1a good yield (67%) and with excellent stereoselectivity (>20:1 dr). Unfortunately, efforts to couple
a two-carbon electrophile were met with failure. Vinyl bromide proved to be too volatile and led to polymerization side products when employed as the electrophilic coupling partner under the reaction conditions. TMS-protected variants of vinyl bromide primarily led to β-hydride elimination. Dichloroethane and dibromoethane also proved to be incompatible substrates for the desired coupling reactions.

Table 5.1 Synthesis of 5-6 cis-bicyclic ureas.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG substrate</th>
<th>R-Br Product</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMB 5-3a</td>
<td>Z-bromobutene 5-1a</td>
<td>67</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td>PMB 5-3a</td>
<td>Vinyl bromide – – –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PMB 5-3a</td>
<td>1-TMS-vinyl bromide – – –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PMB 5-3a</td>
<td>(E)-2-TMS-vinyl bromide – – –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PMB 5-3a</td>
<td>Dibromoethane – – –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PMB 5-3a</td>
<td>Dichloroethane – – –</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction Conditions: 1.0 equiv 5-3a, 4.0 equiv R-Br, 5.0 equiv NaOtBu, 3 mol % Pd$_{2}$dba$_{3}$, 12 mol % PCy$_{3}$HBF$_{4}$, toluene (0.1 M), 110 °C. [b] Isolated yield.

Application of the syn-aminopalladation chemistry developed in chapter 2 for the synthesis of 6-6 cis-bicyclic ureas was next examined. The carboamination reaction of 5-3b and 1-bromobutene using the optimized conditions for the synthesis of 5-6 fused bicyclic ureas afforded 6-6 bicyclic urea 5-1b in good yield and with good selectivity (Scheme 5.4). Vinyl bromide electrophiles, as was the case with pyrrolidinyl substrate 5-3a, proved to be incompatible coupling partners with piperidinyl substrate 5-3b.

Scheme 5.4 Synthesis of 6-6 cis-bicyclic urea via a Pd-catalyzed carboamination reaction.
Following the successful synthesis of both 5-6 and 6-6 \textit{cis}-bicyclic ureas, Pd-catalyzed carboamination reactions for the construction of bicyclic sulfamides featuring a \textit{trans}-configuration were explored. To this end, sulfamide substrates 4-8c and 4-12 were subjected to the reaction conditions developed in the Wolfe group’s original report on \textit{anti}-aminopalladation for the coupling of aryl and alkenyl bromides (Scheme 5.5).\textsuperscript{50} The coupling of pyrrolidinyl derivative 4-8c with 1-bromobutene generated the desired 5-6 \textit{trans}-bicyclic sulfamide 5-2a in moderate yield and diastereoselectivity. 1-bromobutene proved to be a better substrate for the carboamination with piperidinyl sulfamide 4-12, undergoing the desired transformation in much better yield and with slightly higher selectivity. Disappointingly, electrophiles possessing two carbons, such as vinyl bromide and dibromoethane, led to significant amounts of side products. Current studies are focused on improving the yield and selectivity of these reactions by employing vinyl triflates, as opposed to vinyl bromides. Additionally, the coupling of 2-substituted thiophene derivatives would represent another possibility to introducing the four-carbon subunit as 2-alkyl thiophenes can be reduced to 1-substituted butanes in a single step.\textsuperscript{115}

\begin{center}
\textbf{Scheme 5.5} Synthesis of \textit{trans}-bicyclic cyclic sulfamides.
\end{center}

\begin{center}
\includegraphics[width=\textwidth]{scheme55}
\end{center}

5.4 Efforts Towards the Total Synthesis of Tetraponerine T-5

As previously described, we anticipated that carboamination products 5-1 and 5-2 could be converted into the tetraponerine natural products in just a few steps (Scheme 5.3). Importantly, 1-bromobutene proved to be a viable coupling partner for all four sets of substrates (\textit{cis}-5-6, \textit{cis}-6-6, \textit{trans}-5-6, and \textit{trans}-6-6), affording bicyclic products that have the potential to serve as key intermediates in the synthesis of tetraponerines T-5, T-6, T-7 and T-8. Admittedly, the current inability to couple two-carbon electrophiles is a substantial limitation of this methodology and future work is needed in this area in order to develop an efficient synthesis of tetraponerines T-1, T-2, T-3 and T-4 using this annulation strategy. The remainder of this chapter describes our preliminary efforts to convert bicyclic urea 5-1a into tetraponerine T-5.
Scheme 5.6 Initial synthetic efforts towards tetraponerine T-5.

Conversion of cis-bicyclic urea 5-1a to tetraponerine T-5 commenced with hydrogenation of the olefin and concomitant removal of the p-methoxybenzyl protecting group as shown in Scheme 5.6. Unfortunately, initial efforts to reduce urea 5-5 with LiAlH₄ in refluxing ether or THF were unsuccessful.

Scheme 5.7 Reduction of urea bridge.

Interestingly, by reversing the order of reactions, urea 5-1a could be reduced to diamine 5-6 via the two-step process depicted in Scheme 5.7. Hydrogenation of the olefin present in 5-6 was accomplished with Pd/C under a H₂ atmosphere. However, the PMB group was not removed under the mild hydrogenolysis conditions (room temperature and H₂ balloon). A more thorough examination of deprotection conditions, including increasing the temperature and pressure of the hydrogenolysis reaction, is needed to test the feasibility of this transformation. Future work in this area is warranted, given that completion of the natural product could be accomplished in just a single step following the successful removal of the PMB group. It should be noted that a similar synthetic strategy should be feasible for the synthesis of tetraponerine alkaloids that feature a trans-stereochemical configuration, such as tetraponerines T-6 and T-8, as the reduction of bicyclic sulfamide 4-9c with LiAlH₄ proceeded with 80% conversion after 16 hours in refluxing THF (Scheme 5.8).
**Scheme 5.8** Removal of sulfamide bridge via LiAlH₄.

![Scheme 5.8](image)

**5.4 Conclusions**

In all, the Pd-catalyzed carboamination reactions developed in chapters 2-4 have been utilized to access the core of the tetraponerine alkaloids. One of the bicyclic carboamination products has been explored as an intermediate in the total synthesis of tetraponerine T-5, and after preliminary studies, only two more steps are required to complete the synthesis of the natural product. Importantly, the total synthesis efforts described in this chapter, paired with methodology developed in chapters 2-4, has laid the foundation to complete the total synthesis of tetraponerines T-6, T-7 and T-8. Overall, the research developed in chapter 5, along with work described in chapters 2-4, demonstrates the utility of Pd-catalyzed carboamination reactions for the total synthesis of structurally and stereochemically complex natural products and analogs thereof.

*Part of the work described in this chapter was carried out by Grace McKenna including the synthesis of 4-12, 5-2b, and 5-3b.*

**5.5 Experimental**

**General:** All reactions were carried out under a nitrogen atmosphere unless otherwise noted. Tris(dibenzylidene)acetone dipalladium, and palladium acetate were purchased from Strem Chemical Co. and used without purification. All phosphine ligands were obtained from commercial sources and were used without further purification. All other reagents were obtained from commercial sources and were used as obtained unless otherwise noted. (Z)-1-bromobutene was prepared according to a slight modification of a literature procedure; the preparation was conducted at rt instead of using microwave heating as described in chapter 2. *tert*-Butyl 2-allylpyrrolidine-1-carboxylate, *tert*-butyl 2-allylpiperidine-1-carboxylate, N-(4-methoxyphenyl)-2-oxooxazolidine-3-sulfonamide, and N-benzyl-2-oxooxazolidine-3-sulfonamide were prepared according to published procedures. Lithium *tert*-butoxide, sodium
tert-butoxide, and lithium triflate were stored in a glovebox and removed prior to use. Toluene, THF, diethyl ether and dichloromethane were purified using a GlassContour solvent purification system. Benzotrifluoride was purified by distillation under N₂ prior to use. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ¹H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment. Structural and stereochemical assignments were made based on analogy to the compounds prepared in chapters 2 and 4, which were determined through 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by ¹H NMR analysis.

Preparation and Characterization of Substrates

General Procedure for the Synthesis of Urea Substrates 5-3. A round-bottom flask equipped with a stirbar was charged with tert-butyl 2-allylpyrrolidine-1-carboxylate (1.0 equiv) and dichloromethane (0.2 M). Trifluoroacetic acid (1.0 M) was added to the flask and the mixture was stirred until the starting material had been completely consumed as judged by TLC analysis (ca. 30 min). The solution was diluted with water, basified with NH₄OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in dichloromethane (0.2 M) and the appropriate isocyanate (1.1–1.5 equiv) was added. The reaction mixture was stirred at rt until starting material had been completely consumed as judged by TLC analysis (ca. 1 h). The crude reaction mixture was concentrated in vacuo, and purified by flash chromatography on silica gel.

(±)-2-Allyl-N-(4-methoxybenzyl)pyrrolidine-1-carboxamide (5-3a). The title compound was prepared from 4-methoxybenzyl isocyanate (1.8 mL, 12.6 mmol) and tert-butyl 2-allylpyrrolidine-1-carboxylate (1.77 g, 8.4 mmol) in two steps via the general procedure described above. This procedure afforded 862 mg (37%) of the title compound as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, J = 8.0 Hz, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 5.78
(dddd, \( J = 16.9, 10.2, 7.8, 6.6 \) Hz, 1 H), 5.10–5.00 (m, 2 H), 4.43–4.30 (m, 3 H), 3.97 (m, 1 H), 3.80 (s, 3 H), 3.34–3.23 (m, 2 H), 2.54–2.49 (m, 1 H), 2.18–2.08 (m, 1 H), 2.02–1.82 (m, 3 H), 1.78–1.73 (m, 1 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \( \delta \) 158.8, 156.6, 135.3, 131.9, 129.1, 117.1, 113.9, 56.8, 55.3, 46.0, 44.1, 38.8, 29.4, 23.6; IR (film) 3324, 1626 cm\(^{-1}\). MS (ESI) 275.1747 (275.1754 calcd for C\(_{16}\)H\(_{22}\)N\(_2\)O\(_2\), M + H\(^+\)).

(\( \pm \))-2-Allyl-N-(4-methoxyphenyl)piperidine-1-carboxamide (5-3b). The title compound was prepared from 4-methoxyphenyl isocyanate (1.07 g, 7.2 mmol) and \textit{tert}-butyl 2-allylpiperidine-1-carboxylate (1.35 g, 6.0 mmol) in two steps via the general procedure described above. This procedure afforded 526 mg (35\%) of the title compound as a pale brown solid: mp = 53–56 °C.

\(^1\)H NMR (700 MHz, CDCl\(_3\)) \( \delta \) 7.21 (d, \( J = 9.1 \) Hz, 2 H), 6.81 (d, \( J = 9.1 \) Hz, 2 H), 6.28 (s, 1 H), 5.80 (ddt, \( J = 17.2, 10.1, 7.2 \) Hz, 1 H), 5.12 (dd, \( J = 17.1, 1.5 \) Hz, 1 H), 5.07 (dd, \( J = 10.2, 2.0 \) Hz, 1 H), 4.25 (m, 1 H), 3.92 (d, br, \( J = 11.9 \) Hz, 1 H), 3.76 (s, 3 H), 2.94 (td, \( J = 13.2, 2.9 \) Hz, 1 H), 2.50 (dddt, \( J = 13.8, 8.2, 6.9, 1.3 \) Hz, 1 H), 2.33–2.26 (m, 1 H), 1.71–1.58 (m, 5 H), 1.48 (m, 1 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \( \delta \) 155.6, 135.4, 132.4, 122.1, 117.3, 114.0, 55.5, 51.1, 39.2, 34.3, 27.8, 25.4, 18.7 (one carbon signal is absent to due incidental equivalence); IR (film) 3306, 1628 cm\(^{-1}\). MS (ESI) 275.1755 (275.1754 calcd for C\(_{16}\)H\(_{22}\)N\(_2\)O\(_2\), M + H\(^+\)).

**Preparation and Characterization of Bicyclic Products**

**General Procedure A: Synthesis of Bicyclic Ureas 5-1.**

A flame-dried Schlenk tube equipped with a stirbar was cooled under vacuum and charged with Pd\(_2\)(dba)\(_3\) (0.02 equiv), PCy\(_3\)HBF\(_4\) (0.08 equiv), NaOrBu (4.0 equiv) and the appropriate substrate (1.0 equiv). The flask was evacuated and purged with N\(_2\). The appropriate substrate if oil (1.0 equiv) in toluene (0.2 M) was added via syringe, followed by the appropriate alkenyl bromide (5.0 equiv). The tube was heated to 110 °C and stirred overnight. The mixture was cooled to room temperature and saturated aqueous NH\(_4\)Cl (5 mL/mmols substrate) and ethyl
acetate (5 mL/mmol substrate) were added. The layers were separated and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

**General Procedure B: Synthesis of Bicyclic Sulfamides 5-2.**

A test tube equipped with a stirbar was charged with Pd(OAc)$_2$ (0.04 equiv), CPhos (0.1 equiv), NaOtBu (4.0 equiv) and LiOTf (5.0 equiv). The test tube was purged with N$_2$ then the appropriate alkenyl bromide (4.0 equiv) was added, followed by the appropriate substrate (1.0 equiv) in benzotrifluoride (0.2 M). The tube was heated to 100 ºC and stirred overnight. The mixture was cooled to room temperature and saturated aqueous NH$_4$Cl (5 mL/mmol substrate) and dichloromethane (5 mL/mmol substrate) were added. The layers were separated and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

(±)-(Z,3R*,4aR*)-2-(4-Methoxybenzyl)-3-(pent-2-en-1-yl)hexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (5-1a). General procedure A was employed for the coupling of 5-3a (274 mg, 1.0 mmol) and (Z)-1-bromobutene (2.0 mL, 4.0 mmol, 2.0 M solution in toluene), using NaOtBu (384 mg, 4.0 mmol) and a catalyst composed of Pd$_2$dba$_3$ (18.3 mg, 0.02 mmol), and PCy$_3$HBF$_4$ (29.5 mg, 0.08 mmol). This procedure afforded 219 mg (67%) of the title compound as a brown oil and as a >20:1 mixture of diastereomers as determined by $^1$H NMR analysis. Data are for the major isomer. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.21 (d, $J = 8.4$ Hz, 2 H), 6.83 (d, $J = 8.4$ Hz, 2 H), 5.50–5.44 (m, 1 H), 5.23–5.17 (m, 1 H), 5.13 (d, $J = 15.1$ Hz, 1 H), 4.03 (d, $J = 15.1$ Hz, 1 H), 3.79 (s, 3 H), 3.60 (dt, $J = 10.5$, 6.0 Hz, 1 H), 3.58–3.54 (m, 1 H), 3.49 (dt, $J = 9.1$, 1.8 Hz, 1 H), 3.25–3.21 (m, 1 H), 2.38 (dd, $J = 13.5$, 6.7 Hz, 1 H), 2.19 (dt, $J = 14.4$, 9.4 Hz, 1 H), 2.09–1.94 (m, 5 H), 1.80 (ttdd, $J = 12.5$, 9.6, 6.6 Hz, 1 H), 1.43 (qd, $J = 11.9$, 7.1 Hz, 1 H), 1.25 (td, $J = 12.3$, 5.0 Hz, 1 H), 0.95 (t, $J = 7.5$ Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 158.6, 155.0, 134.5, 131.3, 129.1, 124.5, 113.8, 55.2, 53.4, 52.6, 47.9, 46.1, 33.9, 30.6, 30.1, 23.5, 20.8, 14.2; IR (film) 1626 cm$^{-1}$. MS (ESI) 329.2221 (329.2224 calcd for C$_{20}$H$_{28}$N$_2$O$_2$, M + H$^+$).
(±)-(Z,3R*,4aR*)-2-(4-Methoxyphenyl)-3-(pent-2-en-1-yl)octahydro-1H-pyrido[1,2-c]pyrimidin-1-one (5-1b). General procedure A was employed for the coupling of 5-3b (55 mg, 0.2 mmol) and (Z)-1-bromobutene (500 µL, 1.0 mmol, 2.0 M solution in toluene), using NaOrBu (96 mg, 1.0 mmol) and a catalyst composed of Pd₃dba₃ (5.5 mg, 0.006 mmol), and PCy₃HBF₄ (9.0 mg, 0.024 mmol). This procedure afforded 45 mg (69%) of the title compound as a brown oil and as a 10:1 mixture of diastereomers as determined by ¹H NMR analysis. Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 7.14 (d, J = 9.1 Hz, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 5.47–5.41 (m, 1 H), 5.17–5.14 (m, 1 H), 4.58 (d, J = 13.3 Hz, 1 H), 3.79 (s, 3 H), 3.59–3.55 (m, 1 H), 3.30 (dddd, J = 13.7, 11.0, 6.1, 3.6 Hz, 1 H), 2.57 (td, J = 12.7, 2.9 Hz, 1 H), 2.42–2.39 (m, 1 H), 2.27 (dt, J = 14.2, 9.4 Hz, 1 H), 2.04–1.93 (m, 3 H), 1.84 (d, J = 12.6 Hz, 1 H), 1.74–1.68 (m, 2 H), 1.50–1.35 (m, 2 H), 1.31–1.24 (m, 2 H), 0.93 (t, J = 7.7 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 157.6, 155.0, 136.4, 134.5, 129.0, 124.1, 114.0, 57.1, 55.4, 50.8, 43.5, 33.6, 32.8, 30.9, 25.3, 24.0, 20.8, 14.1; IR (film) 1637 cm⁻¹. MS (ESI) 329.2228 (329.2224 calcd for C₂₀H₂₈N₂O₂, M + H⁺).

(±)-(Z,3S*,4aR*)-2-Benzyl-3-(pent-2-en-1-yl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine-1,1-dioxide (5-2a). General procedure B was employed for the coupling of 4-8c (56 mg, 0.2 mmol) and (Z)-1-bromobutene (400 µL, 0.8 mmol, 2.0 M solution in PhCF₃), using NaOrBu (96 mg, 1.0 mmol) and LiOTf (156 mg, 1.0 mmol) a catalyst composed of Pd(OAc)₂ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 20 mg (30%) of the title compound as a pale yellow brown oil and as a 5:1 mixture of diastereomers as determined by ¹H NMR analysis. Data are for the major isomer. ¹H NMR (700 MHz, CDCl₃) δ 7.44–7.29 (m, 4 H), 7.14–7.05 (m, 2 H), 7.00–6.90 (m, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 5.50–5.30 (m, 1 H), 5.18–5.00 (m, 1 H), 4.60 (d, J = 13.3 Hz, 1 H), 3.80 (s, 3 H), 3.58–3.50 (m, 1 H), 3.30 (dddd, J = 13.7, 11.0, 6.1, 3.6 Hz, 1 H), 2.50–2.30 (m, 1 H), 2.25 (dt, J = 14.2, 9.4 Hz, 1 H), 2.03–1.90 (m, 3 H), 1.82 (d, J = 12.6 Hz, 1 H), 1.72–1.55 (m, 2 H), 1.30–1.21 (m, 2 H), 0.91 (t, J = 7.7 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 156.9, 155.3, 136.2, 134.3, 128.9, 125.0, 124.0, 114.0, 57.1, 55.3, 50.8, 43.5, 33.6, 32.8, 30.9, 25.3, 24.0, 20.8, 14.1; IR (film) 1637 cm⁻¹. MS (ESI) 329.2228 (329.2224 calcd for C₂₀H₂₈N₂O₂, M + H⁺).
7.24 (t, J = 7.4 Hz, 1 H), 5.41–5.37 (m, 1 H), 5.19–5.13 (m, 1 H), 4.50 (d, J = 16.2 Hz, 1 H), 4.11 (d, J = 16.2 Hz, 1 H), 3.90–3.85 (m, 1 H), 3.47 (td, J = 9.0, 5.4 Hz, 1 H), 3.40–3.31 (m, 1 H), 3.24 (td, J = 9.3, 6.1 Hz, 1 H), 2.25–2.08 (m, 3 H), 1.95–1.80 (m, 5 H), 1.59–1.45 (m, 2 H), 0.88 (t, J = 7.7 Hz, 3 H); 13C NMR (175 MHz, CDCl3) δ 138.7, 134.7, 128.4, 127.6, 127.1, 123.9, 60.9, 60.6, 49.2, 45.9, 31.7, 31.6, 31.3, 21.0, 20.7, 13.9; IR (film) 1334, 1156 cm⁻¹. MS (ESI) 335.1793 (335.1788 calcd for C18H26N2O2S, M + H⁺).

(±)-(Z,3S*,4aR*)-2-(4-Methoxyphenyl)-3-(pent-2-en-1-yl)octahydropyrido[1,2-b][1,2,6]thiadiazine-1,1-dioxide (5-2b). General procedure B was employed for the coupling of 4-12 (62 mg, 0.2 mmol) and (Z)-1-bromobutene (400 µL, 0.8 mmol, 2.0 M solution in PhCF₃), using NaOrBu (96 mg, 1.0 mmol) and LiOTf (156 mg, 1.0 mmol) a catalyst composed of Pd(OAc)₂ (1.8 mg, 0.008 mmol), and CPhos (8.7 mg, 0.02 mmol). This procedure afforded 60 mg (82%) of the title compound as a pale yellow oil and as a 5:1 mixture of diastereomers as determined by 1H NMR analysis. Data are for the major isomer. 1H NMR (700 MHz, CDCl₃) δ 7.38 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 9.1 Hz, 2 H), 5.51–5.40 (m, 1 H), 5.25–5.19 (m, 1 H), 4.13–4.06 (m, 1 H), 3.80 (s, 3 H), 3.67–3.62 (m, 1 H), 3.49 (ddd, J = 10.8, 6.6, 3.7 Hz, 1 H), 2.99 (ddd, J = 11.7, 8.4, 3.5 Hz, 1 H), 2.04 (dt, J = 13.8, 6.0 Hz, 1 H), 1.92–1.66 (m, 8 H), 1.62–1.45 (m, 3 H), 0.88 (t, J = 7.5 Hz, 3 H); 13C NMR (175 MHz, CDCl₃) δ 159.3, 134.7, 131.1, 130.0, 123.5, 114.2, 59.5, 56.7, 55.4, 44.1, 32.1, 31.7, 31.4, 24.9, 21.5, 20.7, 13.9; IR (film) 1506, 1339, 1248, 1159 cm⁻¹. MS (ESI) 365.1905 (365.1893 calcd for C19H28N2O3S, M + H⁺).

Conversion of 5-1a to Tetraponerine T-5.
(±)-(3R,4aR)-3-Pentylhexahydropyrrolo[1,2-c]pyrimidin-1(2H)-one (5-5). A flame-dried flask was cooled under vacuum and charged with 10% Pd/C (120 mg). The flask was capped with a rubber septum, evacuated and backfilled with nitrogen. A solution of 5-1a (66 mg, 0.2 mmol) in methanol (8 mL) was added to the flask via a syringe, followed by acetic acid (0.2 mL). The flask was briefly flushed with hydrogen and then a hydrogen-filled balloon attached to a needle (via an adaptor) was connected to the flask through the septum. The mixture was placed in an oil bath at 50 °C and the reaction was stirred overnight (ca. 16 h). The crude material was then filtered through a plug of celite to remove the Pd/C and washed with methanol (5 mL). The crude material was concentrated in vacuo and purified by flash chromatography on silica gel to afford 38.5 mg (92%) of the title compound as a pale yellow solid: mp = 63–66 ºC. ¹H NMR (700 MHz, CDCl₃) δ 4.79 (s, br, 1 H), 3.54–3.44 (m, 3 H), 3.39–3.32 (m, 1 H), 2.15–2.08 (m, 1 H), 1.97–1.92 (m, 2 H), 1.80–1.74 (m, 2 H), 1.54–1.25 (m, 9 H), 0.88 (t, J = 7.0 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 155.3, 52.3, 50.0, 45.3, 36.8, 33.6, 32.2, 31.6, 25.7, 23.0, 22.6, 14.0; IR (film) 3214, 1650 cm⁻¹. MS (ESI) 211.1812 (211.1805 calcd for C₁₂H₂₁N₂O, M + H⁺).

(±)-(Z,R,R)-N-(4-Methoxybenzyl)-1-(pyrrolidin-2-yl)hept-4-en-2-amine (5-5). This compound was prepared via a modification of a published procedure by Trost. A flame-dried flask was cooled under vacuum and charged with LAH (190 mg, 5.0 mmol). A reflux condenser was attached to the flask and the apparatus was evacuated and backfilled with nitrogen. Diethyl ether (4 mL) was added, followed by a solution of 5-1a (66 mg, 0.2 mmol) in diethyl ether (4 mL). The flask was placed in an oil bath and allowed to reflux overnight (ca. 16 h). The reaction flask was allowed to cool to rt and then the mixture was diluted with ether (10 mL). The reaction flask was placed in an ice bath and quenched slowly with water (2 mL). 1M NaOH (2 mL) was added, followed by more water (2 mL) and the biphasic mixture was stirred vigorously for 15 min. The mixture was decanted, dried with Na₂SO₄, and concentrated in vacuo. The crude product appeared to be clean by ¹H NMR and taken unto the next step without further purification. A round bottom flask, equipped with a stirbar was charged with the crude product and aqueous
0.01% HCl (10 mL). H$_2$NOH·HCl (69 mg, 1.0 mmol) was added and the reaction mixture was heated to 60 °C in an oil bath and stirred until the starting material had been consumed as judged by ESI' MS analysis (ca. 60 min). The reaction was cooled to rt and aqueous 1M HCl (20 mL) was added. The solution was then washed with CHCl$_3$ (2 x 20 mL) and then the aqueous layer was carefully basified with Na$_2$CO$_3$ and extracted with CHCl$_3$ (3 x 20 mL). The combined organic layers were dried with Na$_2$SO$_4$ and concentrated in vacuo to afford 35 mg (57%) of the title compound as a pale yellow oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.22 (d, $J$ = 8.2 Hz, 2 H), 6.85 (d, $J$ = 8.4 Hz, 2 H), 5.52–5.46 (m, 1 H), 5.33–5.30 (m, 1 H), 3.79 (s, 3 H), 3.75 (d, $J$ = 12.8 Hz, 1 H), 3.69 (d, $J$ = 12.8 Hz, 1 H), 3.17 (s, br, 1 H), 2.97–2.94 (m, 1 H), 2.85–2.80 (m, 1 H), 2.73 (m, 1 H), 2.28 (dt, $J$ = 13.9, 6.7 Hz, 1 H), 2.22 (dt, $J$ = 14.1, 6.7 Hz, 1 H), 2.06 (m, 2 H), 1.85 (td, $J$ = 12.6, 7.3 Hz, 1 H), 1.63–1.51 (m, 2 H), 1.25 (m, 1 H), 0.95 (t, $J$ = 7.6 Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 158.6, 134.3, 129.3, 125.2, 113.8, 56.3, 55.3, 54.9, 50.5, 46.2, 39.8, 31.9, 31.8, 25.1, 20.8, 14.3 (one carbon signal is absent due to incidental equivalence); IR (film) 3002, 1611, 1511, 1246 cm$^{-1}$. MS (ESI) 303.2427 (303.2431 calcd for C$_{19}$H$_{30}$N$_2$O, M + H$^+$).
References


