New Developments in Heterocycle Synthesis:

Applications of an *Anti*-Aminopalladation Mechanism

by

Luke J. Peterson

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in the University of Michigan
2017

Doctoral Committee:

Professor John P. Wolfe, Chair
Professor John Montgomery
Professor Melanie S. Sanford
Professor Matthew B. Soellner

Luke Jeffrey Peterson

lukejpet@umich.edu

ORCID iD: 0000-0002-9152-2386

Dedication

To my family and friends, who have always been there for me.

I cannot thank you enough for all of the love and support that you have given me.

I could not have accomplished this without you.

Acknowledgements

First, and most importantly, I would like to thank God for giving me the opportunity to study at one of the greatest Universities in the world. His guidance has been a presence in my life from the beginning, and I am forever grateful.

Secondly, I would like to thank Dr. John Wolfe for being the best advisor and mentor that I could hope for. I always felt extremely comfortable talking to him about any and all things, both inside and outside the world of chemistry. His relaxed and even keeled attitude perfectly fit with my own, and I do not think that I would have had a better five years working in any other lab on campus.

Aside from Dr. Wolfe, I have had many synthetic chemists act as mentors to me during my time here at the University of Michigan. Dr. Anne McNeil has been a great resource for me to learn about teaching, both the in class as well as out of class aspects. Dr. Nick Babij was a senior graduate student in the Wolfe lab when I started my own graduate career, and his strong work ethic and impressive synthetic knowledge gave me an ideal to strive toward. Also, I cannot thank Jeremia Alicea enough for helping me get acclimated to the Wolfe lab while sharing a desk cubby with me for two years, and for teaching me the everyday ins-and-outs of being a synthetic chemist.

I would also like to thank the other three members of the Wolfe group that I share a graduating class with. I will always be thankful to Dr. Zachary Garlets for our talks about West Michigan, as well as his willingness to bounce ideas back and forth and share his

input on any project I happen to be working on. I am thankful to also have worked in close proximity to Dr. Derick White for over four years, as we share an immense love of music. I always enjoyed our discussions about bands both new and old. I also always appreciate his insightful input into any difficulties I was having with my chemistry. Lastly, I am very thankful to have become good friends with Dr. Jordan Boothe, as we share a similar style of humor and love of all things associate with nerd culture. I could not have asked for a better person to go through the dual degree program at the School of Education with, and will always be grateful that I had someone to share the burden of those courses with.

I am also grateful to the younger members of the Wolfe lab that I have had the pleasure of working with. Thank you to Elsa Hinds, who has been another friend to endure School of Education classes with, as well as someone with whom I could have countless discussions about the many aspects of teaching chemistry to undergrads. Also, thank you to Janelle Kirsch, with whom I have been able to reminisce about Hope College on a daily basis. Kelly and I have become to consider you our adoptive little sister. Lastly, thank you to Jenny Luo, whom I have had the pleasure of mentoring over the past two years. I have enjoyed watching you grow as a student and as a chemist.

I would also like to thank my family for all of their love and support throughout the past five years of my life while I completed my degree. Thank you to my parents, Jeff and Tammy, for being an inspiration to me, as well as for raising me with love and wisdom. I could not have made it here without you. I am also thankful to my sisters, Cassy and Alyssa, for the love and support they have shown me. Finally, I would like to say thank you to my wonderful wife Kelly. You have been such an amazing person for me to share my life with for the past few years, and I will always be appreciative of how understanding

you have been when I had to work long hours in lab. Thank you for standing by my side every step of the way, and I am looking forward to the next steps we will take as a family with our new daughter, Emily.

Table of Contents

Dedication……ii

Acknowledgements……iii

List of Tables……viii

List of Schemes……ix

List of Equations……x

List of Abbreviations……xi

Abstract……xiii

Chapter 1: Synthetic Interest in and Methods Toward Nitrogen Containing Hetereocycles……1

1-1 Introduction……1

1-2 Transition Metal Catalyzed Routes Toward Substituted Pyrrolidines……2

1-3 Wolfe Group Efforts Toward Pyrrolidines via Carbomanation Reactions…….3

1-4 Mechanistic Analysis of *Syn*-Aminopalladation……4

1-5 Development of *Anti*-Aminopalladation Methodology……..7

1-6 Projects Described Herein……9

Chapter 2: Palladium-Catalyzed Alkene Carboamination Reactions of Electron-Poor Nitrogen Nucleophiles……..11

2-1 Introduction……...11

2-2 Previous Work……..12

2-3 Optimization Studies……...13

2-4 Scope……14

2-5 Formal Synthesis of (±)-aphanorphine……18

2-6 Mechanistic Studies via Deuterium Labelling……19

2-7 Conclusion……22
2-8 Note From the Author……23
2-9 Experimental……23
Chapter 3: Synthesis of Cyclic Guanidines Bearing *N*-Arylsulfonyl and *N*-Cyano Protecting Groups via Pd-Catalyzed Alkene Carboamination Reactions…….56
3-1 Introduction……...56
3-2 Previous Efforts Toward Cyclic Guanidines……56
3-3 Optimization Studies……...57
3-4 Scope……59
3-5 Mechanistic Studies via Deuterium Labelling……63
3-6 Protecting Group Cleavage……65
3-7 Conclusion……67
3-8 Note From the Author……67
3-9 Experimental……67
Chapter 4: Palladium-Catalyzed Couplings of *N*-Allyl Guanidine Substrates with Amine Electrophiles to Synthesize Amino-Substituted Cyclic Guanidines……..132
4-1 Introduction……132
4-2 Optimization Studies……134
4-3 Scope……..136
4-4 Mechanistic Studies via Deuterium Labelling……...138
4-5 Conclusion……..139
4-6 Experimental……..140
References……...164

List of Tables

Table 1-1. Incompatability of Electron-poor Nucleophiles with *Syn* Conditions……6

Table 2-1. Optimization Studies……..14

Table 2-2. Pd-Catalyzed Carboamination Reactions Between Phenyl Triflate and *N*-tosyl-pent-4-enylamine Derivatives……15

Table 2-3. Pd-Catalyzed Carboamination Reactions Between Aryl Triflates and *N*-tosyl-pent-4-enylamine……16

Table 2-4. Pd-Catalyzed Carboamination Reactions Between Aryl Bromides and *N*-tosyl-pent-4-enylamine……..17

Table 2-5. Pd-catalyzed carboamination reactions between phenyl triflate and *N*-trifluoroacetyl-pent-4-enylamine……...18

Table 3-1. Optimization Studies……..58

Table 3-2. Scope of Carboamination of *N*-Protected Guanidines……..60

Table 3-3. Diastereoselectivity Studies……..62

Table 4-1. Optimization Studies……135

Table 4-2. Electrophile Scope with *N*-Cyano and *N*-Tosyl Guanidine Substrates……136

Table 4-3. Electrophile Scope with Urea Substrate **4-5**……137

Table 4-4. Diastereoselectivity Studies……137

List of Schemes

Scheme 1-1. Biologically Active Compounds Containing the Pyrrolidine Scaffold……1

Scheme 1-2. Examples of Pyrrolidine Formation via Carbopalladation……..4

Scheme 1-3. The *Syn*-Aminopalladation Mechanism……5

Scheme 1-4. Total Synthesis of (+)-Aphanorphine……...6

Scheme 1-5. *Syn* vs. *Anti*-Aminopalladation of Sulfonamide **1-11**……..7

Scheme 1-6. *Anti*-Aminopalladation Mechanism……8

Scheme 2-1. *Syn*-Aminopalladation Formation of Pyrrolidine **2-4**……13

Scheme 2-2. Formal synthesis of (±)-aphanorphine……19

Scheme 2-3. *Anti*-Aminopalladation Mechanism……..21

Scheme 2-4. Pathway for Diastereomer Formation……21

Scheme 3-1. Mechanism of Reation……..65

Scheme 3-2. Synthesis/Deprotection of *N*-Mtr Guanidine **3-20**……66

Scheme 3-3. Synthesis/Deprotection of *N*-Ts Guanidine **3-24**……..67

Scheme 4-1. Biologically Active Compounds Containing Cyclic Guanidines and/or 1,2 Diamines……132

List of Equations

Eq. 1-1……2
Eq. 1-2……3
Eq. 1-3……3
Eq. 1-4……4
Eq. 1-5……9
Eq. 2-1……12
Eq. 2-2……12
Eq. 2-3……20
Eq. 2-4……20
Eq. 3-1……57
Eq. 3-2……57
Eq. 3-3……57
Eq. 3-4……64
Eq. 3-5……64
Eq. 3-6……64
Eq. 3-7……66
Eq. 3-8……66
Eq. 4-1……133
Eq. 4-2……134
Eq. 4-3……134
Eq. 4-4……139
Eq. 4-5……139
Eq. 4-6……139
Eq. 4-7……139

List of Abbreviations

Ac ..... acetyl

Ar ..... aryl

Bn..... benzyl

Boc ..... *tert*-butyloxycarbonyl

n-Bu..... butyl

^{t}Bu ..... *tert*-butyl

Bz.....benzoyl

CPhos.....2-Dicyclohexylphosphino-2′,6′-bis(*N,N*-dimethylamino)biphenyl

Cy ..... cyclohexyl

dba ..... dibenzylideneacetone

DCM.....dichloromethane

DIAD ..... diisopropyl azodicarboxylate

DMF ..... N,N-dimethylformamide

dr.....diastereomeric ratio

Et ..... ethyl

HCl.....hydrochloric acid

Me ..... methyl

Mtr……..……4-methoxy-2,3,6-trimethylbenzenesulfonyl

PG ..... protecting group

Ph ..... phenyl

PMB ..... *para*-methoxybenzyl

PMP ..... *para*-methoxyphenyl

Pr ..... propyl

RuPhos……..…….2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

s-BuLi……. *sec*-butyl

SPhos……..…2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl

Tf ..... trifluoromethylsulfonyl

TFA ..... trifluoroacetic acid

THF ..... tetrahydrofuran

TMS ..... trimethylsilyl

Ts……..……...tosyl

XPhos ..... 2-di-t*ert*-butylphosphino-2',4',6'-tri-*iso*-propylbiphenyl

Abstract

Biologically active compounds, such as molecules isolated from natural sources like plants and marine sponges, have long been of interest to the synthetic chemistry community. Synthetic routes towards these biologically interesting compounds are constantly being sought after and improved upon by synthetic chemists, because efficient synthetic routes yield not only the compound in question in mass quantitites, but also allow for the formation of a library of compounds bearing small changes in structure that are not found in the originally isolated compound. These small changes can potentially have dramatic effects on the biological activity of the compounds in question.

Nitrogen containing heterocycles appear in a wide variety of these aforementioned biologically active compounds, and for this reason have long been an attractive target to the synthetic community. Heterocyclic scaffolds such as substituted pyrrolidines are present in compounds that display a wide variety of biological activity, such as antifungal, antibiotic, and antitumor properties. Cyclic guanidines are also present in a large number of biologically interesting molecules, such as compounds that display antibiotic, immunosuppressive, and neurotoxic properties. While synthetic methodologies to access the scaffolds in question currently exist, the majority of them rely on preexisting substitution present in the substrate to afford the desired substituted products. This precludes the ability to rapidly synthesize a library of compounds with various substitution patterns that can then be assayed for changes in biological activity.

The research described in this dissertation details the development of a methodology to synthesize substituted, nitrogen containing heterocycles in a palladium catalyzed, modular coupling reaction. Chapter 1 outlines the biological relevance of nitrogen containing heterocycles, and it details the previous efforts of the Wolfe group to synthesize the molecular scaffolds in question. Chapter 2 describes the synthesis of substituted pyrrolidines via a newly developed, *anti*-aminopalladation methodology. Substituted pyrrolidine products bearing previously unusable *N*-tosyl and *N*-trifluoroacetyl protecting groups were afforded in good yield. Chapters 3 and 4 detail the synthesis of substituted, cyclic guanidines from acyclic *N*-allyl guanidine substrates. Chapter 3 focuses on coupling said guanidine substrates with aryl halides/triflates, in which substrates bearing cleavable *N*-cyano and *N*-tosyl protecting groups were utilized. Finally, Chapter 4 describes the successful coupling of guanidine substrates bearing *N*-cyano and *N*-tosyl protectin groups with OBz-protected amine electrophiles in a variation on a 1,2-diamination reaction.

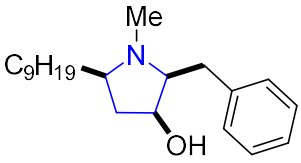
Chapter 1

Synthetic Interest in and Methods Toward Nitrogen Containing Hetereocycles

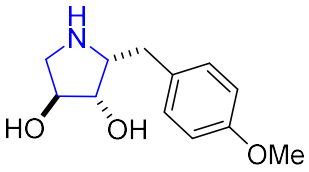
1-1 Introduction

The prevalence of nitrogen containing heterocycles in biologically active natural products and pharmaceuticals has made these compounds highly attractive targets in synthetic chemistry for many years.[1] Specifically, the pyrrolidine moiety appears as an important subunit in many biologically interesting compounds, such as preussin (antifungal activity), anisomycin (antibiotic activity), and broussonetine (glycosidase inhibitor).[2] To this extent new methodology to synthesize these aforementioned and novel pyrrolidine compounds is highly sought after in the chemical community.

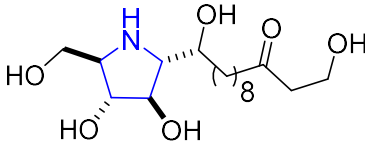
Scheme 1-1. Biologically Active Compounds Containing the Pyrrolidine Scaffold



Preussin



Anisomycin

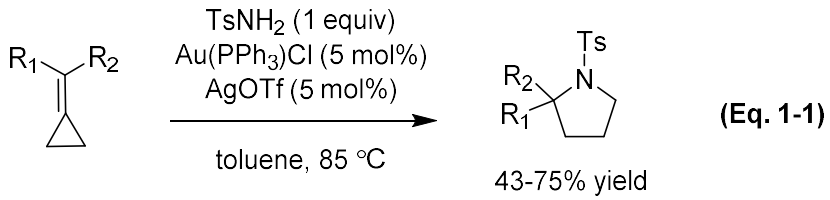


Broussonetine

1-2 Transition Metal Catalyzed Routes Toward Substituted Pyrrolidines

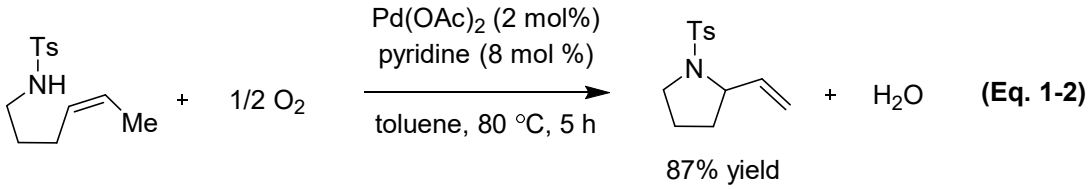
In recent years, transition metal catalysis has been utilized to access substituted pyrrolidine cores in multiple ways. Tang and coworkers utilized a gold(I)-catalyzed domino ring-opening ring-closing hydroamination of methylenecyclopropanes with sulfonamides

to produce geminally substituted pyrrolidines in modest to good yields **(Eq. 1-1)**.[3] This method tolerates an array of groups for R_1 and R_2, such as phenyl, naphthyl, and aliphatic substituents. However, this method is limited in that substitution is only afforded at the 2 position on the pyrrolidine ring and in many cases the yields are moderate at best.

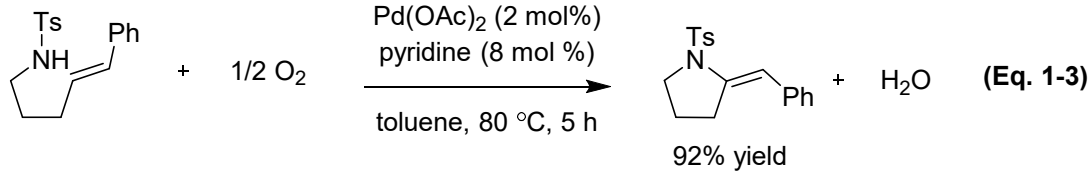


(Eq. 1-1)

Another method of pyrrolidine formation is the cyclization of an amine that is tethered to an alkene.[4] This cyclization is promoted by an electrophile such as a strong Brønsted acid or transition metal, and results have shown that these reactions can be accomplished catalytically using palladium as said electrophile.[5] This method has been used by Stahl and coworkers to afford the pyrrolidine core in good yields, via an oxidative, Aza-Wacker cyclization, with tolerance of alkyl and aryl substituents on the alkene **(Eq. 1-2,1-3)**.[6] However, one drawback of these reactions is the fact that only a monofunctionalization of the alkene is accomplished. This does not allow for the rapid formation of a library of compounds.



(Eq. 1-2)

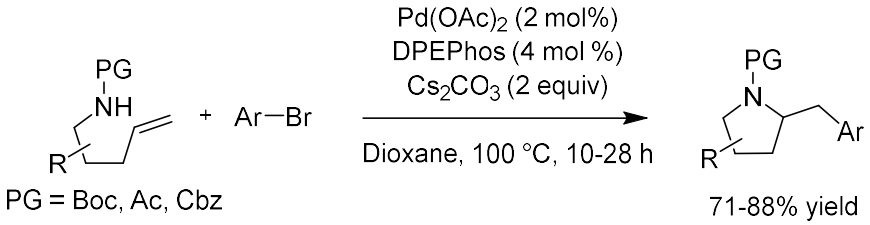


(Eq. 1-3)

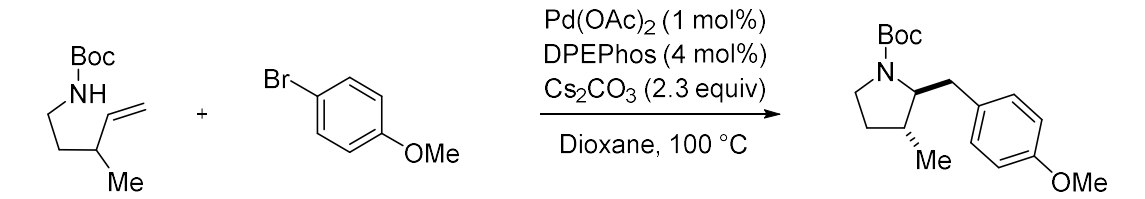
1-3 Wolfe Group Efforts Toward Pyrrolidines via Carbomanation Reactions

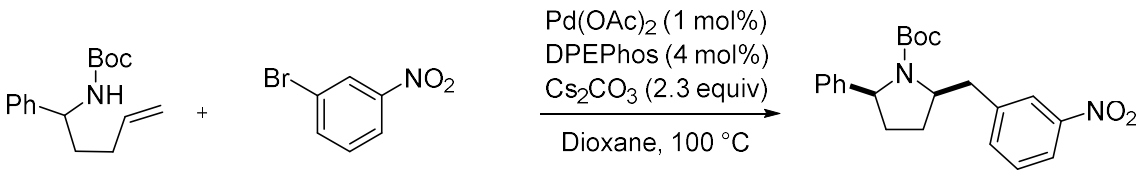
The existing limitations on pyrrolidine synthesis have led the Wolfe group to explore alkene difunctionalization, via carboamination reactions, as a potential route to access substituted pyrrolidines. This method involves the formation of a new C-C bond simultaneous to the C-N bond forming cyclization event. Carboamination reactions have been employed by our group over the past 10+ years to generate substituted pyrrolidine cores in good yields and with good diastereoselectivity **(Scheme 1-2)**.[7]

Scheme 1-2. Examples of Pyrrolidine Formation via Carbopalladation.



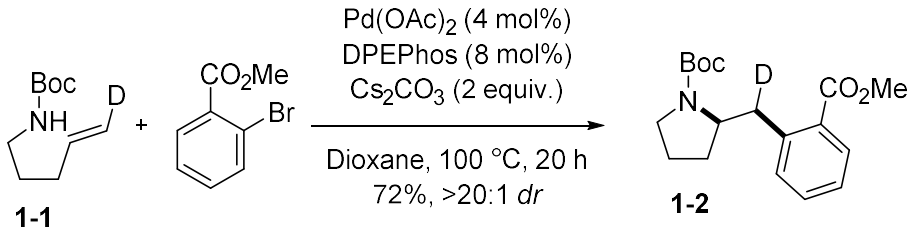
Examples:





1-4 Mechanistic Analysis of *Syn*-Aminopalladation

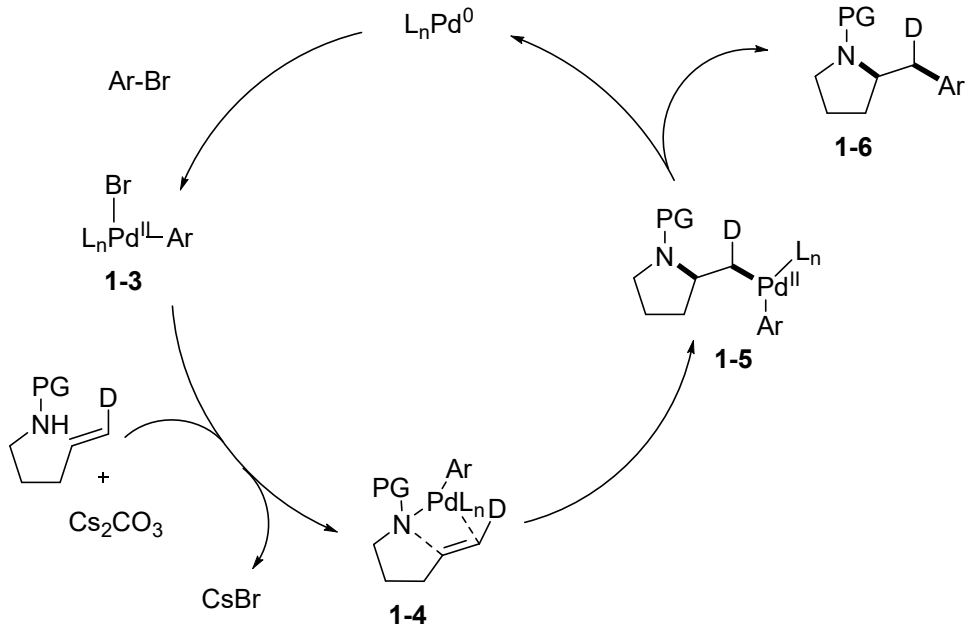
In order to probe the mechanism by which the pyrrolidine forming carboamination reaction was operating, deuterium-labelled substrate **1-1** was subjected to previously described reaction conditions.[7]



1-1 **1-2** **(Eq. 1-4)**

Analysis of product **1-2** led to the conclusion that these reactions were proceeding via a *syn*-aminopalladation mechanism **(Scheme 1-3)**. The catalytic cycle begins with oxidative addition of Pd(0) into the aryl bromide bond to give **1-3**. Simultaneous deprotonation and coordination of the amine substrate leads to the formation of palladium amido-complex **1-4**, which is then followed by *syn* addition across the alkene to give **1-5**. Subsequent reductive elimination of the palladium complex gives desired product **1-6** and reforms the original Pd(0) complex, allowing re-entry into the catalytic cycle.

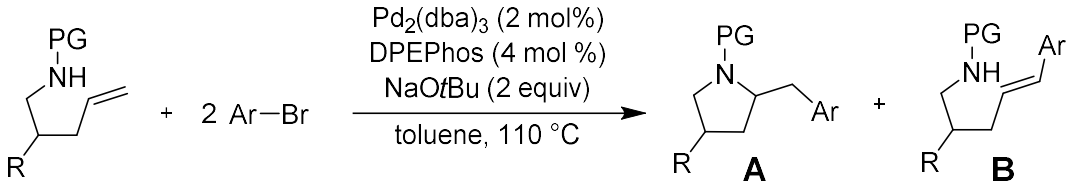
Scheme 1-3. The *Syn*-Aminopalladation Mechanism.



One drawback of the previously described carboamination methodology was discovered, however - the catalytic system was found to be incompatible with substrates

containing increasingly electron-poor nitrogen atoms, such as benzoyl and tosyl protected amines **(Table 1-1)**. Reactions employing the use of electron-poor cyclizing groups afford exclusively undesired Heck side product under *syn*-aminopalladation reaction conditions.[8]

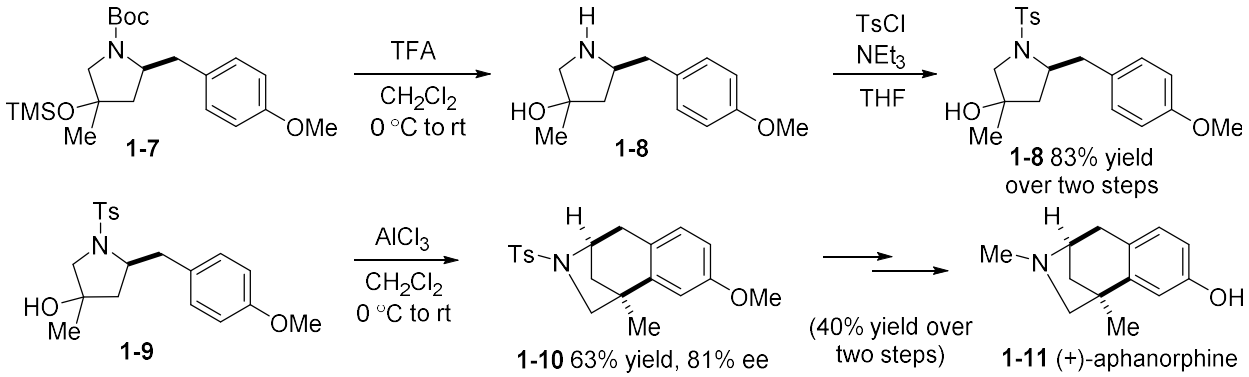
Table 1-1. Incompatability of Electron-Poor Nucleophiles with *Syn* Conditions.



		Ratio	
PG	R	A	B
4-MeO-Bz	H	77	23
Bz	H	48	42
4-F_3C-Bz	H	-	~100
Ts	Ph	-	~100

The development of a catalyst system that tolerates these electron-poor substrates would greatly increase the scope and utility of this methodology. Our group has already had to deal with protecting group issues in the total synthesis of (+)-aphanorphine, in which the Boc group required for the carboamination step was not compatible with the subsequent Friedl-Crafts alkylation, and the tosyl protecting group required for the Friedl-Crafts step was not compatible with the preceeding carbomamination reaction. This resulted in inefficient protecting group manipulation and a longer overall synthetic route **(Scheme 1-4)**.[9]

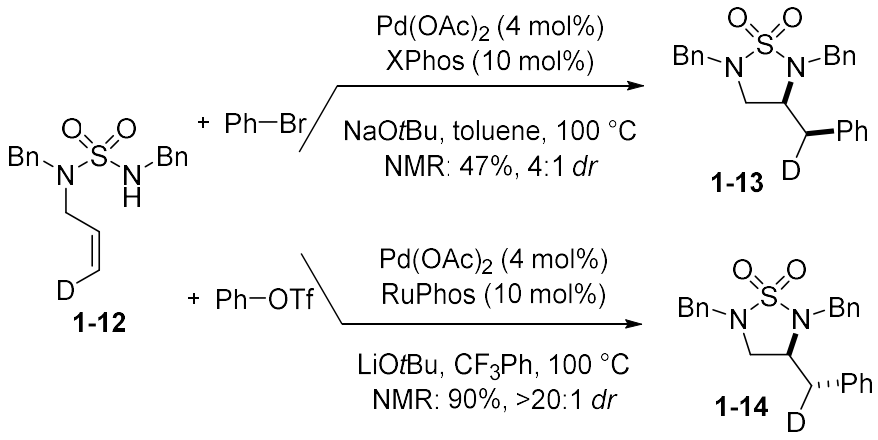
Scheme 1-4. Total Synthesis of (+)-Aphanorphine.



1-5 Development of *Anti*-Aminopalladation Methodology

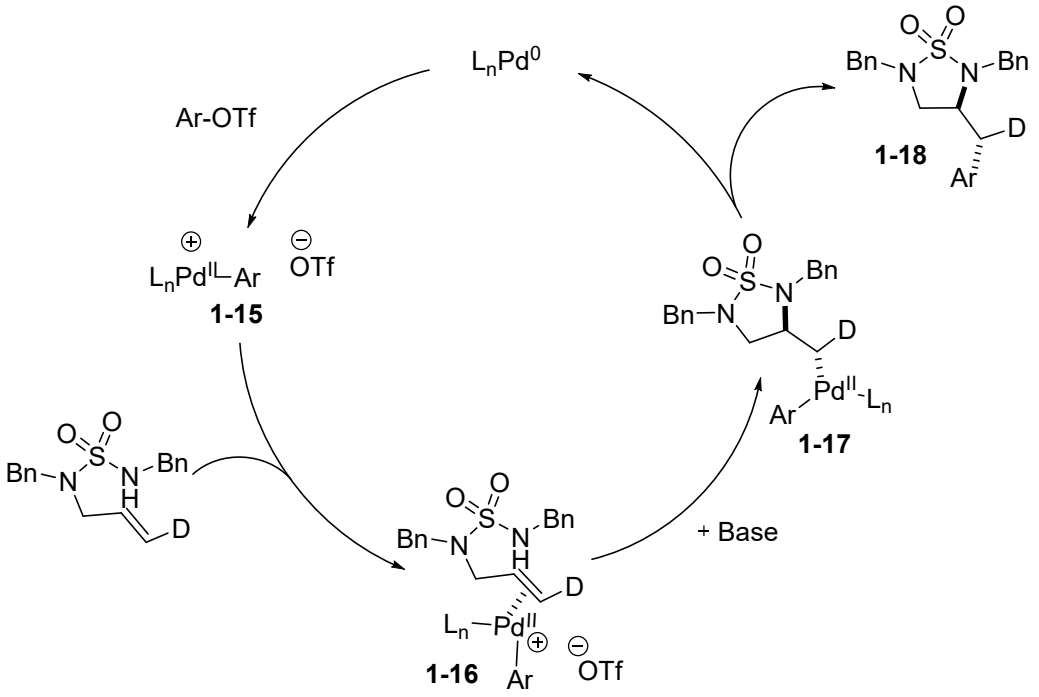
Beginning in the fall of 2012, the issue of electron poor substrates undergoing the Heck reaction preferentially to the desired carboamination reaction had begun to be explored by Mr. Ryan Fornwald. He found that the reactivity of sulfonamide substrates was greatly affected by the catalyst systems that they were exposed to. As expected, electron-poor substrates only gave the desired cyclized product in modest yields when exposed to our previously established *syn*-aminopalladation conditions (aryl bromide electrophile, NaO*t*Bu base, and toluene solvent). However, a change in conditions (aryl triflate electrophile, LiO*t*Bu base, and benzotrifluoride solvent) with RuPhos as the ligand afforded the desired cyclized product in good yield. Furthermore, the change in conditions led to a change in the operative mechanism of the reaction from *syn*-aminopalladation to *anti*-aminopalladation, as supported by the preparation and reaction of deuterium labelled substrate **1-12 (Scheme 1-5)**.[10]

Scheme 1-5. *Syn* vs. *Anti*-Aminopalladation of Sulfonamide **1-12**.

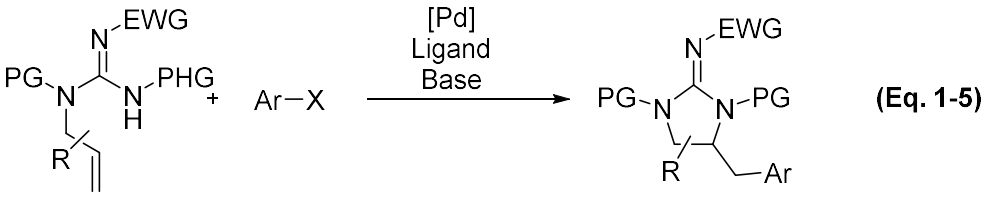


The aforementioned *anti*-aminopalladation catalytic cycle begins with oxidative addition of Pd(0) into the aryl-triflate bond. We hypothesize that the weakly coordinating triflate anion results in cationic palladium complex **1-15**. The formation of this cationic palladium complex, combined with decreased nucleophilicity of the electron-poor nitrogen atom, results in the formation of **1-16**, wherein the palladium complex is coordinated to the alkene instead of the nitrogen atom. Subsequent *anti* attack of the nitrogen results in **1-17**, which affords desired cyclized product **1-18** upon undergoing reductive elimination.

Scheme 1-6. *Anti*-Aminopalladation Mechanism.



This discovery led us to hypothesize that substrates bearing significantly electron-withdrawing protecting groups, such as tosyl and trifluoroacetyl protected amines, could potentially afford the desired substituted heterocyclic products that were not available to us previously via our *syn*-aminopalladation methodology. Furthermore, we hypothesized that other substrate scaffolds in which the nucleophilic nitrogen atom is in an electron poor environment could be amenable to this new *anti*-aminopalladation methodology. One such scaffold that has been of particular interest in our group is the guanidine moiety **(Eq. 1-5)**, as cyclic guanidines are present in a wide variety of biologically active compounds.[11]



(Eq. 1-5)

These new substrates were found to be amenable to these newly developed *anti*-aminopalladation conditions, and the operative mechanistic pathway was confirmed to be *anti* through the use of deuterium labelling studies. A comparison of substrates and conditions reveals that amines bearing Boc or aryl protecting groups will undergo *syn*-aminopalladation preferentially, while amines bearing *N*-tosyl or *N*-trifluoroacetyl protectin groups will undergo *anti*-aminopalladation preferentially. Furthermore, guanidine substrates bearing PMP protecting groups can be expected to undergo *syn*-aminopalladation, while guanidines bearing CN/Bn or Ts/Bn protecting group combinations preferentially undergo *anti*-aminopalladation (see Eq. 3-1).

1-6 Projects Described Herein

Contained in this dissertation is the description of the three projects that I have worked on during the time of my PhD research. Chapter 2 details efforts to synthesize substituted pyrrolidines from tosyl and acetyl protected amine substrates via *anti*-aminopalladation. The desired products were afforded in good yields, but low diastereoselectivities were generally observed. Chapter 3 details efforts to synthesized cyclic guanidines via *anti*-aminopalladation. Furthermore, this project represented an expansion of the scope of previous efforts by Blane Zavesky and Nick Babij to include guanidine substrates bearing cleavable tosyl and cyano protecting groups. Chapter 4 details a somewhat new direction for the carboamination chemistry than is typically studied by the Wolfe group, as OBz-protected amine electrophiles were utilized, in place

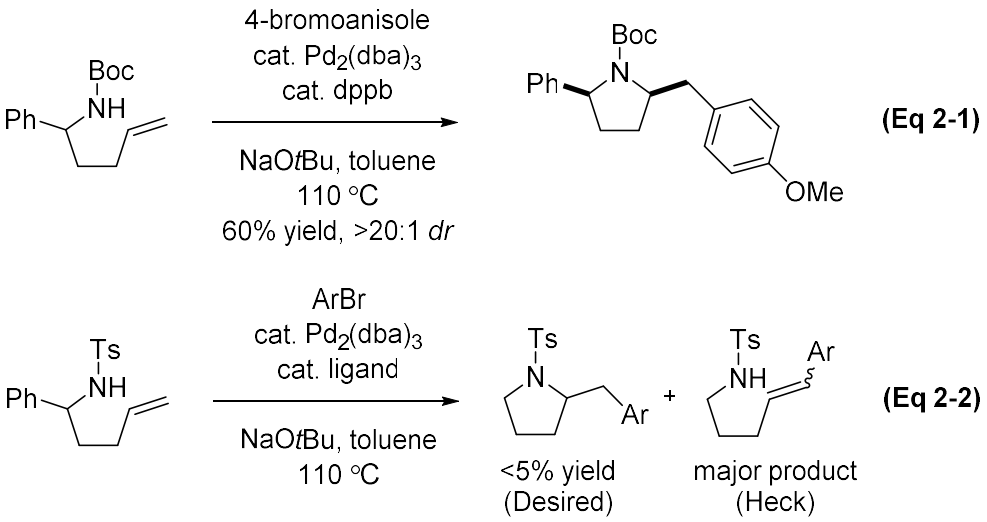
of the aryl or pseudo-aryl halides that our group typically utilizes, with guanidine substrates to afford cyclic amino-guanidine products in an aminopalladation variation of a diamination reaction.

Chapter 2

Palladium-Catalyzed Alkene Carboamination Reactions of Electron-Poor Nitrogen Nucleophiles

2-1 Introduction

Over the past decade our group has developed and investigated a series of Pd-catalyzed alkene carboamination reactions for the synthesis of medicinally relevant nitrogen heterocycles.[12] These transformations effect the cross-coupling of an aryl or alkenyl halide with a nitrogen nucleophile that contains a pendant alkene, and result in the formation of a ring, a C-N bond, a C-C bond, and up to two stereocenters. For example, we have illustrated that this method can be used for the stereoselective construction of *N*-protected pyrrolidines from substituted pent-4-enylamine derivatives **(Eq. 2-1)**.[13] These reactions are broadly effective with substrates bearing *N*-aryl, *N*-acetyl, *N*-Boc, or *N*-Cbz groups. However, the efficacy of these reactions is linked to the nucleophilicity of the cyclizing nitrogen atom, and substrates that contain highly electron-withdrawing protetcting groups, such as *N*-tosyl or *N*-trifluoroacetyl, undergo Heck arylation of the alkene rather than carboamination to afford the desired heterocycle **(Eq. 2-2)**.[14,15,16,17]

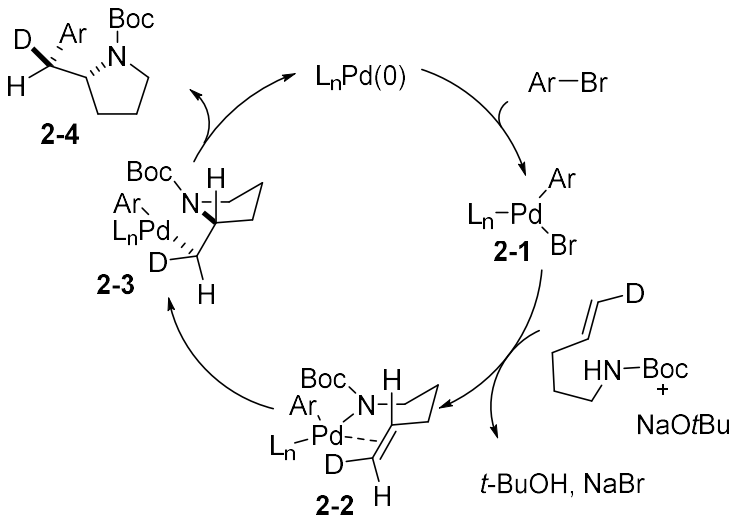


2-2 Previous Work

Our prior studies have shown that the mechanism of these reactions involves oxidiative addition of the aryl halide to Pd(0) to generate **2-1**, which undergoes substitution with the nitrogen nucleophile to afford **2-2 (Scheme 1)**. The key C-N bond-forming event occurs through *syn*-migratory insertion of the alkene into the Pd-N bond of **2-2** to yield **2-3**, which undergoes C-C bond-forming reductive elimination to generate the product **2-4**.[12] The *syn*-aminopalladation step is facilitated by relatively electron-rich nitrogen nucleophiles, and the rate of this step slows dramatically as the nucleophilicity of the nitrogen atom decreases.[18] Thus, for electron-poor nucleophiles such as tosyl-protected amines, Heck-type arylation of the alkene outcompetes the alkene carboamination process. We recently reported a new variant of the Pd-catalyzed alkene carboamination reactions whereby *N*-allylsulfamides were transformed to cyclic sulfamides.[19] During the course of those studies we discovered that reaction conditions that favored the *syn*-aminopalladation mechanistic pathway illustrated above led to the formation of significant amounts of side products resulting from competing Heck arylation. However, this undesired side reaction was minimized through use of modified conditions

in which the reactions were carried out in a relatively polar solvent ($PhCF_3$) with aryl triflates rather than aryl bromides as coupling partners. Given the success of these conditions with the relatively electron-poor sulfamide substrates, we reasoned that similar conditions may prove useful for Pd-catalyzed carboamination reactions of other electron-poor nitrogen nucleophiles, such as *N*-tosyl or *N*-trifluoroacetyl protected amines. This would broaden the array of nitrogen protecting groups tolerated in these reactions, and would significantly expand the scope of this methodology.

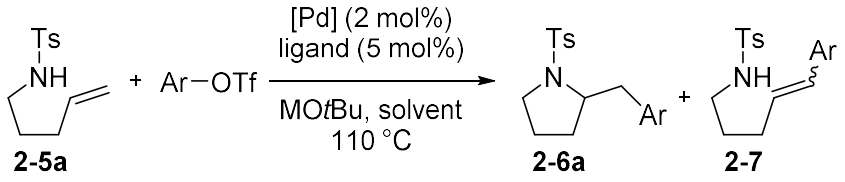
Scheme 2-1. *Syn*-Aminopalladation Formation of Pyrrolidine **2-4**.

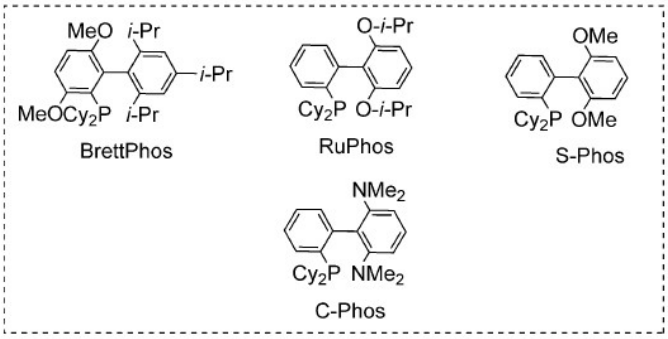


2-3 Optimization Studies

To test this hypothesis we examined the Pd-catalyzed coupling of **2-5a** with phenyl triflate or *p*-tolyl triflate **(Table 2-1)**. A series of Buchwald-type biarylphosphine ligands were surveyed,[20] as these provided optimal results in our prior studies with sulfamides.[19] After some experimentation we found that use of a catalyst composed of $Pd(OAc)_2$ /CPhos, LiO*t*Bu as base, and $PhCF_3$ as solvent provided the highest yield of desired product **2-6a** and only a small amount of Heck arylation side product **2-7**.

Table 2-1. Optimization Studies.[a]





[Pd]	Ligand	M	2-6a [%][b]	7 [%][b]
$Pd_2(dba)_3$	BrettPhos	Na	10[c]	trace
$Pd_2(dba)_3$	RuPhos	Na	38[c]	12
$Pd_2(dba)_3$	SPhos	Na	20[c]	33
$Pd(OAc)_2$	RuPhos	Li	66[c]	<10
$Pd(OAc)_2$	SPhos	Li	66[c]	<10
$Pd(OAc)_2$	CPhos	Li	70[e]	8
$Pd(OAc)_2$	CPhos[d]	Li	76[e]	8

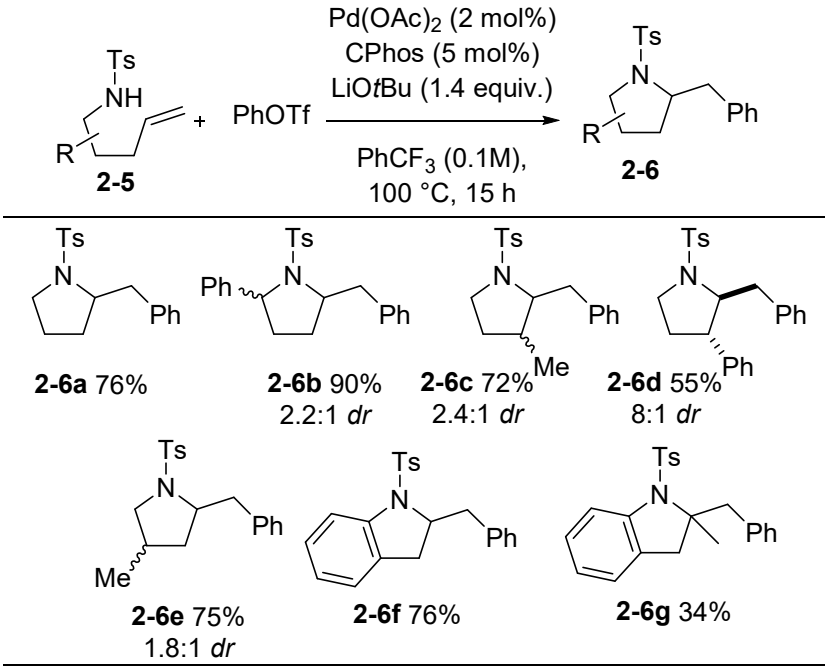
[a] *Conditions*: 1.0 equiv. 2-5a, 1.2 equiv. ArOTf, 1.4 equiv. MO*t*Bu, 1 mol% $Pd_2(dba)_3$ or 2 mol% $Pd(OAc)_2$, toluene (0.1M), 110 °C
[b] Yield determined by ^{1}H NMR using 1,10-phenanthrene as an internal standard. In most instances the mass balance consisted of unreacted starting material 2-5a.
[c] Ar = *p*-Tol.
[d] $PhCF_3$ was used as solvent with a reaction temperature of 100 °C.
[e] Ar = Ph

2-4 Scope

Following our preliminary optimization studies we proceeded to examine the coupling of phenyl triflate with several *N*-tosyl-pent-4-enylamine derivatives. As shown in **Table 2-2**, in most instances reactions proceed in good yield. However, in contrast to analogous transformations of *N*-Boc or *N*-acetyl protected pentenylamines,

diastereoselectivities were low (ca. 1–2:1) in most cases. Substitution at the internal alkene carbon atom was tolerated to some extent, although the yield for product **2-6g** was modest. Efforts to employ substrates bearing internal alkenes were unsuccessful. In addition, attempts to form six-membered heterocycles using this method provided low yields (<35%) of the desired products.

Table 2-2. Pd-Catalyzed Carboamination Reactions Between Phenyl Triflate and *N*-tosyl-pent-4-enylamine derivatives.[a]

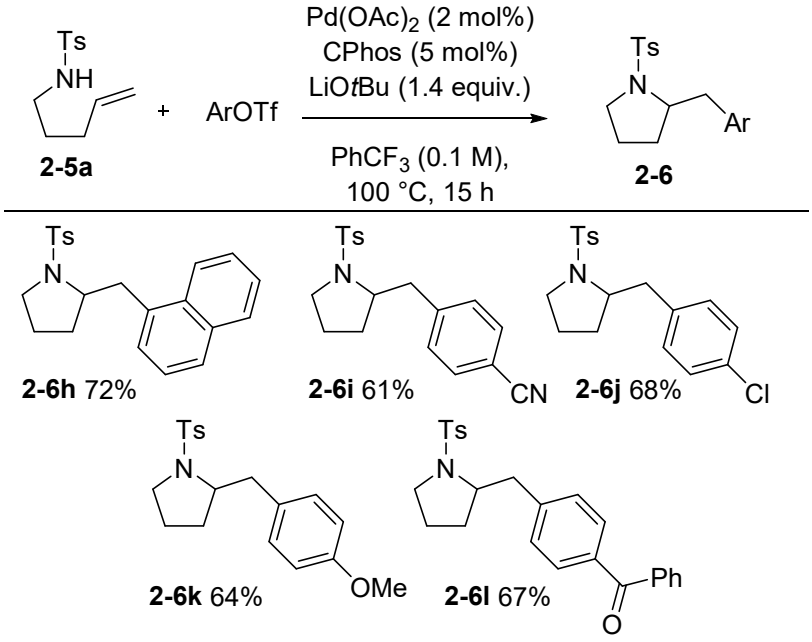


[a] *Conditions:* 1.0 equiv. **2-5**, 1.2 equiv. ArOTf, 1.4 equiv. LiO*t*Bu, 2 mol% $Pd(OAc)_2$, $PhCF_3$ (0.1M), 100 °C, 15 h. Yields are isolated yields (average of two experiments).

The reactivity of several different aryl triflates was also examined **(Table 2-3)**, and the presence of electron-donating groups and electron-withdrawing groups was tolerated. Moreover, the sterically hindered 1-naphthyl triflate was successfully coupled with *N*-tosyl-pent-4-enylamine in 72% yield to afford **2-6h**. The presence of functional groups

such as aryl chlorides, nitriles, and non-enolizable ketones did not have a deleterious effect on reactivity or chemical yield.

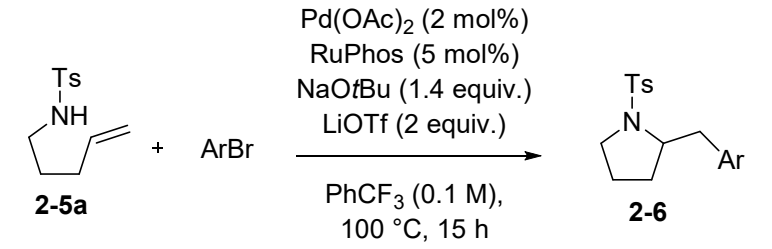
Table 2-3. Pd-Catalyzed Carboamination Reactions Between Aryl Triflates and *N*-tosyl-pent-4-enylamine.[a]

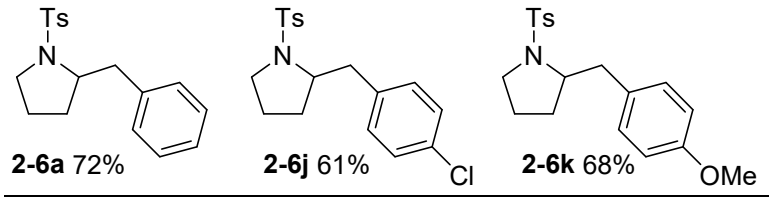


[a] *Conditions:* 1.0 equiv. **2-5a**, 1.2 equiv. ArOTf, 1.4 equiv. LiO*t*Bu, 2 mol% $Pd(OAc)_2$, $PhCF_3$, 100 °C, 15 h. Yields are isolated yields (average of two experiments.

Finally, the Pd-catalyzed carboamination of **2-5a** with several different aryl bromide electrophiles was achieved by using RuPhos as ligand, NaO*t*Bu as base, and 2 equiv. of LiOTf as an additive for these reactions **(Table 2-4)**. Under these conditions, yields with aryl bromides were similar to those obtained with aryl triflate electrophiles. The role of the LiOTf additive could be to facilitate *in situ* formation of palladium triflate complexes, or the lithium cation may lead to pseudocationic complexes by binding to the halide ligand on Pd.[21] Alternatively LiOTf may also increase the polarity (ionic strength) of the reaction medium.[22]

Table 2-4. Pd-Catalyzed Carboamination Reactions Between Aryl Bromides and *N*-tosyl-pent-4-enylamine.[a]

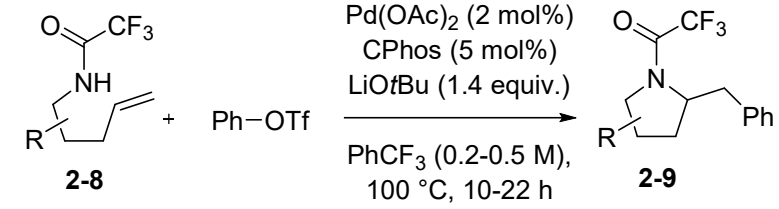




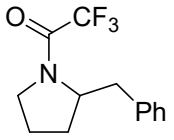
[a] *Conditions:* 1.0 equiv. **2-5a**, 1.2 equiv. ArBr, 1.4 equiv. NaO*t*Bu, 2.0 equiv. LiOTf, 2 mol% $Pd(OAc)_2$, 5 mol% RuPhos, $PhCF_3$, 100 °C, 15 h. Yields are isolated yields (average of two experiments.

We also explored the reactivity of pent-4-enylamine substrates bearing *N*-trifluoroacetyl groups. As shown in **Table 2-5**, these transformations were also effective with a range of different amine substrates, although yields were generally lower than for the analogous tosyl-protected derivatives. Diastereoselectivities were also modest, with the exception of **2-9e**, which contains a relatively bulky phenyl substituent.

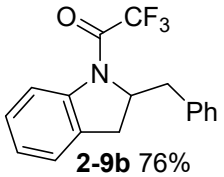
Table 2-5. Pd-catalyzed carboamination reactions between phenyl triflate and *N*-trifluoroacetyl-pent-4-enylamine.[a]



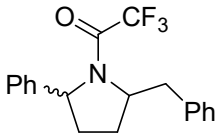
2-8 **2-9**



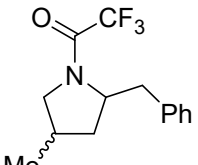
2-9a 61%



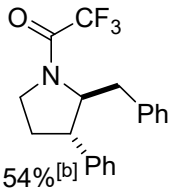
2-9b 76%



2-9c 87%
2:1 *dr*



2-9d 69%
1.3:1 *dr*



2-9e 54%[b]
7:1 *dr*

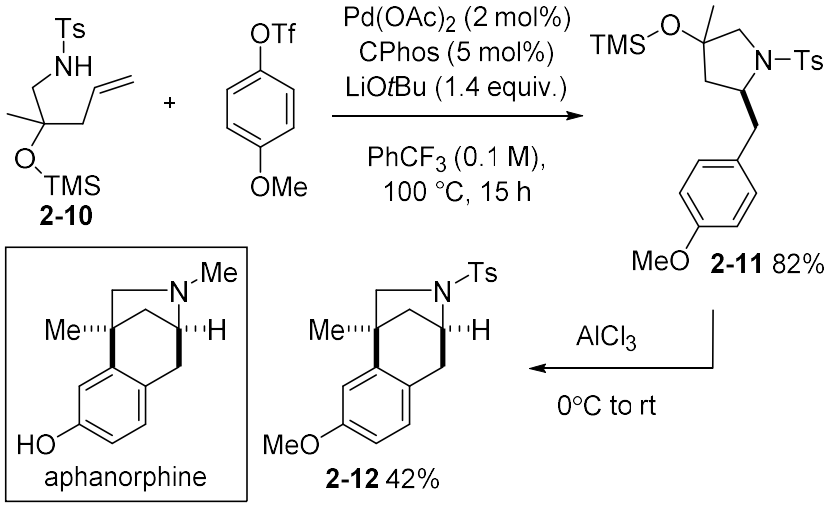
[a] *Conditions:* 1.0 equiv. **2-8**, 1.2 equiv. ArOTf, 1.4 equiv. LiO*t*Bu, 2 mol% $Pd(OAc)_2$, $PhCF_3$ (0.2 M), 100 °C, 15 h. Yields are isolated yields (average of two experiments). [b] The reaction was conducted using 2 equiv. PhOTf, 4 mol% $Pd(OAc)_2$, and 10 mol% CPhos.

2-5 Formal Synthesis of (±)-aphanorphine

To illustrate the potential utility of this transformation, we carried out a short formal synthesis of (±)-aphanorphine **(Scheme 2-2)**. We had previously prepared an intermediate closely related to **2-11** via Pd-catalyzed carboamination of a Boc-protected pentenylamine derivative analogous to **2-10** followed by cleavage of the Boc-group and reprotection with TsCl.[23] We were unable to directly access **2-11** via Pd-catalyzed carboamination due to the poor reactivity of substrate **2-10**. However, use of our newly developed conditions led to the conversion of **2-10** to **2-11** in 82% yield. Subsequent

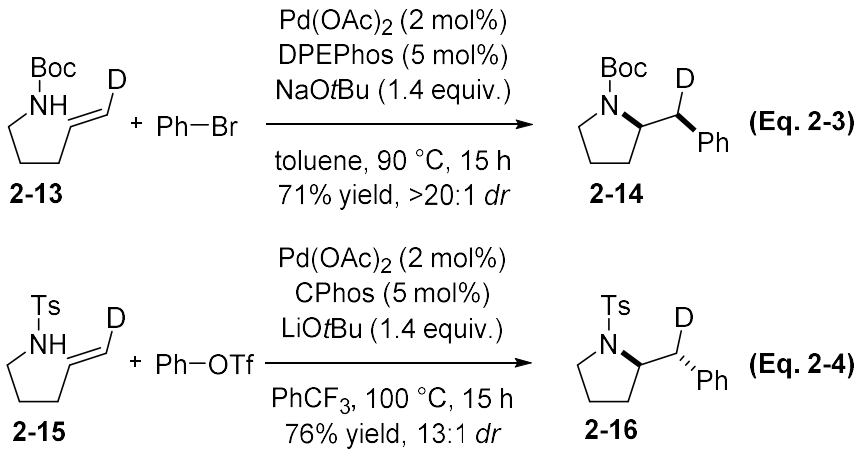
intramolecular Friedel–Crafts alkylation of **2-11** afforded **2-12**, which is an *N*- and *O*-protected analog of aphanorphine.[24]

Scheme 2-2. Formal synthesis of (±)-aphanorphine.



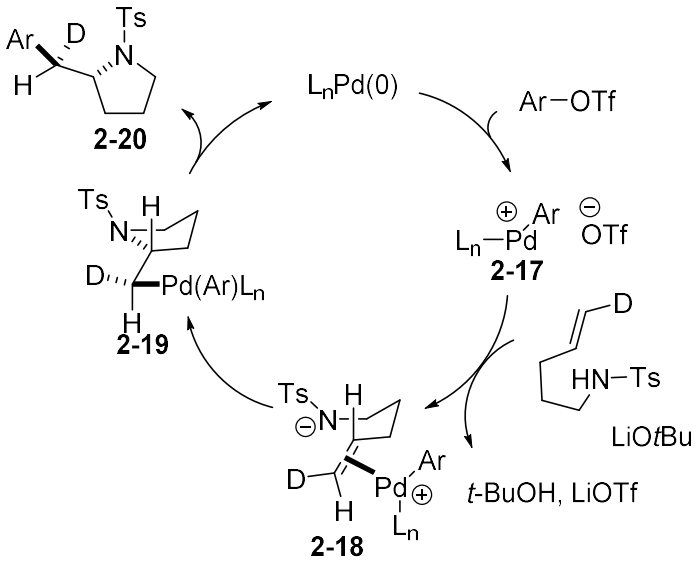
2-6 Mechanistic Studies via Deuterium Labelling

The contrast in stereocontrol observed in reactions of *N*-tosyl vs. *N*-Boc protected pentenylamines prompted us to explore the stereochemistry of the alkene addition process, as we felt this could indicate that the two types of substrates react via different mechanisms.[25] We have previously shown that carboamination reactions of Boc-protected substrates proceed with *syn*-addition of the nitrogen atom and the aryl group to the alkene.[13d] For example, the coupling of deuterated substrate **2-13** with bromobenzene using a $Pd(OAc)_2$/DPEPhos catalyst afforded **2-14** in 71% yield and >20:1 *dr* **(Eq. 2-3)**. In contrast, we found that the coupling of tosyl-protected substrate **2-15** with phenyl triflate using our optimized conditions described above provided **2-16** in 76% yield and 13:1 *dr* **(Eq. 2-4)**. This product results from *anti*-addition of the nitrogen atom and the aryl group to the double bond in **2-15**.[26]



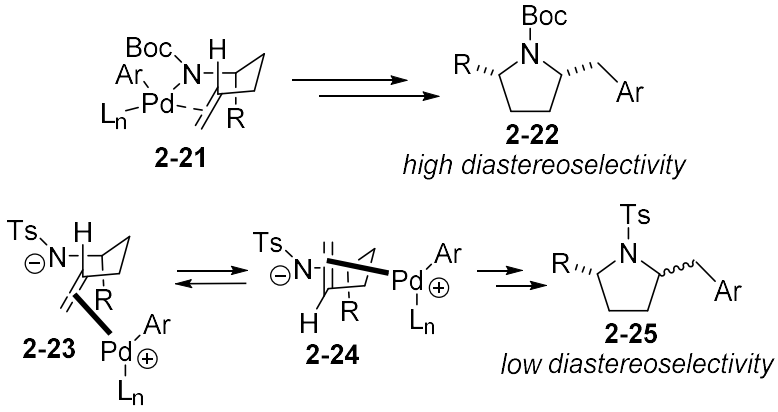
These results suggest that the mechanism of Pd-catalyzed alkene carboamination reactions of *N*-tosylpent-4-enylamines with aryl triflates is indeed different from that of the analogous Boc-protected substrates with aryl bromides. As shown below **(Scheme 2-3)**, the mechanism with tosyl-protected derivatives is initiated by oxidative addition of the aryl triflate to Pd(0). However, upon formation intermediate **2-17** binds to the alkene to afford **2-18**, which then undergoes *anti*-aminopalladation[27] to generate **2-19**. Reductive elimination then leads to C-C bond formation to yield the product **2-20** with regeneration of the Pd(0) catalyst.

Scheme 2-3. *Anti*-Aminopalladation Mechanism.



The modest diastereoselectivity observed in reactions of *N*-tosylamine derivatives (e.g., in the formation of **2-6b** or **2-9c**) is likely due to the possibility of the aminopalladation step occurring from either conformer **2-23** or **2-24**, which are likely close in energy **(Scheme 2-4)**.[28] In contrast, reactions that proceed via *syn*-aminopalladation appear to occur via a highly organized transition state (**2-21**) in which the alkene π-bond is eclipsed with the Pd-N bond.

Scheme 2-4. Pathway for Diastereomer Formation.



2-7 Conclusion

The results presented above, along with those described in our recent studies on Pd-catalyzed alkene carboamination reactions of *N*-allyl sulfamides[19] and *N*-tosyl-*N*-propargyl guanidines,[29] illustrate that transformations of relatively non-nucleophilic substrates that fail under *syn*-aminopalladation conditions can (in cases examined thus far) be achieved using conditions that promote *anti*-aminopalladation. Our prior mechanistic studies have shown that the rate of *syn*-aminopalladation is directly related to the nucleophilicity of the *N*-atom; electron-withdrawing *N*-substituents dramatically slow this process.[18] In addition, Stahl has illustrated that alkene aminopalladation reactions are reversible when the *N*-atom bears an electron-withdrawing group.[30] Thus, the *syn*-aminopalladation/reductive elimination sequence is unfavorable for electron-poor nucleophiles, and competing Heck arylation predominates. In contrast, it appears that when *anti*-aminopalladation conditions are employed the rates of *anti*-aminopalladation from **2-18** and subsequent reductive elimination from **2-19** are faster than the carbopalladation that would lead to Heck-arylation side products.

In conclusion, we have developed new reaction conditions for Pd-catalyzed alkene carboaminations that allow for use of electron-withdrawing *N*-tosyl and *N*-trifluoroacetyl protecting groups. Although diastereoselectivities are typically modest, chemical yields are generally good, and this represents a useful expansion in the scope of alkene carboamination methodology.

2-8 Note from the Author

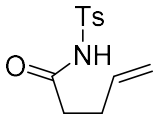
This thesis chapter represents work that has been previously published in a peer-reviewed journal, which has been reproduced or adapted here with permission from the authors.

2-9 Experimental

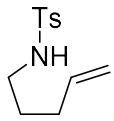
General: All reactions were carried out at under a nitrogen atmosphere in flame-dried glassware. Palladium(II) acetate and RuPhos were purchased from Strem Chemical Co. and used without purification, and CPhos was purchased from Sigma-Aldrich Co. and was used without further purification. Aryl triflates were prepared according to a procedure published by Frantz and coworkers,[31] except the compounds were purified by column chromatography. All other reagents were obtained from commercial sources and were used as obtained unless otherwise noted. (±)-4-Methyl-*N*-{2-methyl-2-[(trimethylsilyl)oxy]pent-4-en-1- yl}benzenesulfonamide **(10)** was prepared as previously reported.[32] Bulk quantities of lithium tert-butoxide and sodium tert-butoxide were stored in nitrogen-filled glove box and small amounts were removed shortly before use. Toluene, THF, dichloromethane and diethyl ether were purified using a GlassContour solvent purification system. Ratios of diastereomers were determined by 1 H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in **Tables 2–5**, **Scheme 2-2**, and **Equations 2-3–2-4** are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in **Tables 2–5**, **Scheme 2-2**, and **Equations 2-3–2-4**. Due to the presence of

diastereomers for compounds **2-8b**−**2-8e**, **S2** and **2-9b**−**2-9e**, it was not possible to accurately determine coupling constants for fluorine-coupled carbons. As such, for these compounds a simple list of all ^{13}C signals observed for the mixture is provided.

Experimental Procedures and Compound Characterization Data

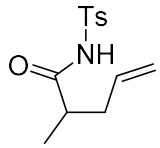


***N*-Tosylpent-4-enamide (2-S1)**.[33] A flame-dried flask equipped with a rubber septum and a stirbar was cooled under a stream of nitrogen and charged with 4-pentenoic acid (1 g, 10 mmol) and THF (20 mL), then *p*-toluenesulfonyl isocyanate (1.5 mL, 10 mmol) was added. After stirring at rt for 10 min the septum was removed and triethylamine (1.4 mL, 10 mmol) was added dropwise to the open flask, allowing for the release of the formed CO_2. The resulting mixture was stirred at rt for 3 h then was diluted with 20 mL EtOAc, transferred to a separatory funnel, and then washed with HCl and brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield 2.42 g (96%) of a white crystalline solid that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, br, 1 H), 7.94 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 5.76–5.69 (m, 1 H), 5.02–4.97 (m, 2 H), 2.45 (s, 3 H), 2.37– 2.3 (m, 4 H).

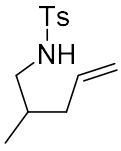


4-Methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide (2-5a).[34] A flame dried flask was cooled under a stream of nitrogen and charged with **2-S1** (2.42 g, 9.05 mmol) and THF (27 mL). The mixture was cooled to 0 °C then lithium aluminum hydride (27.2 mL, 1 M in

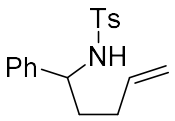
THF) was added slowly, and the reaction mixture was warmed to rt and stirred overnight. The mixture was then cooled to °C and quenched with H_2O (9 mL). Diethyl ether (27 mL) was added, followed by a solution of 10 M aqueous NaOH (27 mL). The organic layer was decanted, and the remaining white solid was washed with diethyl ether (2 x 27 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and evaporated in vacuo to afford a clear, colorless oil. The crude product was purified via flash chromatography on silica gel to afford 1.54 g (71%) of the desired product as a colorless oil. Spectroscopic data for the compound are consistent with those previously reported.[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.73–5.68 (m, 1 H), 4.99–4.95 (m, 2 H), 4.38 (s, br, 1 H), 2.96 (q, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H), 2.05 (q, *J* = 7.1 Hz, 2 H), 1.56 (p, *J* = 7.0 Hz, 2 H).



2-Methyl-*N*-tosylpent-4-enamide (2-S2). A procedure similar to that for used for the preparation of **2-S1** was employed for the conversion of 2-methyl-4-pentenoic acid (0.685 g, 6.0 mmol) to the title compound. This procedure afforded 1.53 g (95%) of the desired product as a white solid that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, br, 1 H), 7.94 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 5.66–5.56 (m, 1 H), 5.00–4.94 (m, 2 H), 2.45 (s, 3 H), 2.35–2.14 (m, 2 H), 2.15–2.08 (m, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H).

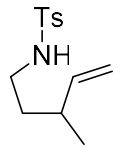


4-Methyl-*N*-(2-methylpent-4-en-1-yl)benzenesulfonamide (2-5b).[35] A procedure similar to that used for the preparation of **2-5a** was employed for the conversion of **2-S2** to the title compound. This procedure afforded 0.60 g (42%) of the desired product as a colorless oil. Spectroscopic data for the compound are consistent with those previously reported.[35] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 5.72−5.64 (m, 1 H), 5.02–4.94 (m, 2 H), 4.35 (s, br, 1 H), 2.86 (dt, *J* = 12.8, 6.4 Hz, 1 H), 2.76 (dt, 12.8, 6.4 Hz, 1 H), 2.43 (s, 3 H), 2.10–2.01 (m, 1 H), 1.96−1.84 (m, 1 H), 1.74–1.61 (m, 1 H), 0.87 (d, *J* = 6.8 Hz, 3 H).

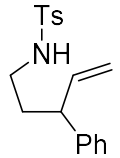


4-Methyl-*N*-(1-phenylpent-4-en-1-yl)benzensulfonamide (2-5c).[34] A flame dried flask was cooled under a stream of nitrogen and charged with 1-phenylpent-4-en-1-amine[36] (0.39 g, 2.4 mmol) and THF (24 mL). Tosyl chloride (0.52 g, 2.9 mmol) was then added, followed by triethylamine (0.4 mL, 2.9 mmol) and the solution was stirred at rt overnight. The reaction was then quenched with 2 M HCl (12 mL) and the mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford an off-white solid. The crude product was purified via flash chromatography on silica gel to yield 0.52 g (69%) of a white solid, mp 66−68 °C. Spectroscopic data for the compound are consistent with those previously reported.[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2 H), 7.16–7.15 (m, 3 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 7.00–6.98 (m, 2 H), 5.75–5.60 (m, 1 H), 4.97– 4.91 (m, 2 H),

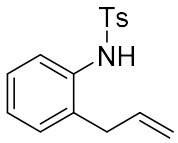
4.75 (s, br, 1 H), 4.29 (q, *J* = 7.2 Hz, 1 H), 2.35 (s, 3 H), 1.99–1.88 (m, 3 H), 1.86–1.75 (m, 1 H).



4-Methyl-*N*-(3-methylpent-4-en-1-yl)benzensulfonamide (2-5d).[37] A flame dried flask was cooled under a stream of nitrogen and charged with a solution of 3-methylpent-4-en-1-amine[37] (85 mL, 8.5 mmol, 0.1 M in diethyl ether). *p*-Toluenesulfonyl chloride (1.94 g, 10.2 mmol) was then added, followed by triethylamine (1.4 mL, 10.2 mL) and the resulting solution was stirred at rt overnight. The reaction was then quenched with 2 M HCl (50 mL) and the mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a colorless oil. The crude product was purified via flash chromatography on silica gel to yield 1.19 g (55%) of the desired product as a colorless oil. Spectroscopic data for the compound are consistent with those previously reported.[37] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 5.61–5.54 (m, 1 H), 4.94–4.90 (m, 2 H), 4.36 (s, br, 1 H), 3.00–2.90 (m, 2 H), 2.43 (s, 3 H), 2.17–2.12 (m, 1 H), 1.51–1.41 (m, 2 H), 0.95 (d, *J* = 7.0 Hz, 3 H).

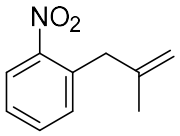


4-Methyl-*N*-(3-phenylpent-4-en-1-yl)benzenesulfonamide (2-5e). A flame dried flask was cooled under a stream of nitrogen and charged with 3-phenylpent-4-en-1-amine[36] (0.30 g, 1.86 mmol) and diethyl ether (19 mL). *p*-Toluenesulfonyl chloride (0.43 g, 2.2 mmol) was then added, followed by triethylamine (0.31 mL, 2.2 mmol) and the resulting solution was stirred at rt overnight. The reaction was then quenched with 2 M HCl (20 mL) and the mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified via flash chromatography on silica gel to yield 1.19 g (55%) of the desired product as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2 H), 7.30–7.26 (m, 4 H), 7.22–7.10 (m, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 5.91–5.82 (m, 1 H), 5.04–4.98 (m 2 H), 4.26 (s, br, 1 H), 3.28 (q, *J* = 7.6 Hz, 1 H), 2.92 (q, *J* = 7.0 Hz, 2 H), 2.43 (s, 3 H), 1.94−1.82 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 142.8, 140.9, 136.9, 129.7, 128.7, 127.4, 127.1, 126.6, 114.9, 47.0, 41.4, 35.0, 21.5; IR (film) 3277, 2930, 1320, 1154 cm^{-1}; MS (ESI+) 316.1371 (316.1366 calcd for C18H21NO2S, M + H^+).



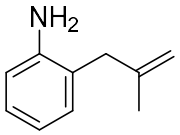
***N*-(2-Allylphenyl)-4-methylbenzenesulfonamide (2-5f)**. A flame-dried flask was cooled under a stream of nitrogen and charged with 2-allylaniline[39] (1.00 g, 7.50 mmol) and diethyl ether (55 mL). *p*-Toluenesulfonyl chloride (1.72 g, 9.00 mmol) was added followed by triethylamine (1.25 mL, 9.00 mmol), at which point the solution became cloudy. The

reaction mixture was stirred at rt overnight then was concentrated in vacuo to yield a brown, viscous oil. The crude product was purified via flash chromatography on silica gel to afford 1.40 g (65%) of the title compound as a tan solid, mp 68−69 °C. Spectroscopic data for the compound are consistent with those previously reported.[38] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.21–7.19 (m, 3 H), 7.12 (t, *J* = 7.0 Hz, 1 H), 7.07 (d, *J* = 7.0 Hz, 1 H), 6.49 (s, br, 1 H), 5.82–5.74 (m, 1 H), 5.12 (d, *J* = 10.0 Hz, 1 H), 4.94 (d, *J* = 17.0 Hz, 1 H), 3.01 (d, *J* = 4.0 Hz, 2 H), 2.39 (s, 3 H).

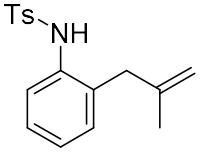


1-(2-Methylallyl)-2-nitrobenzene (2-S3). A flame-dried flask was cooled under a stream of nitrogen and charged with nitrobenzene (2.26 g, 9.09 mmol) and THF (36 mL) and cooled to -40 ºC. A solution of phenylmagnesium bromide (10 mL, 10 mmol, 1 M in THF) was then added dropwise, and the resulting mixture stirred at -40 °C for 5 min. A solution of CuCN·LiCl (18.2 mL, 18.2 mmol, 1 M in THF) was then added dropwise. The mixture was stirred at -40 °C for 30 min then 3-bromo-2-methylpropene (1.1 mL, 10.91 mmol) was added dropwise and the solution was stirred at -40 ºC for 1.5 hours. The reaction was quenched with NH_4Cl (40 mL) and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer was washed with water (40 mL) and brine (40 mL), and then was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a brown oil. The crude product was purified via flash chromatography to afford 0.76 g (47%) of the title compound as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* =

8.0 Hz, 2 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.38–7.35 (m, 2 H), 4.84 (s, 1 H), 4.51 (s, 1 H), 3.64 (s, 2 H), 1.74 (s, 3 H).

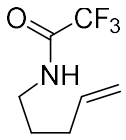


2-(2-Methylallyl)aniline (2-S4). A flame-dried flask was cooled under a stream of nitrogen and charged with zinc dust (2.77 g, 4.24 mmol), then 1-(2-methylallyl)-2-nitrobenzene (0.50 g, 2.8 mmol) in distilled ethanol (20 mL) was added, followed by acetic acid (2.4 mL, 4.24 mmol). The reaction mixture was stirred at rt for 1 h, then was filtered through a plug of celite. The celite was rinsed with ethyl acetate and the combined organic layers were concentrated. A solution of saturated aqueous $NaHCO_3$ (15 mL) was added to the resulting crude product, then the mixture was extracted with ethyl acetate (3 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 0.292 g (70%) of an orange oil that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.02 (m, 2 H), 6.75 (t, *J* = 7.2 Hz, 1 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 4.87 (s, 1 H), 4.74 (s, 1 H), 3.72 (s, br, 2 H), 3.28 (s, 2 H), 1.74 (s, 3 H).

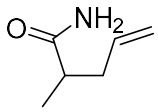


4-Methyl-*N*-[2-(2-methylallyl)phenyl]benzenesulfonamide (2-5g). A flame-dried flask was cooled under a stream of nitrogen and charged with 2-(2-methylallyl)aniline (0.29 g, 1.99 mmol) and dichloromethane (20 mL). The solution was cooled to 0 ºC, *p*-toluenesulfonyl chloride (0.38 g, 1.99 mmol) was added, followed by triethylamine (0.42

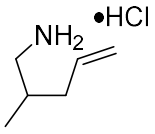
mL, 2.98 mmol), and the reaction mixture was stirred at rt overnight. The mixture was then concentrated in vacuo to yield a crude oil that was purified via flash chromatography on silica gel to afford 0.42 g (71%) of the title compound as a viscous orange oil. Spectroscopic data for the compound are consistent with those previously reported.[40] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.23–7.20 (m, 3 H), 7.11 (t, *J* = 7.0 Hz, 1 H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.68 (s, br, 1 H), 4.89 (s, 1 H), 4.62 (s, 1 H), 2.92 (s, 2 H), 3.93 (s, 3 H), 1.57 (s, 3 H).



2,2,2-Trifluoro-*N*-(pent-4-en-1-yl)acetamide (2-8a). A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of pent-4-en-1-amine (50 mL, 5.0 mmol, 0.1 M in diethyl ether) and cooled to 0 ºC. Triethylamine (1.4 mL, 10.0 mmol) was added, followed by trifluoroacetic anhydride (0.77 mL, 5.5 mmol). The resulting mixture was stirred at rt overnight then was diluted with water (20 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a red-orange oil. The crude product was purified via flash chromatography to yield 412 mg (45%) of the title compound as a clear, colorless oil. The compound was found to exist as a mixture of rotamers by ^{1}H NMR analysis; data are for the major rotamer. Spectroscopic data for the compound are consistent with those previously reported.[41] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, br, 1 H), 5.75 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H), 5.14–4.84 (m, 2 H), 3.35 (q, *J* = 6.8 Hz, 2 H), 2.05 (q, *J* = 7.2 Hz, 2 H), 1.68 (p, *J* = 7.2 Hz, 2 H).

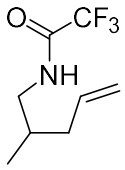


2-Methylpent-4-enamide (2-S5). A flame-dried flask was cooled under a stream of nitrogen and charged with 2-methylpent-4-enoic acid (1.71 g, 15 mmol) and benzene (30 mL), and was then cooled to 0ºC. Oxalyl chloride (2.6 mL, 30 mmol) was then added slowly, and the reaction mixture was stirred at rt for 3 h. The mixture was then concentrated in vacuo, and the resulting crude material was dissolved in THF (30 mL) and then slowly added to aqueous NH_4OH at 0 ºC. The resulting mixture was then stirred at rt overnight. The mixture was concentrated, then diluted with water (15 mL) and ethyl acetate (30 mL) and transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 1.53 g (90%) of a white solid that was used without further purification.



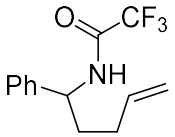
2-Methylpent-4-en-1-aminium chloride (2-S6). A flame-dried flask was cooled under a stream of nitrogen and charged with 2-methylpent-4-enamide (1.53 g, 13.5 mmol) and THF (40 mL), and the solution was cooled to 0 ºC. Lithium aluminum hydride (40.5 mL, 40.5 mmol, 1 M in THF) was added slowly then the mixture was warmed to rt and stirred for 24 h. The mixture was then cooled to 0 ºC and quenched with water (13.5 mL), 1 M NaOH (13.5 mL), then additional water (40.5 mL). The organic layer was decanted and the remaining solids were washed with ether and the ether solution was decanted. The

combined ether layers were dried over Na_2SO_4 and filtered to afford a solution of 2-methylpent-4-en-1-amine in ether. To this solution HCl (5 mL, 4 M in dioxanes) was slowly added, and then the mixture was concentrated in vacuo to afford 1.46 g (80%) of the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, br, 3 H), 5.80−5.67 (m, 1 H), 5.13–5.08 (m, 2 H), 3.0–2.94 (m, 1 H), 2.79–2.72 (m, 1 H), 2.19– 2.15 (m, 1 H), 2.09–1.99 (m, 2 H), 1.07 (d, *J* = 6.5 Hz, 3 H).

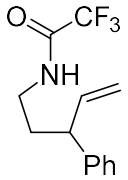


2,2,2-Trifluoro-*N*-(2-methylpent-4-en-1-yl)acetamide (2-8b). A flame-dried flask was cooled under a stream of nitrogen and charged with 2-methylpent-4-en-1-aminium chloride (1.46 g, 10.8 mmol) and dichloromethane (20 mL), and then the solution was cooled to 0 ºC. Triethylamine (4.5 mL, 32.5 mmol) was added, followed by trifluoroacetic anhydride (1.8 mL, 13.0 mmol). The solution was then allowed to stir at rt overnight, and the reaction was treated with water (15 mL), then separated. The aqueous layer was extracted with dichloromethane (10 mL), and the combined organics were washed with brine. The layers were separated, and the organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified via column chromatography on silica gel to yield 1.48 g (70%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl3) δ 6.47 (s, br, 1 H), 5.81−5.73 (m, 1 H), 5.09–5.05 (m, 2 H), 3.32–3.27 (m, 1 H), 3.25–3.19 (m, 1 H), 2.13–2.07 (m, 1 H), 2.03–1.98 (m, 1 H), 1.09–1.80 (m, 1 H), 0.95 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 157.1,

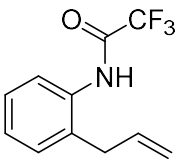
135.8, 117.1, 115.9 (q, *J* = 286 Hz), 45.3, 38.8, 32.8, 17.4; IR (film) 3307, 2966, 1701, 1154 cm^{-1}; MS (ESI+) 196.0939 (196.0944 calcd for $C_8H_{12}F_3NO$, M + H^+).



2,2,2-Trifluoro-*N*-(1-phenylpent-4-en-1-yl)acetamide (2-8c). A flame-dried flask was cooled under a stream of nitrogen and charged with 1-phenylpent-4-en-1-amine[36] (0.678 g, 4.2 mmol) and dichloromethane (5 mL). The solution was cooled to 0 ºC, and then triethylamine (1.17 mL, 8.4 mmol) was added followed by trifluoroacetic anhydride (0.64 mL, 4.6 mmol). The resulting mixture was stirred at rt overnight, then water was added (5 mL) and the mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with dichloromethane (10 mL), and then the combined organics layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified via flash column chromatography on silica gel to yield 0.69 g (64%) of the title compound as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.32 (m, 2 H), 7.33–7.31 (m, 1 H), 7.29–7.28 (m, 2 H), 6.43 (s, br, 1 H), 5.83−5.76 (m, 1 H), 5.08–4.96 (m, 3 H), 2.13–1.99 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 156.2, 155.9, 139.7, 136.8, 129.0, 128.2, 126.6, 116, 115.8 (q, *J* = 287.3 Hz), 53.9, 34.5, 30.1; IR (film) 3296, 1696, 1162 cm^{-1}; MS (ESI+) 258.1095 (258.1100 calcd for $C_{13}H_{14}F_3NO$, M + H^+).



2,2,2-Trifluoro-*N*-(3-phenylpent-4-en-1-yl)acetamide (2-8d). A flame-dried flask was cooled under a stream of nitrogen and charged with 3-phenylpent-4-en-1-amine[36] (0.69 g, 4.3 mmol) and dichloromethane (5 mL). The solution was cooled to 0 ºC then triethylamine (1.2 mL, 8.6 mmol) was added followed by trifluoroacetic anhydride (0.66 mL, 4.7 mmol). The resulting mixture was stirred at rt overnight then water (5 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with dichloromethane (10 mL), and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a red-orange oil. The crude product was purified via flash chromatography to yield 0.49 g (44%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, 2 H), 7.29–7.21 (m, 1 H), 7.20–7.18 (m, 2 H), 6.19 (s, br, 1 H), 5.96 (m, 1 H), 5.10 (dd, *J* = 13.9, 3.2 Hz, 2 H), 3.45−3.38 (m, 1 H), 3.34– 3.26 (m, 2 H), 2.10–1.99 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 157.2, 156.9, 156.6, 142.7, 140.8, 128.9, 127.4, 126.9, 115.8 (q, *J* = 286 Hz), 115.1, 47.7, 38.6, 34.1; IR (film) 3300, 3084, 1700, 1152 cm^{-1}; MS (ESI+) 258.1096 (258.1100 calcd for $C_{13}H_{14}F_3NO$, M + H^+).



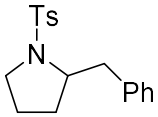
***N*-(2-Allylphenyl)-2,2,2-trifluoroacetamide (2-8e)**. A flame-dried flask was cooled under a stream of nitrogen and charged with 2-allylaniline (0.75 g, 5.6 mmol) and dichloromethane (5.6 mL). The solution was cooled to 0 ºC, and then triethylamine (1.6 mL, 11.2 mmol) was added followed by trifluoroacetic anhydride (0.9 mL, 6.2 mmol). The resulting mixture was stirred at rt overnight then water (10 mL) was added and the mixture

was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with dichloromethane (10 mL), and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified via column chromatography to yield 1.03 g (80%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, br, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.35–7.29 (m, 1 H), 7.26–7.20 (m, 2 H), 6.00–5.91 (m, 1 H), 5.26–5.14 (m, 2 H), 3.42 (d, *J* = 6.0 Hz, 2 H), ^{13}C NMR (125 MHz, CDCl3) δ 155.4, 155.1, 154.8, 154.5, 135.5, 133.6, 130.7, 130.3, 127.9, 127.0, 123.3, 117.5, 115.9 (q, J = 287 Hz), 37.1; IR (film) 3276, 1703, 1159 cm^{-1}; MS (ESI+) 230.0785 (230.0787 calcd for $C_{11}H_{10}F_3NO$, M + H$^+$).

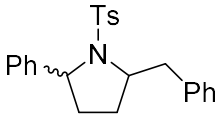
Experimental Procedures and Compound Characterization Data for Pyrrolidine Products

General Procedure for Pd-Catalyzed Carboamination Reactions of Aryl Triflates.

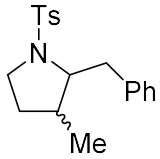
An oven dried test tube equipped with a magnetic stirbar and a rubber septum was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol %), CPhos or RuPhos (5 mol %), and LiO*t*Bu (1.4 equiv). The tube was purged with nitrogen and then a solution of the aryl triflate (1.2 equiv) in $PhCF_3$ (1 mL) was added and the resulting mixture was stirred at rt for 1 min. A solution of the *N*-protected amine substrate (1 equiv) in $PhCF_3$ (1.5 mL) was added, and the mixture was heated to 100 ºC for 15 h. The mixture was then cooled to rt, saturated aq NH_4Cl (2 mL) was added, the organic layer was removed, and the aqueous layer was extracted with dichloromethane (4 x 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified via flash chromatography.



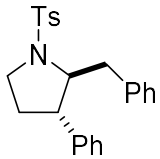
2-Benzyl-1-tosylpyrrolidine (2-6a). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (49 µL, 0.30 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (60 mg, 0.25 mmol). This procedure afforded 60 mg (76%) of the title compound as a white solid, m.p. 91−93 °C. Spectroscopic data for the compound are consistent with those previously reported.[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2 H), 7.32–7.20 (m, 6 H), 3.85−3.79 (m, 1 H), 3.43–3.36 (m, 1 H), 3.25 (dd, J = 13.3, 3.5 Hz, 1 H), 3.16−3.10 (m, 1 H), 2.75 (dd, *J* = 13.3, 9.6 Hz, 1 H), 2.42 (s, 3 H), 1.68–1.60 (m, 2 H), 1.49–1.40 (m, 2 H).



2-Benzyl-5-phenyl-1-tosylpyrrolidine (2-6b). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (40 µL, 0.24 mmol) with 4-methyl-*N*-(1-phenylpent-4-en-1-yl)benzensulfonamide **(2-5c)** (62.8 mg, 0.20 mmol). This procedure afforded 70 mg (90%) of the title compound as a pale yellow viscous oil. This compound was found to exist as a 2.2:1 mix of diastereomers by 1 H NMR analysis; data are for the major diastereomer. Spectroscopic data for the compound are consistent with those previously reported.[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2 H), 7.39–7.20 (m, 9 H), 7.12–7.02 (m, 2 H), 6.95 (d, *J* = 7.5 Hz, 1 H), 4.73–4.70 (m, 1 H), 4.01–3.94 (m, 1 H), 3.54 (ddd, *J* = 13.0, 5.5, 3.2 Hz, 1 H), 2.78 (ddd, *J* = 13.0, 10.7, 2.1 Hz, 1 H), 2.40 (s, 3 H), 1.90-1.86 (m, 2 H), 1.68–1.55 (m, 1 H), 1.48–1.42 (m, 1 H).

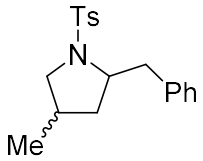


2-Benzyl-3-methyl-1-tosylpyrrolidine (2-6c). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (40 µL, 0.24 mmol) with 4-methyl-*N*-(3-methylpent-4-en-1-yl)benzensulfonamide **(2-5d)** (50.7 mg, 0.20 mmol) using 2 mL of benzotrifluoride. This procedure afforded 46 mg (70%) of the title compound as a pale yellow solid, m.p. 80–82 °C. This compound was found to exist as a 2.6:1 mix of diastereomers by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 0.8 H), 7.34–7.26 (m, 9.8 H), 3.94 (td, *J* = 7.9, 4.4 Hz, 0.4 H), 3.43–3.38 (m, 1.4 H), 3.31–3.16 (m, 3.4 H), 3.07 (m, 0.4 H), 2.91–2.85 (m, 1.4 H), 2.42 (s, 4.2 H), 1.98 (ddp, *J* = 10.8, 6.8, 3.9, 3.3 Hz, 1 H), 1.81–1.55 (m, 1.8 H), 1.25–1.20 (m, 0.4 H), 1.08 (ddt, *J* = 12.1, 7.0, 5.0 Hz, 1 H), 0.92 (d, *J* = 6.9 Hz, 1.2 H), 0.37 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.3, 143.2, 139.1, 138.3, 134.9, 134.6, 129.7, 129.6, 129.5, 128.3, 128.2, 127.5, 127.4, 126.3, 126.1, 68.3, 64.4, 47.5, 47.4, 42.1, 37.7, 37.2, 36.8, 31.5, 31.2, 21.5, 18.5, 14.4; IR (film) 2954, 1338, 1157 cm^{-1}; MS (ESI+) 330.01524 (330.1522 calcd for $C_{19}H_{23}NO_2S$, M + H^+).



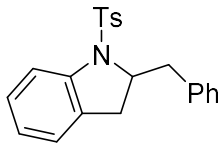
(±)-(2S,3S)-2-Benzyl-3-phenyl-1-tosylpyrrolidine (2-6d). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (40 µL, 0.24 mmol) with 4-methyl-*N*-(3-phenylpent-4-en-1-yl)benzenesulfonamide **(2-5e)** (63 mg, 0.20 mmol) in 2

mL benzotrifluoride using RuPhos (4.7 mg, 5 mol %) as the ligand. This procedure afforded 40 mg (51%) of the title compound as a white solid, m.p. 160–162 °C. This compound was found to exist as an 8:1 mixture of diastereomers by ^{1}H NMR analysis; data are for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2 H), 7.38–7.27 (m, 6 H), 7.25–7.20 (m, 1 H), 7.15–7.04 (m, 3 H), 6.58 (d, *J* = 7.0 Hz, 2 H), 3.91 (ddd, *J* = 7.1, 6.0, 3.2 Hz, 1 H), 3.54 (ddd, *J* = 11.8, 7.2, 5.1 Hz, 1 H), 3.19 (m, 2 H), 3.10–2.99 (m, 2 H), 2.46 (s, 3 H), 1.90–1.78 (m, 1 H), 1.45 (dq, *J* = 12.6, 7.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 141.7, 137.4, 134.9, 130.4, 129.7, 128.5, 128.3, 127.5, 126.9, 126.5, 126.4, 67.9, 49.1, 48.1, 40.6, 32.3, 21.6; IR (film) 2926, 1339, 1159 cm^{-1}; MS (ESI+) 392.1683 (392.1679 calcd for $C_{24}H_{25}NO_2S$, M + H^+).

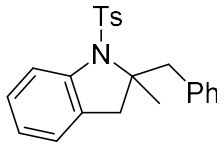


2-Benzyl-4-methyl-1-tosylpyrrolidine (2-6e). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (49 µL, 0.30 mmol) with 4-methyl-*N*-(2-methylpent-4-en-1-yl)benzenesulfonamide **(2-5b)** (63.3 mg, 0.25 mmol). This procedure afforded 60 mg (73%) of the title compound as a white solid, m.p. 115–117 °C. This compound was found to exist as a 1.8:1 mix of diastereomers by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 3 H), 7.33–7.18 (m, 10.5 H), 3.84 (dddd, *J* = 10.1, 8.5, 3.6, 2.0 Hz, 0.5 H), 3.75 (tdd, *J* = 9.3, 6.9, 3.7 Hz, 1 H), 3.59–3.52 (m, 1.5 H), 3.45 (dd, *J* = 13.2, 3.7 Hz, 1 H), 3.26 (dd, *J* = 13.3, 3.4 Hz, 0.4 H), 2.84–2.71 (m, 2.5 H), 2.56 (t, *J* = 9.4 Hz, 0.5 H), 2.43 (s, 4.7 H), 2.22–2.08 (m, 0.4 H), 1.84–1.77 (m, 1 H), 1.72 (ddt, *J* = 12.6, 6.1, 1.2 Hz, 0.5 H), 1.58–1.39 (m, 1 H), 1.26–1.18

(m, 1.4 H), 1.06–1.0 (m, 0.5 H), 0.83 (d, *J* = 6.5 Hz, 3 H), 0.80 (d, J = 6.5 Hz, 1.5 H); ^{13}C (125 MHz, $CDCl_3$) δ 143.3, 138.6, 138.3, 135.2, 134.3, 129.7, 129.6, 128.4, 128.3, 127.6, 127.4, 126.4, 126.3, 62.4, 61.7, 56.3, 55.9, 43.0, 42.9, 40.1, 37.6, 32.5, 31.2, 21.5, 16.9, 16.5; IR (film) 2926, 1341, 1156 cm^{-1}; MS (ESI+) 331.0523 (331.0522 calcd for $C_{19}H_{23}NO_2S$, M + H^+).

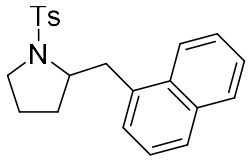


2-Benzyl-1-tosylindoline (2-6f). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (49 μL, 0.30 mmol), with *N*-(2-allylphenyl)-4-methylbenzenesulfonamide **(2-5f)** (71.8 mg, 0.25 mmol). This procedure afforded 82 mg (87%) of the title compound as a white solid, m.p. 124−126 °C. Spectroscopic data for the compound are consistent with those previously reported.[42] ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.34–7.27 (m, 2 H), 7.26–7.20 (m, 4 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 3.5 Hz, 2 H), 4.45 (ddt, *J* = 11.1, 6.7, 4.7 Hz, 1 H), 3.35 (dd, *J* = 13.4, 4.3 Hz, 1 H), 2.78 (dd, *J* = 13.4, 10.2 Hz, 1 H), 2.59 (d, *J* = 5.5 Hz, 2 H), 2.33 (s, 3 H).

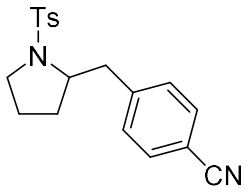


2-Benzyl-2-methyl-1-tosylindoline (2-6g). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (49 μL, 0.30 mmol), with 4-methyl-*N*-[2-(2-methylallyl)phenyl]benzenesulfonamide **(2-5g)** (75.3 mg, 0.25 mmol). This procedure

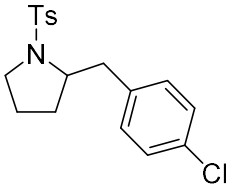
afforded 28 mg (30%) of the title compound as a white solid, m.p. 50–52 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 8.2 Hz, 1 H), 7.26–7.20 (m, 7 H), 7.14–7.07 (m, 1 H), 7.00 (dd, *J* = 7.4, 1.3 Hz, 1 H), 6.89 (td, *J* = 7.4, 1.0 Hz, 1 H), 3.40 (d, *J* = 13.2 Hz, 1 H), 3.21 (t, *J* = 13.0 Hz, 2 H), 2.65 (d, *J* = 16.0 Hz, 1 H), 2.19 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 142.3, 139.4, 136.7, 130.8, 129.6, 12834, 128.0, 127.5, 126.6, 124.7, 122.7, 114.2, 73.1, 46.4, 41.8, 25.9, 21.5; IR (film) 2923, 1343, 1160 cm^{-1}; MS (ESI+) 378.1524 (378.1522 calcd for $C_{23}H_{23}NO_2S$, M + H^+).



2-(Naphthalen-1-ylmethyl)-1-tosylpyrrolidine (2-6h). The general procedure was employed for the reaction of 1-napthyl trifluoromethanesulfonate (59 µL, 0.30 mmol), with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (60 mg, 0.25 mmol). This procedure afforded 61 mg (67%) of the title compound as a white solid, m.p. 139–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.5 Hz, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 7.78–7.74 (m, 3 H), 7.65 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1 H), 7.57–7.50 (m, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.29–7.26 (m, 3 H), 4.00 (ddd, *J* = 9.4, 6.3, 3.3 Hz, 2 H), 3.56 (ddd, *J* = 10.5, 7.0, 4.0 Hz, 1 H), 3.16 (td, *J* = 9.2, 6.8 Hz, 1 H), 2.92 (dd, *J* = 14.0, 11.6 Hz, 1 H), 2.39 (s, 3 H), 1.95−1.85 (m, 1 H), 1.67 (ddt, *J* = 13.2, 6.7, 3.6 Hz, 1 H), 1.56–1.52 (m, 1 H), 1.25–1.19 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 134.9, 134.5, 133.9, 132.2, 129.7, 128.7, 127.7, 127.5, 127.4, 126.3, 125.8, 125.4, 124.5, 60.4, 49.3, 40.6, 29.9, 23.8, 21.5; IR (film) 2943, 1340, 1156 cm^{-1}; MS (ESI+) 366.1525 (366.1522 calcd for $C_{22}H_{23}NO_2S$, M + H^+).

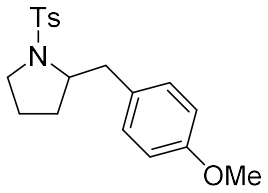


4-[(1-Tosylpyrrolidin-2-yl)methyl]benzonitrile (2-6i). The general procedure was employed for the reaction of 4-cyanophenyl trifluoromethanesulfonate (60.2 mg, 0.24 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (59.8 mg, 0.25 mmol) in 2 mL of benzotrifluoride. This procedure afforded 42 mg (61%) of the title compound as a white solid, m.p. 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 3.83–3.79 (m, 1 H), 3.36–3.31 (m, 1 H), 3.22 (dd, *J* = 13.4, 3.6 Hz, 1 H), 3.15–3.10 (m, 1 H), 2.91 (dd, *J* = 13.3, 8.8 Hz, 1 H), 2.43 (s, 3 H), 1.58–1.43 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 143.6, 134.3, 132.2, 130.5, 129.8, 127.5, 118.9, 110.4, 60.9, 49.2, 42.7, 30.0, 23.8, 21.5; IR (film) 2955, 1338, 1158 cm^{-1}; MS (ESI+) 341.1323 (341.1318 calcd for $C_{19}H_{20}N_2O_2S$, M + H^+).

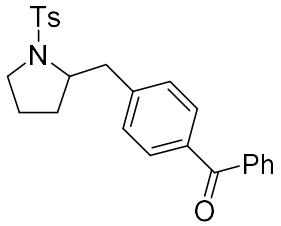


2-(4-Chlorobenzyl)-1-tosylpyrrolidine (2-6j). The general procedure was employed for the reaction of 4-chlorophenyl trifluoromethanesulfonate (62.5 mg, 0.24 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (47.8 mg, 0.20 mmol). This procedure afforded 46 mg (67%) of the title compound as a white solid, m.p. 95−96 °C. Spectroscopic data for the compound are consistent with those previously reported.[44] ^{1}H

NMR (700 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 3.78 (tt, *J* = 7.5, 3.5 Hz, 1 H), 3.36–3.34 (m, 1 H), 3.17–3.10 (m, 2 H), 2.79 (dd, *J* = 13.4, 9.1 Hz, 1 H), 2.43 (s, 3 H), 1.61–1.55 (m, 2 H), 1.47–1.44 (m, 2 H).

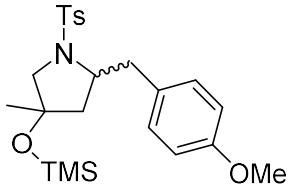


2-(4-Methoxybenzyl)-1-tosylpyrrolidine (2-6k). The general procedure was employed for the reaction of 4-methoxyphenyl trifluoromethanesulfonate (61.4 mg, 0.24 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (59.8 mg, 0.25 mmol) in 2 mL of benzotrifluoride. This procedure afforded 43 mg (62%) of the title compound as a pale yellow solid, m.p. 98–100 °C. ^{1}H NMR (500 MHz, CDCl3) δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 3.80–3.75 (m, 1 H), 3.79 (s, 3H), 3.39–3.33 (m, 1 H), 3.17–3.12 (m, 2 H), 2.72 (dd, *J* = 13.5, 9.5 Hz, 1 H), 2.42 (s, 3 H), 1.62–1.58 (m, 2 H), 1.47–1.40 (m, 2 H); ^{13}C NMR δ 158.2, 143.3, 134.8, 130.6, 130.5, 129.6, 127.5, 113.8, 61.7, 55.2, 19.2, 41.7, 29.8, 23.8, 21.5; IR (film) 2952, 1340, 1156 cm^{-1}; MS (ESI+) 346.1771 (346.1471 calcd for $C_{19}H_{23}NO_3S$, M + H^+).



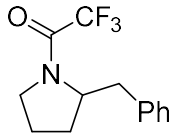
Phenyl-{4-[(1-tosylpyrrolidin-2-yl)methyl]phenyl}methanone (2-6l). The general procedure was employed for the reaction of 4-benzoylphenyl trifluoromethanesulfonate

(99 mg, 0.30 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (59.8 mg, 0.25 mmol) in 2 mL of benzotrifluoride. This procedure afforded 66 mg (63%) of the title compound as a white solid, m.p. 44–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.75 (m, 6 H), 7.61–7.57 (m, 1 H), 7.50–7.47 (m, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 7.5 Hz, 2 H), 3.90–3.84 (m, 1 H), 3.42–3.35 (m, 1 H), 3.31 (dd, *J* = 13.3, 3.6 Hz, 1 H), 3.18–3.14 (m, 1 H), 2.89 (dd, *J* = 13.3, 9.3 Hz, 1 H), 2.43 (s, 3 H), 1.66–1.61 (m, 2 H), 1.54–1.42 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 137.7, 135.8, 134.5, 132.3, 130.3, 130.0, 129.7, 129.6, 128.3,127.5, 61.2, 49.2, 42.7, 30.0, 23.8, 21.5; IR (film) 2928, 1653, 1340, 1156 cm^{-1}; MS (ESI+) 420.1635 (420.1628 calcd for $C_{25}H_{25}NO_3S$, M + H$^+$).

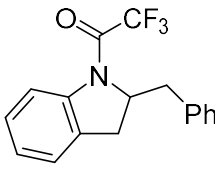


2-(4-Methoxybenzyl)-4-methyl-1-tosyl-4-[(trimethylsilyl)oxy]pyrrolidine (2-10). The general procedure was employed for the reaction of 4-methoxyphenyl trifluoromethanesulfonate (54 µL, 0.30 mmol), with (±)-4-methyl-*N*-{2-methyl-2-[(trimethylsilyl)oxy]pent-4-en-1- yl}benzenesulfonamide[2] (85.4 mg, 0.25 mmol). This procedure afforded 92 mg (82%) of the title compound as a viscous oil. This compound was found to exist as a 1:1 mixture of diastereomers by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.74 (m, 4 H), 7.31 (d, *J* = 7.7 Hz, 4 H), 7.16–7.13 (m, 4 H), 6.89–6.80 (m, 4 H), 3.80–3.75 (m, 1 H), 3.79 (s, 6 H), 3.49–3.38 (m, 3 H), 3.33 (d, *J* = 3.8 Hz, 1 H), 3.22 (d, *J* = 11.3 Hz, 1 H), 3.12 (d, *J* = 10.5 Hz, 1 H), 2.97 (dd, *J* = 13.1, 10.4 Hz, 1 H), 2.87 (dd, *J* = 13.6, 9.1 Hz, 1 H), 2.42 (s, 6 H), 1.86–1.69 (m, 2 H), 1.61–1.50 (m, 1 H), 1.49–1.39 (m, 1 H), 1.25–1.19 (m, 1 H), 1.24 (s, 3 H), 1.02 (s,

3 H), 0.12 (s, 9 H), –0.23 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 143.4, 143.1, 135.0, 130.8, 130.6, 130.2, 129.6, 129.5, 128.0, 127.7, 127.5, 114.0, 113.7, 78.3, 77.5, 63.9, 61.9, 61.2, 61.1, 55.2, 46.2, 44.6, 41.4, 40.7, 26.1, 25.2, 21.5, 2.1, 1.9; IR (film) 2954, 1512,1340, 1248, 1157 cm^{-1}; MS (ESI+) 448.1976 (448.1972 calcd for $C_{23}H_{33}NO_4SSi$, M + H^+).

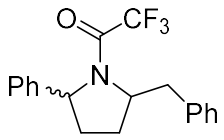


1-(2-Benzylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (2-9a). The general procedure was employed for the reaction of phenyl trilfuoromethanesulfonate (40 µL, 0.24 mmol) with 2,2,2- trifluoro-*N*-(pent-4-en-1-yl)acetamide **(2-8a)** (36.2 mg, 0.20 mmol) in 2 mL benzotrifluoride for 13 hours. This procedure afforded 33 mg (64%) of the title compound as a colorless oil. This compound was found to exist as a 6:1 mixture of rotamers via 1 H NMR; data are for the major rotamer. Spectroscopic data for the compound are consistent with those previously reported.[43] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.21 (m, 2 H), 7.23–7.10 (m, 3 H), 4.37–4.32 (m, 1 H), 3.70– 3.41 (m, 2 H), 3.1 (dd, *J* = 13.1, 3.4 Hz, 1 H), 2.67–2.55 (m, 1 H), 1.98–1.70 (m, 4 H).



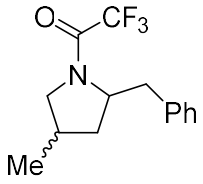
1-(2-Benzylindolin-1-yl)-2,2,2-trifluoroethan-1-one (2-9b). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (78 µL, 0.48 mmol) with *N*-(2-allylphenyl)-2,2,2-trifluoroacetamide **(2-8e)** (91.7 mg, 0.4 mmol) in 2 mL of

benzotrifluoride for 15 hours. This procedure afforded 89 mg (73%) of the title compound as a white solid, m.p. 66– 67 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.1 Hz, 1 H), 7.35–7.26 (m, 5 H), 7.21–7.18 (m, 3 H), 4.86 (t, *J* = 10 Hz, 1 H), 3.19–3.12 (m, 2 H), 2.89 (d, *J* = 15.7 Hz, 1 H), 2.67 (dd, *J* = 13.4, 11.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 154.0, 140.8, 136.3, 130.9, 129.4, 128.8, 127.8, 127.1, 126.2, 125.4, 119.0, 116.4 (q, *J* = 285.4 Hz), 61.8, 40.8, 33.2; IR (film) 1690, 1146 cm^{-1}; MS (ESI+) 306.1097 (306.1100 calcd for $C_{17}H_{14}F_3NO$ M + H^+).

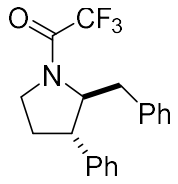


1-(2-Benzyl-5-phenylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (2-9c). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (49 µL, 0.30 mmol) with 2,2,2-trifluoro-*N*-(1-phenylpent-4-en-1-yl)acetamide **(2-8c)** (64.3 mg, 0.25 mmol) in 1.25 mL benzotrifluoride. This procedure afforded 73 mg (88%) of the title compound as a colorless oil. This compound was found to exist as a mixture of rotamers and as a 2:1 mixture of diastereomers via 1 H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, CDCl3) δ 7.40–7.04 (m, 15 H), 5.33–5.27 (m, 1.55 H), 5.11 (t, J = 9.0 Hz, 1 H), 4.65 (td, J = 8.9, 2.9 Hz, 0.41 H), 4.47 (ddd, J = 10.9, 7.2, 2.7 Hz, 1 H), 4.34 (ddt, J = 10.6, 7.6, 3.8 Hz, 1 H), 3.77 (dd, J = 12.5, 3.1 Hz, 1 H), 3.32 (dd, J = 13.1, 3.0 Hz, 0.35 H), 3.26 (dd, J = 13.3, 3.0 Hz, 1 H), 3.11 (dd, J = 13.5, 3.0 Hz, 0.50 H), 2.76 (t, *J* = 12.5 Hz, 1 H), 2.73–2.64 (m, 1.50 H), 2.53–2.44 (m, 1 H), 2.24–2.20 (m, 1.50 H), 2.14–2.02 (m, 2.30 H), 1.97–1.57 (m, 5.80 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 157.3, 156.4, 156.0, 143.3, 141.5, 141.4, 138.3, 138.2, 137.4, 129.5, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 127.4, 127.3, 127.0, 126.7, 126.6, 125.4, 125.3, 124.9, 124.7, 116.5 (q,

286.3 Hz), 116.1 (q, 286.3 Hz), 64.0, 63.4, 62.9, 62.6, 62.3, 61.2, 41.0, 40.0, 37.3, 35.0, 33.7, 31.7, 28.8, 27.7, 23.7; IR (film) 2951, 1684, 1145 cm^{-1}; MS (ESI+) 334.1411 (334.1413 calcd for $C_{19}H_{18}F_3NO$, M + H^+).



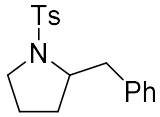
1-(2-Benzyl-4-methylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (2-9d). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (146 µL, 0.90 mmol) with 2,2,2-trifluoro-*N*-(2-methylpent-4-en-1-yl)acetamide **(2-8b)** (146 mg, 0.75 mmol) in 1.5 mL benzotrifluoride for 18 hours. This procedure afforded 135.5 mg (67%) of the title compound as a pale yellow oil. This compound was found to exist as a mixture of rotamers and as a 1.3:1 mixture of diastereomers via ^1H NMR analysis; data are for the mixture. ^1H NMR (500 MHz $CDCl_3$) δ 7.34–7.15 (m, 9 H), 4.42 (t, *J* = 8.8 Hz, 0.8 H), 4.35–4.39 (m, 1 H), 3.85–3.82 (m, 1 H), 3.78–3.72 (m, 0.8 H), 3.36 (dd, *J* = 13.1, 3.3 Hz, 1 H), 3.22–3.14 (m, 1.7 H), 3.02 (dd, *J* = 13.3, 3.4 Hz, 0.1 H), 2.78–2.66 (m, 2 H), 2.66–2.61 (m, 1 H), 2.34−2.27 (m, 0.8 H), 2.15–2.06 (m, 2 H), 1.97 (dd, *J* = 12.7, 6.3 Hz, 0.2 H), 1.89 (ddd, *J* = 12.8, 6.2, 2.4 Hz, 0.9 H), 1.47 (ddd, *J* = S19 12.6, 10.0, 8.1 Hz, 1 H), 1.38–1.24 (m, 1 H), 1.10 (d, *J* = 6.5 Hz, 0.6 H), 1.02–0.99 (m, 5.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 155.6, 155.4, 155.3, 138.0, 137.4, 129.6, 129.5, 129.2, 128.8, 128.5, 128.4, 126.9, 126.6, 126.5, 116.3 (q, *J* = 286.4 Hz), 116.2 (q, *J* = 286.3 Hz), 60.9, 60.7, 54.4, 54.2, 53.8, 40.9, 38.9, 38.4, 38.1, 37.7, 37.6, 35.7, 33.3, 31.6, 31.1, 28.3, 18.0, 17.4, 16.4; IR (film) 2954, 1686, 1144 cm^{-1}; MS (ESI+) 272.1255 (272.1257 calcd for $C_{14}H_{16}F_3NO$, M + H^+).



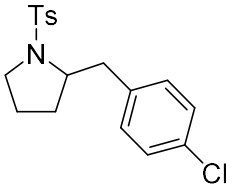
(±)-(2S,3S)-1-(2-Benzyl-3-phenylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (2-9e). The general procedure was employed, using 4 mol % $Pd(OAc)_2$ and 10 mol % CPhos, for the reaction of phenyl trifluoromethanesulfonate (146 μL, 0.90 mmol) with 2,2,2-trifluoro-*N*-(3-phenylpent-4-en-1-yl)acetamide **(2-8d)** (192.8 mg, 0.75 mmol) in 1.5 mL benzotrifluoride for 24 hours. This procedure afforded 143.2 mg (57%) of the title compound as a pale yellow oil. This compound was found to exist as a 7:1 mixture of diastereomers by ^{1}H NMR analysis; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.18 (m, 8 H), 7.11 (d, *J* = 7.5 Hz, 2 H), 4.52 (ddd, *J* = 7.9, 5.9, 3.2 Hz, 1 H), 3.85–3.81 (m, 1 H), 3.36–3.32 (m, 1 H), 3.23 (q, *J* = 6.7 Hz, 1 H), 3.14 (dd, *J* = 13.7, 7.3 Hz, 1 H), 3.02 (dd, *J* = 13.7, 3.2 Hz, 1 H), 2.24–2.17 (m, 1 H), 2.02–1.94 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 155.4, 141.4, 136.8, 129.9, 128.8, 128.5, 127.1, 127.0, 126.8, 116.3 (q, *J* = 285.3 Hz), 66.2, 46.7, 45.6, 36.3, 32.9; IR (film) 2928, 1685, 1143 cm^{-1}; MS (ESI+) 334.1416 (334.1413 calcd for $C_{19}H_{18}F_3NO$, M + H^+).

General Procedure for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. An oven dried test tube equipped with a magnetic stirbar and a rubber septum was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol %), RuPhos (5 mol %), LiOTf (2 equiv) and NaO*t*Bu (2 equiv). The tube was purged with nitrogen and then a solution of the aryl bromide (2 equiv) in $PhCF_3$ (1 mL) was added and the resulting mixture was stirred at rt for 1 min. A solution of the *N*-protected amine substrate (1 equiv) in $PhCF_3$ (1.5 mL) was added, and the mixture was heated to 100 ºC for 15 h. The mixture was

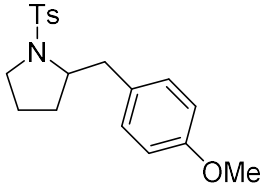
then cooled to rt, saturated aq NH_4Cl (2 mL) was added, the organic layer was removed, and the aqueous layer was extracted with dichloromethane (4 x 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified via flash chromatography.



2-Benzyl-1-tosylpyrrolidine (2-6a). General procedure 2 was employed for the reaction of bromobenzene (79 mg, 0.5 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (60 mg, 0.25 mmol). This procedure afforded 57 mg (72%) of the title compound as a white solid. Spectroscopic data for the compound were identical to those reported above.[34]

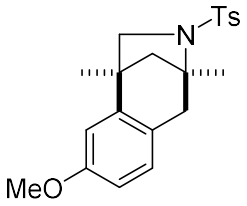


2-(4-Chlorobenzyl)-1-tosylpyrrolidine (2-6j). General procedure 2 was employed for the reaction of 4-bromochlorobenzene (95.7 mg, 0.5 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (60 mg, 0.25 mmol). This procedure afforded 53 mg (61%) of the title compound as a white solid. Spectroscopic data for the compound were identical to those reported above.[34]



2-(4-Methoxybenzyl)-1-tosylpyrrolidine (2-6k). General procedure 2 was employed for the reaction of 4-bromoanisole (93.5 mg, 0.5 mmol) with 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **(2-5a)** (60 mg, 0.25 mmol). This procedure afforded 48 mg (56%) of the title compound as a white solid. Spectroscopic data for the compound were identical to those reported above.

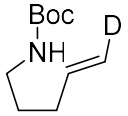
Conversion of 11 to 12



(±)-(1S,4S)-8-methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[*d*]azepine (2-12). A flame-dried flask was cooled under a stream of nitrogen and charged with aluminum chloride (149 mg, 1.12 mmol) and dichloromethane (1 mL). The reaction mixture was then cooled to 0 °C and a solution of 2-(4-methoxybenzyl)-4-methyl-1-tosyl-4-[(trimethylsilyl)oxy]pyrrolidine **(2-11)** (50 mg, 0.11 mmol) in dichloromethane (1 mL) was slowly added. The reaction mixture was warmed to rt and stirred overnight, then was poured into a saturated aqueous solution of sodium bicarbonate (2 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous phase was extracted with dichlormethane (2 x 2 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified via flash chromatography on silica gel to afford 17 mg (42%) of the title compound as a pale yellow solid, mp 137−139 °C. Spectroscopic data for the compound are consistent with those previously reported.[44]

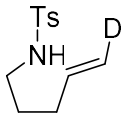
^{1}H NMR (400 MHz, $CDCl_3$), δ 7.70 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 2.5 Hz, 1 H), 6.72 (dd, *J* = 8.3, 2.6 Hz, 1 H), 4.41–4.35 (m, 1 H), 3.78 (s, 3 H), 3.40 (dd, *J* = 8.7, 1.2 Hz, 1 H), 3.11 (d, *J* = 16.6 Hz, 1 H), 3.02 (d, *J* = 8.6 Hz, 1 H), 2.93 (dd, *J* = 16.5, 2.8 Hz, 1 H), 2.42 (s, 3 H), 1.79 (d, *J* = 11.5 Hz, 1 H), 1.50–1.38 (m, 4 H).

Deuterium Labeling Experiments

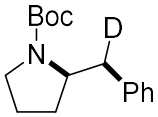


(*E*)-Tert-butyl (pent-4-en-1-yl-5-d)carbamate (2-13). A flame dried flask was cooled under a stream of nitrogen and charged with (*E*)-2-(pent-4-en-1-yl-5-d)isoindoline-1,3-dione[45] (0.96 g, 3.6 mmol) and ethanol (40 mmol). Hydrazine hydrate (198 µL, 7.2 mmol) was then added, and the reaction was heated to reflux for 24 hours. The reaction was then allowed to cool to rt, then diethyl ether (100 mL) was added and a white precipitate formed. The mixture was then charged with Boc anhydride (2.34 g, 10.7 mmol), and the reaction was stirred at rt overnight. The reaction was then concentrated in vacuo, and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified via flash column chromatography on silica gel to afford 67 mg (10%) of the title compound as a pale yellow oil with 80% deuterium incorporation as judged by ^{1}H NMR analysis. Spectroscopic data for the compound are consistent with those previously reported.[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84– 5.77 (m, 1 H), 5.05–4.97

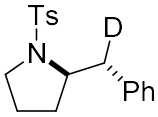
(m, 1 H), 4.52 (s, br, 1 H), 3.13 (q, *J* = 5.6 Hz, 2 H), 2.08 (q, *J* = 7.2 Hz, 2 H), 1.62–1.54 (m, 2 H), 1.45 (s, 9 H).



(*E*)-4-Methyl-*N*-(pent-4-en-1-yl-5-d)benzenesulfonamide (2-15). A flame-dried flask was cooled under a stream of nitrogen and charged with (*E*)-2-(pent-4-en-1-yl-5-d)isoindoline-1,3-dione[45] (0.400 g, 1.5 mmol) and ethanol (30 mL). Hydrazine hydrate (294 µL, 6.0 mol) was then added, and the reaction was heated to reflux for 24 hours. The reaction was allowed to cool to rt, then diethyl ether (80 mL) was added and a white precipitate formed. *p*-Toluenesulfonyl chloride (0.343 g, 1.8 mmol) and triethylamine (251 µL, 1.8 mmol) were then added, and the reaction mixture was stirred at rt for 5 h. The reaction was then quenched with 2 M HCl (20 mL), the mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with diethyl ether (30 mL), and then the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel to afford 75 mg (21%) of the title compound as a colorless oil with 80% deuterium incorporation as judged by ^{1}H NMR analysis. Spectroscopic data for the compound are consistent with those previously reported.[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 5.74–5.68 (m, 1 H), 4.99–4.94 (m, 1 H), 4.33 (s, br, 1 H), 2.96 (q, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H), 2.06 (q, *J* = 7.2 Hz, 2 H), 2.08–2.02 (m, 2 H).



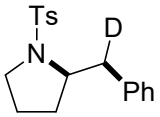
(1'S,2R)-*N*-Boc-2-[1'd-phenylmethyl]pyrrolidine (2-14).[32] An oven dried test tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol%), DPEPhos (5 mol%), and NaO*t*Bu (1.4 equiv). The tube was purged with nitrogen and then a solution of bromobenzene (0.68 mg, 0.43 mmol) in toluene (1 mL) was added, and the solution stirred at rt for 1 minute. A solution of (*E*)-tert-butyl (pent-4-en-1-yl-5-d)carbamate **(2-13)** (0.67 mg, 0.36 mmol) in toluene (1.5 mL) was added, and the solution was heated to 90 °C with stirring for 15 h. The reaction mixture was cooled to rt and saturated aq NH_4Cl (2 mL) was added. The layers were separated, and the aqueous layer was then extracted with dichloromethane (4 x 2 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified via flash column chromatography on silica gel to afford 67.3 mg (71%) of the title compound as a pale yellow oil. Spectroscopic data for the compound are consistent with those previously reported.[32] ^1H NMR (500 MHz, $C_6D_5CD_3$, 100 ºC) δ 7.13–6.98 (m, 5 H), 4.00–3.94 (m, 1 H), 3.32–3.23 (m, 1 H), 3.17–3.04 (m, 2 H), 1.50–1.30 (m, 13 H).



(1'R,2R)-*N*-Tosyl-2-[1'd-phenylmethyl]pyrrolidine (2-16). The general procedure was employed for the reaction of phenyl trifluoromethanesulfonate (39 µL, 0.24 mmol) with (*E*)-4-methyl-*N*-(pent-4-en-1-yl-5-d)benzenesulfonamide **(2-15)** (48 mg, 0.20 mmol) in 2

mL of benzotrifluoride for 15 hours. This procedure afforded 48.4 mg (76%) of the title compound as a white solid, mp 91−92 °C. Spectroscopic data for the compound are consistent with those previously reported.[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.30 (dd, *J* = 10.3, 7.9 Hz, 4 H), 7.28–7.19 (m, 3 H), 3.84−3.78 (m, 1 H), 3.44–3.36 (m, 1 H), 3.13 (dt, *J* = 9.8, 7.1 Hz, 1 H), 2.80–2.70 (m, 1 H), 2.42 (s, 3 H), 1.70–1.59 (m, 2 H), 1.52–1.38 (m, 2 H).

Confirmation of change in stereochemistry. In order to further confirm the change in the stereochemical outcome of the carboamination of **2-12** to **2-13** vs**. 2-14** to **2-15**, a sample of product **2-13** was transformed to **2-S7**, the C1' epimer of **2-15** via cleavage of the boc group followed by *N*-tosylation as described below.



(1'S,2R)-*N*-Tosyl-2-[1'd-phenylmethyl]pyrrolidine (2-S7). A flame dried vial was cooled under a stream of nitrogen and charged with (1'S,2R)-*N*-boc-2-[1'd-phenylmethyl]pyrrolidine **(2-14)** (67.3 mg, 0.26 mmol). Dichloromethane (0.5 mL) and trifluoroacetic acid (0.5 mL) were then added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated in vacuo, then toluene (1 mL) was added and the mixture was concentrated again. This dilution/concentration sequence was repeated two additional times to facilitate azeotropic removal of the trifluoroacetic acid. The resulting crude oil was dissolved in dichloromethane (1 mL) and K_2CO_3 was added. After stirring for 15 minutes, the mixture was filtered and concentrated in vacuo to afford a brown oil that was dissolved in dichloromethane and treated with aqueous NH_4OH until

a pH of >12 was reached. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 5 mL). The organic layer was dried, filtered and concentrated in vacuo to afford a brown oil. The oil was then converted to the *N*-tosyl pyrrolidine using a procedure analogous to that reported above for **2-5c** to afford 60 mg (63%) of the title compound as a white solid, mp 91−93 °C. Spectroscopic data for the compound are consistent with those previously reported.[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.35–7.26 (m, 4 H), 7.25–7.18 (m, 3 H), 3.82 (dt, *J* = 6.9, 3.2 Hz, 1 H), 3.42–3.37 (m, 1 H), 3.27–3.24 (m, 1 H), 3.13 (qd, *J* = 7.2, 3.5 Hz, 1 H), 2.43 (s, 3 H), 1.63 (qt, *J* = 14.7, 9.1 Hz, 2 H), 1.50−1.40 (m, 2 H).

Chapter 3

Synthesis of Cyclic Guanidines Bearing *N*-Arylsulfonyl and *N*-Cyano Protecting Groups via Pd-Catalyzed Alkene Carboamination Reactions

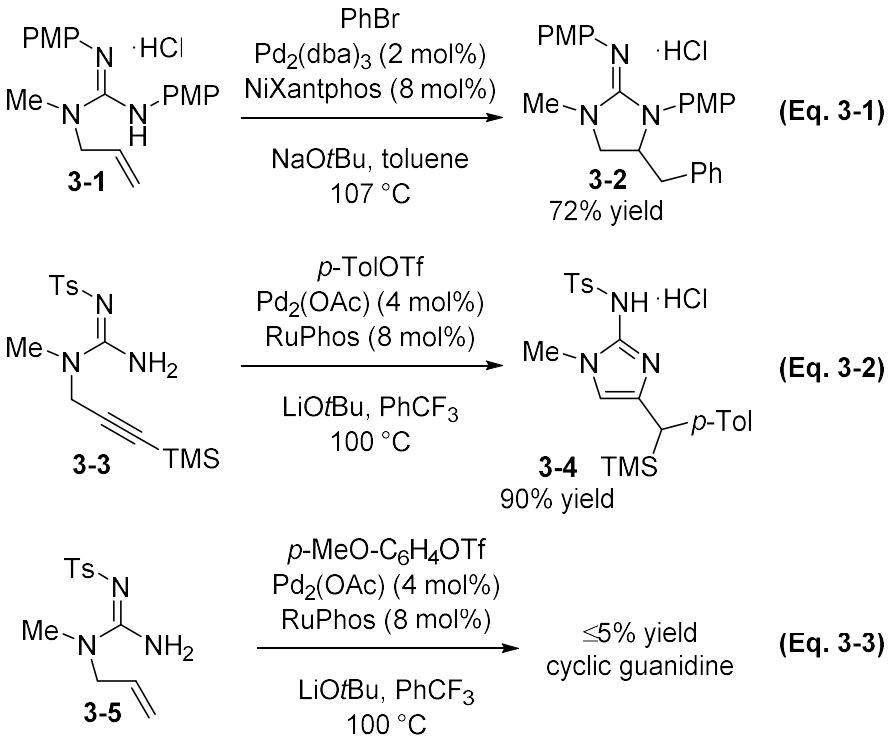
3-1 Introduction

The synthesis of cyclic guanidines has attracted considerable attention due to the presence of cyclic guanidine subunits in a variety of biologically active natural products.[46,47] Many recent approaches to the construction of these motifs have focused on the use of metal catalysts to effect formation of carbon–nitrogen bonds.[48,49] However, aside from our prior studies in the area,[50,51] no existing methods effect formation of a C–N bond, a C–C bond, and the ring in a single transformation.

3-2 Previous Efforts Toward Cyclic Guanidines

Our group previously described a new approach to the preparation of cyclic guanidines via Pd-catalyzed alkene carboamination reactions between PMP-protected *N*-allylguanidines **3-1** and aryl bromides **(Eq 3-1)**.[50] These transformations afforded the desired cyclic guanidines (e.g., **3-2**) in good chemical yield. However, efforts to cleave the PMP-protecting groups were unsuccessful. We have also reported a related series of Pd-catalyzed alkyne carboamination reactions of tosyl-protected *N*-propargyl guanidines **3-3**, which also proceed in good yield under appropriate conditions to afford 2-aminoimidazoles such as **3-4 (Eq 3-2)**, and the *N*-tosyl group proved to be readily cleavable.[51] However, the conditions that provided high yields in reactions of *N*-

propargylguanidines did not work with analogous *N*-allylguanidines; efforts to couple **3-5** with 4-methoxyphenyl triflate afforded little or none of the desired product. In this letter we describe a significant expansion in the scope of this method that allows for transformation of substrates bearing cleavable *N*-arylsulfonyl or *N*-cyano groups.

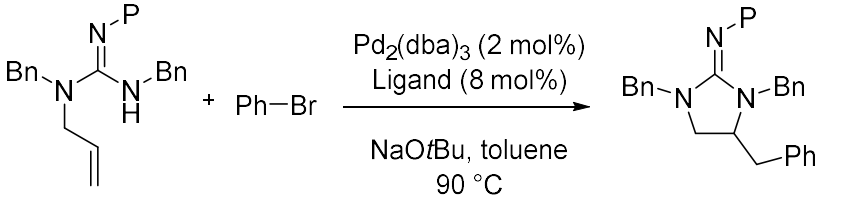


3-3 Optimization Studies

In order to develop Pd-catalyzed carboamination reactions of *N*-allylguanidines bearing cleavable protecting groups, we elected to explore the reactivity of two different substrates, **3-6a** and **3-7a**, which contain benzyl groups on two nitrogen atoms and either a cyano or tosyl group on the third. Our prior studies had indicated it should be possible to cleave the *N*-tosyl group from the products, and *N*-cyano groups can be cleaved from guanidines via treatment with strong acids. Moreover, the *N*-cyanoguanidines appeared to be particularly attractive products to target, as many *N*-cyanoguanidines have interesting biological activities.[52]

Our initial optimization studies were focused on the coupling of **3-6a** and **3-7a** with bromobenzene. As shown in **Table 3-1**, the coupling of **3-6a** afforded good yields of **3-8a** using a number of different phosphine ligands under conditions that have provided good results in many other alkene carboamination reactions.[53] Optimal yields were obtained with the biaryl phosphine XPhos (entry 4). However, efforts to employ these conditions for the coupling of **3-7a** with bromobenzene were not successful, as the desired product **3-9a** was generated in low yield (25%) along with a complex mixture of side products (entry 5). Fortunately, simply employing reaction conditions that previously provided optimal results with *N*-tosyl *N*-propargyl guanidine **3-3** (aryl triflate in place of aryl bromide, $Pd(OAc)_2$ as a palladium source, Li*O*^{t}Bu as a base, and $PhCF_3$ as a solvent) afforded the desired product **3-9a** in 92% yield (entry 7).

Table 3-1. Optimization Studies.[a]



3-6a: P = CN, **3-7a:** P = Ts **3-8a:** P = CN, **3-9a:** P = Ts

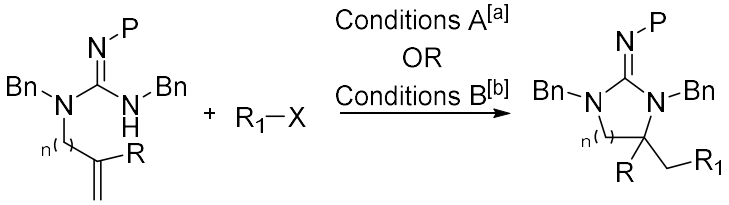
Entry	Substrate	Ligand	Yield (%)[b]
1	3-6a	Xantphos	73 (3-8a)
2	3-6a	Dpe-phos	89 (3-8a)
3	3-6a	CPhos	92 (3-8a)
4	3-6a	XPhos	>99 (3-8a)
5	3-7a	XPhos	25 (3-9a)
6	3-7a	CPhos	33 (3-9a)
7	3-7a	CPhos[c]	92 (3-9a)

[a] *Conditions*: 1.0 equiv. of substrate **3-6a** or **3-7a**, 1.5 equiv. of PhBr, 2.0 equiv. of Na*O*t*Bu*, $Pd_2(dba)_3$ (2 mol%), ligand (8 mol%), toluene (0.1 M), 90 °C, 1 h. Reactions were conducted on a 0.2 mmol scale. [b]NMR yield using phenanthrene as internal standard. [c]The reaction was conducted using PhOTf in place of PhBr, Li*O*t*Bu* in place of Na*O*t*Bu*, $Pd(OAc)_2$ in place of $Pd_2(dba)_3$, and $PhCF_3$ (0.2 M) in place of toluene, and a reaction temperature of 100 °C.

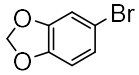
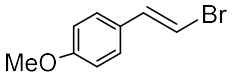
3-4 Scope

We then explored the scope of the Pd-catalyzed carboamination reactions of *N*-cyano and *N*-tosylguanidine substrates. As shown in **Table 3-2**, the transformations are effective with a range of different aryl halide coupling partners, including electron-rich, and -poor derivatives. The reaction of **3-7a** with *o*-methylphenyl triflate also proceeded in good yield, but ca. 10% of an inseparable impurity resulting from competing Heck arylation of the alkene was also generated (entry 7). In most instances comparable yields were obtained when either **3-6** or **3-7** were coupled with the same aryl bromide/triflate (entries 1–2, 3–4, 8–9, 11–12, and 15–16). The reactions were amenable to the construction of both five- and six-membered cyclic guanidines, and substrates **3-6b** and **3-7b** bearing a methyl group at the internal alkene carbon were also efficiently converted to the desired products.

Table 3-2. Scope of Carboamination of *N*-Protected Guanidines.



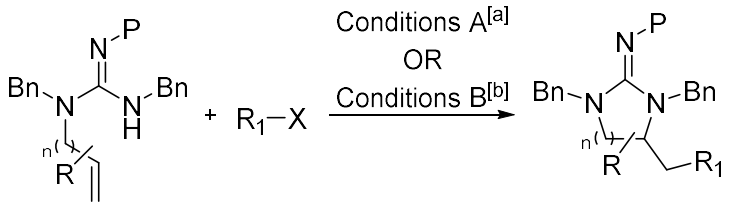
3-6a-c: P = CN; **3-7a-c**: P = Ts **3-8a-c**: P = CN; **3-9a-c**: P = Ts

Entry	Substrate	R_1-X	Product	Yield (%)[c]
1	**3-6a**: R = H, n = 1	PhBr	**3-8a**	86
2	**3-7a**: R = H, n = 1	PhOTf	**3-9a**	92
3	**3-6a**	*p*-Cl-C_6H_4Br	**3-8b**	82
4	**3-7a**	*p*-Cl-C_6H_4OTf	**3-9b**	70
5	**3-6a**	*p*-MeO-C_6H_4Br	**3-8c**	85
6	**3-7a**	2-naphthylOTf	**3-9c**	80
7	**3-7a**	*o*-Me-C_6H_4OTf	**3-9d**	78[d]
8	**3-6b**: R = Me, n = 1	PhBr	**3-8d**	88
9	**3-7b**: R = Me, n = 1	PhOTf	**3-9c**	86[e]
10	**3-6b**	*p*-*t*BuC_6H_4Br	**3-8e**	86
11	**3-6c**: R = H, n = 2	PhBr	**3-8f**	98[f]
12	**3-7c**: R = H, n = 2	PhOTf	**3-9f**	85
13	**3-6c**	*p*-MeO-C_6H_4Br	**3-8g**	94[f]
14	**3-6c**	*p*-MeO-C_6H_4Br	**3-8g**	84[f,g]
15	**3-6c**	*p*-PhC(O)C_6H_4Br	**3-8h**	81[f]
16	**3-7c**	*p*-Ph(O)C_6H_4OTf	**3-9g**	96
17	**3-6c**		**3-8e**	97[f]
18	**3-6c**		**3-8j**	95[h]

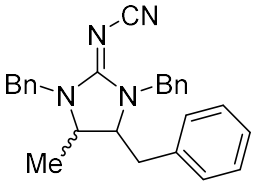
[a] *Conditions A (P = CN)*: 1.0 equiv. of **3-6**, 1.5 equiv. of R_1-Br, 2.0 equiv. of NaO*t*Bu, $Pd_2(dba)_3$ (1 mol%), XPhos (4 mol%), toluene (0.1 M), 90 °C, 1 h.
[b] *Conditions B (P = Ts)*: 1.0 equiv. of **3-7**, 1.5 equiv. of Ar-OTf, 2.0 equiv of LiO*t*Bu, $Pd(OAc)_2$ (2 mol%), CPhos (4 mol%), $PhCF_3$ (0.2 M), 100 °C, 2 h. Reactions were conducted on a 0.2-0.3 mmol scale.
[c] Isolated yield.
[d] This material contained ca. 10% of an inseperable side product resulting from Heck arylation of the alkene.
[e] The reaction was conducted at 0.1 M concentration.
[f] The reaction was conducted using CPhos as the ligand.
[g] The reaction was conducted on a 1 mmol scale.
[h] The reaction was conducted for 2 h at 90 °C.

Surprisingly, the diastereoselectivity obtained in reactions of substrates bearing a substituent adjacent to the *N* atom was quite low (**Scheme 3-1**, **3-8k**–**3-8m** and **3-9h**–**3-9j**, 1.5:1 to 3:1 dr).[54] This is in stark contrast to results obtained in analogous reactions of *N*-allylureas[55] and *N*-allylsulfamides,[56] which typically proceed with ca. 8:1 to >20:1 dr. In addition, although we were gratified to find that substrates bearing an internal alkene were transformed to **3-8n** and **3-9k**–**3-9l**, which result from net *anti*-addition to the alkene, with good to excellent diastereoselectivity,[57] the stereochemistry of **3-8n** was rather surprising. Our prior studies on reactions of sulfamides, ureas, and PMP-protected guanidines[58] suggested that use of an aryl bromide in these guanidine carboamination reactions would lead to *syn*-addition to the double bond, whereas use of an aryl triflate was expected to favor *anti*-addition (as observed).[56]

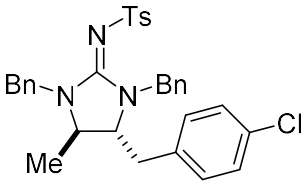
Table 3-3. Diastereoselectivity Studies.



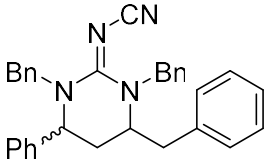
3-6d-g: P = CN; **3-7d-g**: P = Ts **3-8k-n**: P = CN; **3-9h-l**: P = Ts



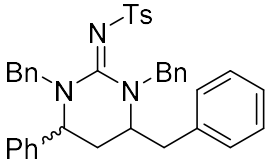
3-8k: 71%, 1.5:1 *dr*



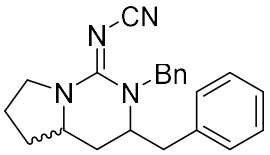
3-9h: 63%, 3:1 *dr*



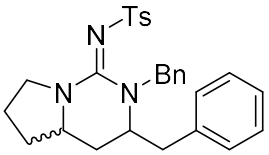
3-8l: 85%, 1.7:1 *dr*



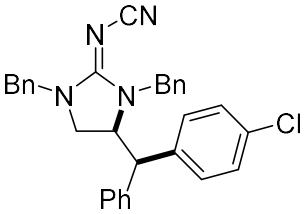
3-9i: 84%, 2:1 *dr*



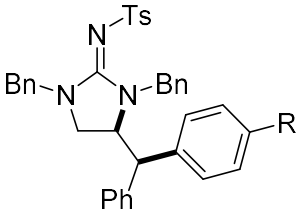
3-8m: 97%, 2:1 *dr*



3-9j: 99%, 2:1 *dr*



3-8n: 24%, >20:1 *dr*
(from *E*-alkene using ArBr)

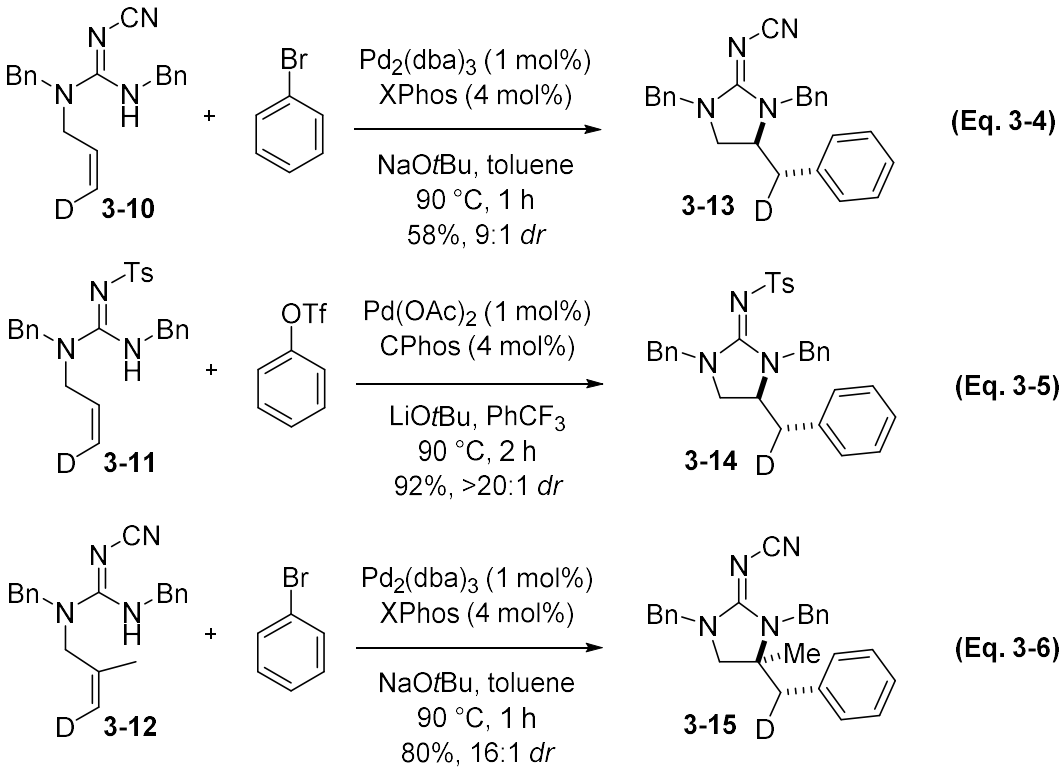


3-9k: R = Cl: 76%, >20:1 *dr*
3-9l: R = OMe: 82%, 10:1 *dr*
(from *E*-alkene using ArOTf)

[a] *Conditions A (P = CN)*: 1.0 equiv. of substrate **3-6**, 1.5 equiv. of R^1-Br, 2.0 equiv of NaO*t*Bu, $Pd_2(dba)_3$ (1 mol%), XPhos (4 mol%), toluene (0.1 M), 90 °C, 1 h. Reactions were conducted on a 0.15-0.2 mmol scale.
[b] *Conditions B (P = Ts)*: 1.0 equiv of substrate **3-7,** 1.5 equiv. of Ar-OTf, 2.0 equiv. of LiO*t*Bu, $Pd(OAc)_2$, CPhos (4 mol%), $PhCF_3$ (0.2 M), 100 °C, 2 h. Reactions were conducted on a 0.3 mmol scale. All yields are isolated yields
[c] The reaction was conducted using CPhos as ligand.

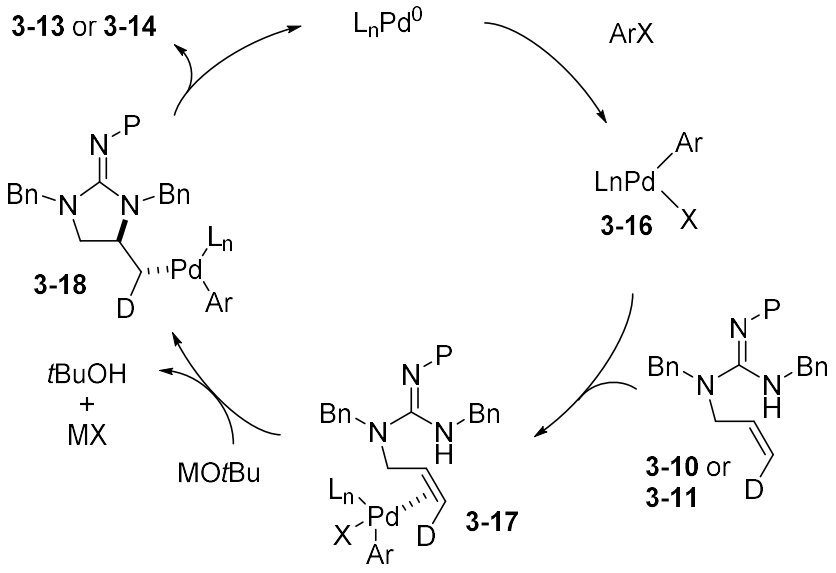
3-5 Mechanistic Studies via Deuterium Labelling

Given the surprising results of these experiments, we further explored *syn*- vs *anti*-addition pathways in transformations of deuterated substrates **3-10**–**3-11**. As shown in **Eq. 3-4**–**3-6**, the coupling of **3-10** with bromobenzene afforded *anti*-addition product **3-13** in 58% yield and 9:1 dr. The reaction of **3-11** with phenyl triflate to yield **3-14** also proceeded via *anti*-addition to the double bond, but with >20:1 dr. In principle the lower selectivity obtained with **3-10** could result either from competing *anti*- vs *syn*-aminopalladation pathways in the catalytic cycle (**3-11a**) or from partial epimerization of the benzylic stereocenter via reversible β-hydride elimination processes that occur after the aminopalladation step.[59] To address this question we examined the reactivity of substrate **3-12** and discovered its coupling with bromobenzene proceeds in 16:1 dr. Since the intermediate alkylpalladium complex derived from **3-12** cannot undergo β-hydride elimination, this result suggests that much of the minor diastereomer formed in the reaction of **3-10** is generated via β-hydride elimination side reactions.



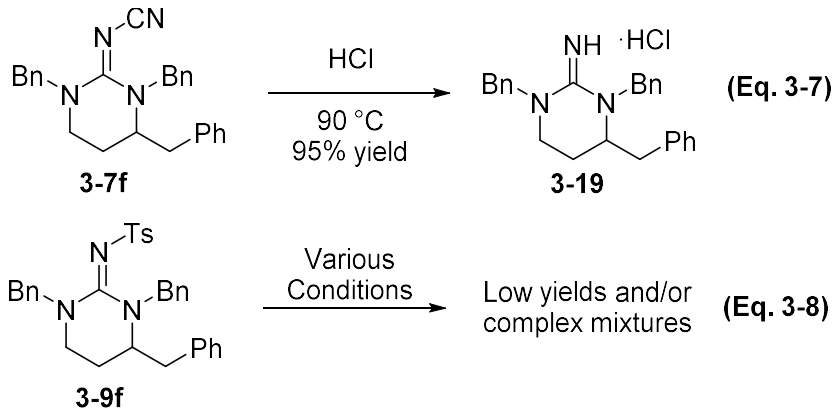
The results of these experiments suggest the mechanism of the carboamination reactions proceeds as shown in **Scheme 3-2**. Oxidative addition of the aryl halide or triflate to the Pd(0) catalyst affords **3-16**. Coordination of the pendant alkene to the metal (**3-17**) followed by *anti*-aminopalladation and deprotonation then generates alkylpalladium complex **3-18**. Reductive elimination of **3-18** affords the observed major stereoisomer **3-13** or **3-14**. The minor stereoisomer is formed from competing β-hydride elimination side reactions of **3-18**.[59] The *anti*-heteropalladation mechanism is likely responsible for the modest diastereoselectivities observed for **3-8k**–**3-8m** and **3-9h**–**3-9j**, as the transition state for *anti*-heteropalladation is less organized than that for a *syn*-heteropalladation process.[60]

Scheme 3-1. Mechanism of Reaction.



3-6 Protecting Group Cleavage

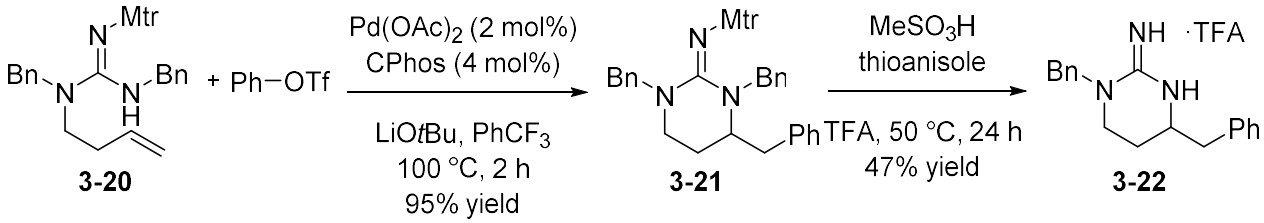
To further demonstrate the utility of this method we briefly explored the cleavage of the *N*-cyano or *N*-tosyl protecting groups from the guanidine products. As shown in **Eq. 3-7**, treatment of **3-7f** with concentrated HCl led to clean deprotection of the *N*-cyano group to afford a 95% yield of **3-19**. However, efforts to cleave the *N*-tosyl group from **3-9f** with either acids or reducing agents did not provide satisfactory results. The detosylated product was obtained in low yield due to competing cleavage of one or both *N*-benzyl groups **(Eq. 3-8)**.



3-7f 3-19 3-9f

Prior studies have shown that electron-rich arylsulfonyl groups are more readily cleaved from guanidines than tosyl groups.[61] As such we prepared Mtr-protected guanidine substrate **3-20** (Mtr = 4-methoxy-2,3,6-trimethylbenzenesulfonyl) and subjected it to our standard reaction conditions to afford guanidine **3-21** in 95% yield **(Scheme 3-3)**. Treatment of **3-21** with methanesulfonic acid and trifluoroacetic acid in the presence of thioanisole led to cleavage of the *N*-Mtr group and one *N*-benzyl group to afford **3-22** in 47% yield.

Scheme 3-2. Synthesis/Deprotection of *N*-Mtr Guanidine **3-20**.

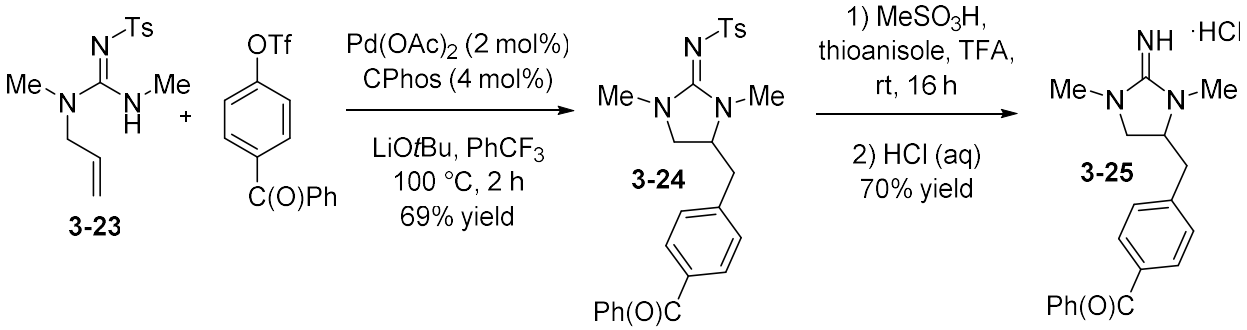


3-20 3-21 3-22

Due to our difficulties with cleanly removing only the *N*-arylsulfonyl group from cyclic guanidines bearing *N*-benzyl groups, we examined the preparation and deprotection of a cyclic *N*-tosyl guanidine bearing methyl groups on the other two nitrogen atoms. As shown in **Scheme 3-3**, the Pd-catalyzed coupling of **3-23** with 4-bromobenzophenone afforded cyclic guanidine **3-24** in 69% yield. We were gratified to

find that cleavage of the *N*-tosyl group from **3-24** proceeded smoothly to provide a 70% yield of **3-25**.

Scheme 3-3. Synthesis/Deprotection of *N*-Ts Guanidine **3-24**.



3-7 Conclusion

In conclusion, we have developed a new approach to the synthesis of five- and six-membered cyclic guanidines bearing cleavable *N*-sulfonyl or *N*-cyano protecting groups. The Pd-catalyzed carboamination reactions proceed in generally good chemical yields and provide products resulting from *anti*-addition to the alkene. Future studies will be directed toward improving diastereoselectivities in these reactions.

3-8 Note from the Author

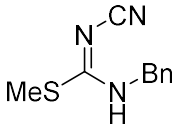
This thesis chapter represents work that has been previously published in a peer-reviewed journal, which has been reproduced or adapted here with permission from the authors.

3-9 Experimental

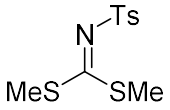
General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium(0) and palladium(II) acetate were purchased from Strem Chemical Co. and used without purification, and C-Phos and X-

Phos were purchased from Sigma-Aldrich Co. and was used without further purification. Aryl triflates were prepared according to a procedure published by Frantz and coworkers,[62] except the products were purified by column chromatography. Bulk quantities of lithium *tert*-butoxide and sodium *tert*-butoxide were stored in nitrogen-filled glove box and small amounts were removed shortly before use. Toluene, THF, dichloromethane 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 ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted.

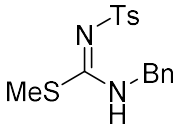
Preparation and Characterization of Substrates



Methyl *N*-benzyl-*N*'-cyanocarbamimidothioate (3-S1). A flame dried flask was cooled under a stream of nitrogen and charged with dimethyl cyanocarbonimidodithioate (2 g, 13.6 mmol) and ethanol (40 mL). Benzylamine (2.2 mL, 20.6 mmol) was then added via syringe, and the solution was heated to reflux with stirring for 2 h. The solution was then cooled to rt, a stream of nitrogen was blown over the solution for 20 min, and then the solution was placed in the freezer overnight. The white precipitate that had formed was then isolated via filtration using a fritted glass funnel to yield 2.61g (94%) of the desired product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 5 H), 6.60 (s, br, 1 H), 4.50 (s, br, 2 H), 2.48 (s, br, 3 H).

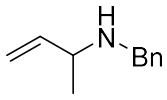


Dimethyl tosylcarbonimidodithioate (3-S2). A flame dried flask was cooled under a stream of nitrogen and charged with 4-methylbenzenesulfonamide (25.68 g, 150 mmol), carbon disulfide (14.2 mL, 240 mmol), and DMF (200 mL). The mixture was cooled to 0 °C in an ice bath, and then a solution of KOH (19.9 g, 354 mmol) in water (60 mL) was added dropwise at a rate sufficiently slow that the reaction temperature remained below 10 °C at all times. The reaction mixture was then stirred at 0 °C for 30 min, and then methyl iodide (21.7 mL, 348 mmol) was added dropwise at a rate sufficiently slow that the reaction temperature remained below 10 °C at all times. The reaction mixture was then warmed to rt and stirred for 30 min. Water was then added (150 mL), and the white precipitate that had formed was then isolated via filtration using a fritted glass funnel. The white solid was washed with water followed by ethanol, then was dried *in vacuo* to afford 31.27 g (75%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 2.53 (s, 6 H), 2.43 (s, 3 H).

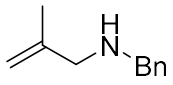


Methyl *N*-benzyl-*N*'-tosylcarbamimidothioate (3-S3). A flame dried flask was cooled under a stream of nitrogen and charged with dimethyl tosylcarbonimidodithioate **(3-S2)** (2.00 g, 7.26 mmol) and ethanol (40 mL). Benzylamine (1.2 mL, 10.89 mmol) was then added slowly, and the reaction was then heated to reflux with stirring for 2 h. The solution was then cooled to rt, a stream of nitrogen was blown over the solution for 20 min, and

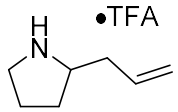
then the solution was placed in the freezer overnight. The white precipitate that had formed was then isolated via filtration using a fritted glass funnel to yield 2.19 g (90%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, br, 1 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.41–7.31 (m, 3 H), 7.31–7.17 (m, 4 H), 4.48 (d, *J* = 5.9 Hz, 2 H), 2.42 (s, 3 H), 2.38 (s, 3 H).



***N*-Benzylbut-3-en-2-ylamine (3-S4).** A flame dried flask was cooled under a stream of nitrogen and charged with *N*-(but-3-en-2-yl)benzamide[63] (1.32 g, 7.53 mmol) in diethyl ether (30 mL). The solution was cooled on an ice bath, and a solution of $LiAlH_4$ (30 mL, 30 mmol, 1 M in THF) was added slowly. The reaction mixture was then heated to reflux with stirring overnight. The mixture was then cooled in an ice bath, and water (7.53 mL) was slowly added followed by 1 M NaOH (7.5 mL). The miture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 10 mL). The organic laywers were combined, dried, filtered, and concentrated *in vacuo* to afford 1.2 g (99%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 4 H), 7.28–7.21 (m, 1 H), 5.80–5.64 (m, 1 H), 5.19–5.02 (m, 2 H), 3.80 (d, *J* = 13.1 Hz, 1 H), 3.68 (d, *J* = 13.1 Hz, 1 H), 3.28–3.16 (m, 1 H), 1.50 (s, br, 1 H), 1.18 (d, *J* = 6.5 Hz, 3 H).

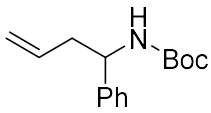


***N*-Benzyl-2-methylprop-2-en-1-ylamine (3-S5).** A flame dried flask was cooled under a stream of nitrogen and charged with benzylamine (10.9 mL, 100.0 mmol) and potassium carbonate (4.15 g, 30.0 mmol), then cooled on an ice bath. 3-bromo-2-methylprop-1-ene (3.38 g, 25.0 mmol) was then added slowly, and the resulting mixture was heated to 65 °C with stirring overnight. The reaction mixture was then cooled to rt and filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was then purified via flash column chromatography on silica gel (ethyl acetate:hexanes = 1:4) to afford 3.00 g (75%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 4 H), 7.30–7.21 (m, 1 H), 4.94–4.82 (m, 2 H), 3.78 (s, 2 H), 3.20 (s, 2 H), 1.78 (s, 3 H).



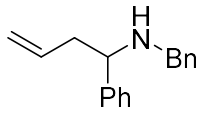
2-Allylpyrrolidinium trifluoroacetate (3-S6). This compound was synthesized by modifying procedure by published by Dieter, et al.[64] A flame dried flask was cooled under a stream of nitrogen and charged with *N*-Boc pyrrolidine (3.40 g, 20.0 mmol), TMEDA (3.6 mL, 24.0 mmol), and diethyl ether (80 mL). The solution was cooled to –78 °C and *s*-BuLi (20 mL, 1.4 M in cyclohexane) was added slowly dropwise. The reaction mixture was stirred at –78 °C for 2 h, then a solution of zinc chloride (3.81 g, 28 mmol) in THF (30 mL) was added slowly. The mixture was stirred at –78 °C for 1.5 h, and then a solution of copper cyanide (2.15 g, 24.0 mmol) and lithium chloride (1.7 g, 40.0 mmol) in THF (60 mL) was added slowly. The mixture was stirred at –78 °C for 1.5 h, and then allyl bromide

(5.2 mL, 60 mmol) was added slowly. The cooling bath was removed and the mixture was allowed to stir at rt overnight. The reaction was then quenched with aqueous ammonium hydroxide (60 mL), and the mixture was stirred at rt for 5 h. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 60 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford *N*-Boc 2-allylpyrrolidine. This material was then dissolved in dichloromethane (23 mL) and the resulting solution was cooled to 0 °C in an ice bath. Trifluoroacetic acid (22.5 mL, 293 mmol) was then added slowly, and the mixture was stirred at rt for 3 h. The mixture was then concentrated and residual trifluoroacetic acid was then removed by adding toluene (10 mL) and then concentrating the resulting solution (this was repeated four times) to afford 3.2 g (97%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, br, 2 H), 5.82–5.68 (m, 1 H), 5.29–5.17 (m, 2 H), 3.69–3.61 (m, 1 H), 3.41–3.31 (m, 2 H), 2.64–2.40 (m, 2 H), 2.29–1.96 (m, 3 H), 1.82–1.74 (m, 1 H).



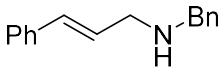
***tert*-Butyl (1-phenylbut-3-en-1-yl)carbamate (S7).** The title compound was prepared by modifying a procedure published by Veenstra *et al*.[65] A flame dried flask was cooled under a stream of nitrogen and charged with dichloromethane (50 mL), benzaldehyde (2.00 g, 18.78 mmol), allyl trimethylsilane (3.0 mL, 18.78 mmol), and *tert*-butyl carbamate (2.20 g, 18.78 mmol). The solution was then cooled to 0 °C in an ice bath, and $BF_3{\cdot}EtO_2$ (1.40 mL, 11.27 mmol) was added slowly. The resulting mixture was stirred at 0 °C for 30 min,

and was then warmed to rt and stirred for 30 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ (30 mL), and transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with dichloromethane (25 mL), and then the combined organic layers were dried, filtered, and concentrated *in vacuo* to afford a white solid. The crude product was purified via flash column chromatography on silica gel (ethyl acetate:hexanes = 1:4) to afford 1.66 g (36%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 5 H), 5.73–5.62 (m, 1 H), 5.19–5.02 (m, 2 H), 4.86 (s, br, 1 H), 2.52 (s, br, 2 H), 1.41 (s, br, 9 H).

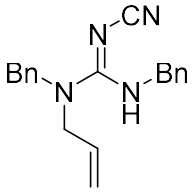


***N*-Benzyl-1-phenylbut-3-en-1-ylamine (3-S8).** A flame dried flask was cooled under a stream of nitrogen and charge with *tert*-butyl (1-phenylbut-3-en-1-yl)carbamate **(3-S7)** (1.66 g, 6.7 mmol) and dichloromethane (10 mL). The resulting solution was cooled to 0 °C then trifluoroacetic acid (10.3 mL, 134 mmol) was added slowly. The mixture was warmed to rt and stirred for 3 h. The mixture was then concentrated and residual trifluoroacetic acid was then removed by adding toluene (10 mL) and then concentrating the resulting solution (this was repeated three times) The resulting crude material was dissolved in THF (10 mL), then potassium carbonate (1.85 g, 13.4 mmol) and benzyl bromide (0.8 mL, 6.7 mmol) were added. The resulting mixture was heated to 50 °C overnight, then was cooled to rt and filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate:hexanes = 1:4) to afford 0.853 g (54%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.13

(m, 10 H), 5.79–5.63 (m, 1 H), 5.14–5.01 (m, 2 H), 3.73–3.59 (m, 2 H), 3.51 (d, *J* = 13.3 Hz, 1 H), 2.48–2.33 (m, 2 H), 1.73 (s, br, 1 H).

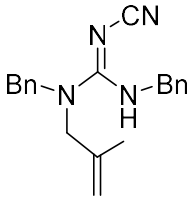


(*E*)-*N*-Benzyl-3-phenylprop-2-en-1-ylamine (3-S9). A flame dried flask was cooled under a stream of nitrogen and charged with benzylamine (8.7 mL, 80.0 mmol) and potassium carbonate (3.32 g, 24.0 mmol). The mixture was cooled to 0 °C and (*E*)-(3-bromoprop-1-en-1-yl)benzene (3.93 g, 20.0 mmol) was then added slowly. The mixture was then warmed to rt and stirred overnight. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate:hexanes = 1:4) to afford 1.30 g (38%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.16 (m, 10 H), 6.54 (d, *J* = 16.0 Hz, 1 H), 6.38–6.28 (m, 2 H), 3.85 (s, 3 H), 3.45 (dd, *J* = 6.3, 1.5 Hz, 2 H).

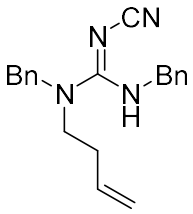


1-Allyl-1,3-dibenzyl-2-cyanoguanidine (3-6a). A round bottom flask was charged with methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.93 g, 4.53 mmol), ethanol (45 mL), and mercuric oxide (1.47 g, 6.80 mmol), then purged with nitrogen. Triethylamine (2.5 mL, 18.12 mmol) was added followed by *N*-benzylprop-2-en-1-ylamine (1.00 g, 6.80 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in*

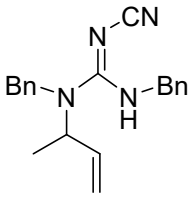
vacuo. The crude product was purified via flash column chromatography on silica gel (ethyl acetate:hexanes 4:6) to yield 1.00 g (72%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 6 H), 7.23–7.18 (m, 4 H), 5.81–5.71 (m, 1 H), 5.28–5.08 (m, 3 H), 4.72 (d, *J* = 5.3 Hz, 2 H), 4.58 (s, 2 H), 3.94 (dt, *J* = 5.6, 1.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 137.0, 135.8, 132.1, 129.0, 128.9, 28.1, 127.7, 127.3, 118.5, 117.2, 52.2, 51.5, 47.7; IR (film) 3255, 2162, 1536 cm^{-1}; MS (ESI+) 305.1758 (305.1761 calcd for $C_{19}H_{20}N_4$, M + H$^+$).



1,3-Dibenzyl-2-cyano-1-(2-methylallyl)guanidine (3-6b). The title compound was prepared from methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.825 g, 4.0 mmol), ethanol (40 mL), mercuric oxide (1.30 g, 6.0 mmol), triethylamine (2.2 mL, 16.0 mmol), and *N*-benzyl-2-methylprop-2-en-1-ylamine **(3-S5)** (0.972 g, 6.0 mmol) using a procedure analogous to that described above for the synthesis of **3-6a**. This procedure afforded 0.589 g (46%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 6 H), 7.24–7.20 (m, 4 H), 5.28 (t, *J* = 5.4 Hz, 1 H), 4.94 (s, 1 H), 4.79 (s, 1 H), 4.74 (d, *J* = 5.4 Hz, 2 H), 4.60 (s, 2 H), 3.80 (s, 2 H), 1.65 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 139.6, 137.1, 135.9, 128.9, 128.1, 128.0, 127.7, 127.5, 117.2, 112.9, 54.2, 52.5, 47.7, 19.8; IR (film) 3268, 2164, 1539 cm^{-1}; MS (ESI+) 319.1915 (319.1917 calcd for $C_{20}H_{22}N_4$, M + H$^+$).

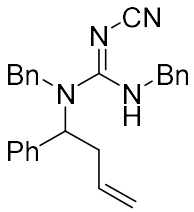


1,3-Dibenzyl-1-(but-3-en-1-yl)-2-cyanoguanidine (3-6c). The title compound was prepared from methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.75 g, 3.65 mol), ethanol (35 mL), mercuric oxide (1.187 g, 5.5 mmol), triethylamine (2.0 mL, 14.6 mmol) and *N*-benzylbut-3-en-1-ylamine (1.147 g, 7.1 mmol) using a procedure analogous to that described above for the synthesis of **3-6a**. This procedure afforded 0.82 g (71%) of the title compound as a pale yellow solid, m.p. 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 6 H), 7.18–7.07 (m, 4 H), 5.73 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1 H), 5.13–4.96 (m, 3 H), 4.67 (d, *J* = 5.3 Hz, 2 H), 4.51 (s, 2 H), 3.48 (t, *J* = 7.2 Hz, 2 H), 2.39–2.32 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 137.1, 135.6, 134.3, 129.2, 128.9, 128.1, 128.0, 127.7, 126.7, 117.9, 52.7, 49.5, 47.7, 32.4; IR (film) 3256, 2161, 1536 cm^{-1}; MS (ESI+) 319.1919 (319.1917 calcd for $C_{20}H_{22}N_4$, M + H$^+$).

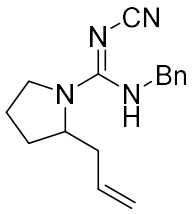


1,3-Dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine (3-6d). The title compound was prepared from methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.888 g, 4.53 mmol), ethanol (40 mL), mercuric oxide (1.40 g, 6.5 mmol), triethylamine (2.4 mL, 17.3 mmol) and *N*-benzylbut-3-en-2-ylamine **(3-S4)** (0.837 g, 5.2 mmol) using a procedure analogous to that described above for the synthesis of **3-6a**. This procedure afforded 0.316 g (23%)

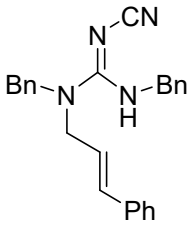
of an off white solid, m.p. 104–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 3 H), 7.26–7.19 (m, 3 H), 7.18–7.16 (m, 2 H), 6.97–6.95 (m, 2 H), 5.92–5.86 (m, 1 H), 5.25–5.15 (m, 2 H), 5.11–5.09 (m, 1 H), 4.97 (d, *J* = 5.3 Hz, 1 H), 4.70–4.58 (m, 2 H), 4.46–4.28 (m, 2 H),1.31 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 137.5, 136.6, 136.3, 129.2, 128.8, 128.0, 127.9, 127.7, 126.4, 117.3, 117.2, 55.1, 48.4, 47.8, 16.6; IR (film) 3265, 2160, 1533 cm^{-1}; MS (ESI+) 319.1920 (319.1917 calcd for $C_{20}H_{22}N_4$, M + H$^+$).



1,3-Dibenzyl-2-cyano-1-(1-phenylbut-3-en-1-yl)guanidine (3-6e). The title compound was prepared from methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.616 g, 3.0 mmol), ethanol (30 mL), mercuric oxide (0.975 g, 4.5 mmol), triethylamine (1.7 mL, 12 mmol), and *N*-benzyl-1-phenylbut-3-en-1-ylamine **(3-S8)** (0.853 g, 3.6 mmol) using a procedure analogous to that described above for the synthesis of **3-6a**. This procedure afforded 0.40 g (34%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.27 (m, 5 H), 7.25–7.13 (m, 6 H), 6.85 (d, *J* = 6.8 Hz, 2 H), 6.78 (d, *J* = 6.4 Hz, 2 H), 6.03 (t, *J* = 7.8 Hz, 1 H), 5.92–5.82 (m, 1 H), 5.24–5.08 (m, 2 H), 4.75 (t, *J* = 4.9 Hz, 1 H), 4.71–4.52 (m, 2 H), 4.32 (d, *J* = 16.9 Hz, 1 H), 4.16 (d, *J* = 17.0 Hz, 1 H), 2.76 (t, *J* = 6.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 138.3, 136.4, 135.6, 134.2, 129.2, 128.9, 128.8, 128.3, 128.2, 128.1, 127.9, 127.8, 126.5, 118.3, 117.3, 59.9, 47.9, 47.8, 35.3; IR (film) 3263, 2163, 1541 cm^{-1}; MS (ESI+) 395.2229 (395.2230 calcd for $C_{26}H_{26}N_4$, M + H$^+$).

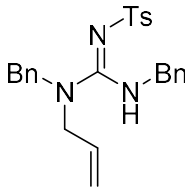


2-Allyl-*N*-benzyl-N'-cyanopyrrolidine-1-carboximidamide (3-6f). The title compound was prepared from methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (1.112 g, 5.4 mmol), ethanol (55 mL), mercuric oxide (1.75 g, 8.1 mmol), triethylamine (3.8 mL, 27 mmol), and 2-allylpyrrolidinium trifluoroacetate **(3-S6)** (1.46 g, 6.5 mmol) using a procedure analogous to that described above for the synthesis of **3-6a**. This procedure afforded 0.628 g (43%) of the title compound as a clear, viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5 H), 5.78–5.64 (m, 1 H), 5.16 (t, *J* = 5.6 Hz, 1 H), 5.10–5.00 (m, 2 H), 4.68–4.51 (m, 2 H), 4.28–4.24 (m, 1 H), 3.51–3.43 (m, 2 H), 2.50–2.46 (m, 1 H), 2.16 (dt, *J* = 14.1, 8.3 Hz, 1 H), 2.02–1.82 (m, 3 H), 1.79–1.74 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 137.8, 133.7, 128.8, 127.9, 127.8, 118.3, 117.9, 58.1, 48.4, 46.9, 37.8, 29.6, 23.4; IR (film) 3252, 2156, 1527 cm^{-1}; MS (ESI+) 269.1760 (269.1761 calcd for $C_{16}H_{20}N_4$, M + H$^+$).



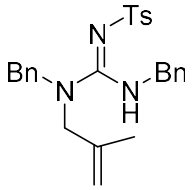
1,3-dibenzyl-1-cinnamyl-2-cyanoguanidine (3-6g). The title compound was prepared from methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.60 g, 2.90 mmol), ethanol (30 mL), mercuric oxide (0.94 g, 4.35 mmol), triethylamine (1.6 mL, 11.60 mmol), and (*E*)-

N-benzyl-3-phenylprop-2-en-1-ylamine **(3-S9)** (0.61 g, 3.5 mmol) using a procedure analogous to that described above for the synthesis of **3-6a**. This procedure afforded 0.438 g (40%) of the title compound as a pale yellow solid, m.p. 74–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.05 (m, 15 H), 6.38 (d, *J* = 16.4 Hz, 1 H), 6.08 (dt, *J* = 16.0, 6.1 Hz, 1 H), 5.38 (t, *J* = 5.4 Hz, 1 H), 4.70 (d, *J* = 5.3 Hz, 2 H), 4.60 (s, 2 H), 4.09 (d, *J* = 6.4 Hz, 2 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.0, 137.1, 135.8, 135.7, 129.0, 128.9, 128.7, 128.2, 128.1, 128.0, 127.8, 127.3, 126.5, 123.1, 117.3, 52.2, 51.2, 47.6; IR (film) 3257, 2164, 1542 cm^{-1}; MS (ESI+) 381.2072 (381.2074 calcd for $C_{25}H_{24}N_4$, M + H$^+$).

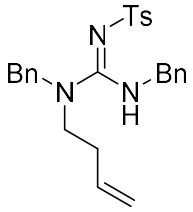


***N*-{[Allyl(benzyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (3-7a).** The title compound was prepared from methyl *N*-benzyl-*N*'-tosylcarbamimidothioate **(3-S3)** (1.06 g, 3.17 mmol), ethanol (30 mL), mercuric oxide (1.03 g, 4.75 mmol), triethylamine (1.8 mL, 12.68 mmol), and *N*-benzylprop-2-en-1-ylamine (0.70 g, 4.75 mmol) using a procedure analogous to that described above for the synthesis of **3-6a** except with a reaction time of 48 h. This procedure afforded 1.06 g (77%) of the title compound as a white solid, m.p. 91–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2 H), 7.34–7.22 (m, 6 H), 7.20–7.08 (m, 6 H), 6.99 (t, *J* = 5.7 Hz, 1 H), 5.74 (ddt, *J* = 16.4, 9.8, 5.8 Hz, 1 H), 5.24–5.05 (m, 2 H), 4.48 (s, 2 H), 4.39 (d, *J* = 5.7 Hz, 2 H), 3.82 (d, *J* = 5.7 Hz, 2 H), 2.39 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 141.7, 141.0, 136.9, 136.4, 132.4, 129.1, 128.9, 128.7, 128.0, 127.6, 127.6, 127.4, 126.1, 118.9, 51.9,

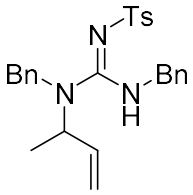
51.8, 49.7, 21.4; IR (film) 3320, 1563 cm^{-1}; MS (ESI+) 434.1894 (434.1897 calcd for $C_{25}H_{27}N_3O_2S$, M + H^+).



***N*-{[Benzyl(2-methylallyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (3-7b).** The title compound was prepared from methyl *N*-benzyl-*N'*-tosylcarbamimidothioate **(3-S3)** (1.30 g, 3.88 mmol), ethanol (30 mL), mercuric oxide (1.26 g, 5.82 mmol), triethylamine (2.2 mL, 15.70 mmol), and *N*-benzyl-2-methylprop-2-en-1-ylamine **(3-S5)** (0.75 g, 4.65 mmol) using a procedure analogous to that described above for the synthesis of **3-6a** except with a reaction time of 48 h. This procedure afforded 0.78 g (45%) of the title compound as a white solid, m.p. 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2 H), 7.35–7.21 (m, 6 H), 7.19–7.05 (m, 6 H), 6.98 (t, *J* = 5.8 Hz, 1 H), 4.92 (s, 1 H), 4.79 (s, 1 H), 4.48 (s, 2 H), 4.42 (d, *J* = 5.8 Hz, 2 H), 3.71 (s, 2 H), 2.39 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.1, 141.6, 141.1, 140.0, 137.0, 136.5, 129.1, 128.9, 128.7, 128.0, 127.8, 127.6, 127.3, 126.1, 113.4, 54.5, 51.8, 49.7, 21.4, 20.0; IR (film) 3316, 1559 cm^{-1}; MS (ESI+) 448.2048 (448.2053 calcd for $C_{26}H_{29}N_3O_2S$, M + H^+).

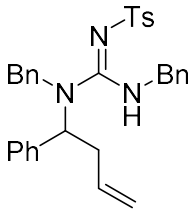


***N*-{[Benzyl(but-3-en-1-yl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (3-7c).** The title compound was prepared from methyl *N*-benzyl-*N*′-tosylcarbamimidothioate **(3-S3)** (1.13 g, 3.37 mmol), ethanol (30 mL), mercuric oxide (1.10 g, 5.09 mmol), triethylamine (1.9 mL, 13.84 mmol) and *N*-benzylbut-3-en-1-ylamine (0.77 g, 5.09 mmol) using a procedure analogous to that described above for the synthesis of **3-6a** except with a reaction time of 48 h. This procedure afforded 1.39 g (91%) of the title compound as a white solid, m.p. 123–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.36–7.22 (m, 7 H), 7.21–7.09 (m, 7 H), 7.06 (t, *J* = 5.7 Hz, 1 H), 5.55 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1 H), 5.01–4.86 (m, 2 H), 4.47 (s, 2 H), 4.36 (d, *J* = 5.7 Hz, 2 H), 3.32–3.20 (m, 2 H), 2.39 (s, 3 H), 2.23–2.19 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.1, 141.7, 140.9, 136.8, 136.3, 134.5, 129.1, 128.9, 128.8, 128.0, 127.7, 127.4, 127.3, 126.1, 117.3, 53.0, 49.9, 48.5, 32.0, 21.4; IR (film) 3313, 1560 cm^{-1}; MS (ESI+) 448.2049 (448.2053 calcd for $C_{26}H_{29}N_3O_2S$, M + H$^+$).



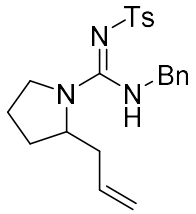
***N*-{[Benzyl(but-3-en-2-yl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (3-7d).** The title compound was prepared from methyl *N*-benzyl-*N*′-tosylcarbamimidothioate **(3-S3)** (1.018 g, 3.05 mmol), ethanol (30 mL),

mercuric oxide (0.991 g, 4.58 mmol), triethyl amine (1.7 mL, 12.2 mmol), and *N*-benzylbut-3-en-2-ylamine **(3-S4)** (0.590 g, 3.66 mmol) using a procedure analogous to that described above for the synthesis of **3-6a** except with a reaction time of 48 h. This procedure afforded 1.21 g (89%) of the title compound as an off white solid, m.p. 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2 H), 7.27–7.11 (m, 6 H), 7.10–7.02 (m, 2 H), 6.97 (dd, *J* = 7.9, 1.9 Hz, 4 H), 6.87 (t, *J* = 5.7 Hz, 1 H), 5.95–5.86 (m, 1 H), 5.24–5.11 (m, 2 H), 4.55–4.50 (m, 1 H), 4.38 (t, *J* = 5.5 Hz, 2 H), 4.31 (s, 2 H), 2.33 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 141.4, 140.6, 138.0, 137.5, 136.7, 129.0, 128.8, 128.5, 127.9, 127.5, 127.0, 126.8, 126.0, 117.3, 57.4, 49.6, 47.4, 21.4, 16.8; IR (film) 3320, 1557 cm^{-1}; MS (ESI+) 448.2056 (448.2053 calcd for $C_{26}H_{29}N_3O_2S$, M + H^+).



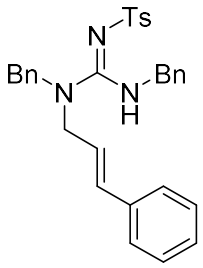
***N*-{[Benzyl(1-phenylbut-3-en-1-yl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (3-7e).** The title compound was prepared from methyl *N*-benzyl-*N*'-tosylcarbamimidothioate **(3-S3)** (1.390 g, 3.9 mmol), ethanol (39 mL), mercuric oxide (1.26 g, 5.8 mmol), triethylamine (2.1 mL, 15 mmol), and *N*-benzyl-1-phenylbut-3-en-1-ylamine **(3-S8)** (1.100 g, 4.6 mmol) using a procedure analogous to that described above for the synthesis of **3-6a** except with a reaction time of 96 h. This procedure afforded 1.46 g (71%) of the title compound as a white solid, m.p. 117–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2 H), 7.33–7.17 (m, 8 H), 7.17–7.05 (m, 5 H),

7.00–6.93 (m, 2 H), 6.92–6.85 (m, 2 H), 6.48 (t, *J* = 5.4 Hz, 1 H), 5.58 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1 H), 5.35 (t, *J* = 7.7 Hz, 1 H), 5.08–4.94 (m, 2 H), 4.53–4.40 (m, 2 H), 4.30 (d, *J* = 16.3 Hz, 1 H), 4.12 (d, *J* = 16.3 Hz, 1 H), 2.81–2.62 (m, 2 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 141.4, 141.3, 138.0, 136.8, 136.6, 129.0, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 127.7, 127.3, 126.7, 126.0, 118.1, 61.9, 49.9, 48.1, 35.6, 21.4; IR (film) 3335, 1495 cm^{-1}; MS (ESI+) 524.2367 (524.2366 calcd for $C_{32}H_{33}N_3O_2S$, M + H$^+$).

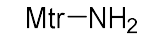


2-Allyl-*N*-benzyl-*N'*-tosylpyrrolidine-1-carboximidamide (3-7f). The title compound was prepared from methyl *N*-benzyl-*N*'-tosylcarbamimidothioate **(3-S3)** (1.60 g, 4.78 mmol), ethanol (40 mL), mercuric oxide (1.50 g, 6.92 mmol), triethylamine (3.3 mL, 23.42 mmol) and 2-allylpyrrolidinium trifluoroacetate **(3-S6)** (7.0 mmol) using a procedure analogous to that described above for the synthesis of **3-6a** except with a reaction time of 48 h. This procedure afforded 0.89 g (48%) of the title compound as a white solid, m.p. 76–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 8.0 Hz, 2 H), 7.38–7.28 (m, 3 H), 7.24–7.13 (m, 4 H), 5.44 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1 H), 4.87 (dd, *J* = 10.3, 2.1 Hz, 1 H), 4.74 (dd, *J* = 17.1, 1.6 Hz, 1 H), 4.36–4.18 (m, 3 H), 3.44–3.38 (m, 1 H), 3.36–3.30 (m, 1 H), 2.38 (s, 3 H), 2.20–2.08 (m, 1 H), 2.03–1.91 (m, 2 H), 1.88 (dtt, *J* = 12.2, 6.0, 2.7 Hz, 1 H), 1.73 (dtt, *J* = 12.0, 10.2, 7.3 Hz, 1 H), 1.57–1.49 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.7, 141.7, 141.1, 137.1, 133.8, 129.1, 128.9, 128.0, 127.5, 126.2, 117.6,

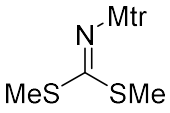
58.4, 51.1, 49.0, 38.1, 29.6, 25.2, 21.4; IR (film) 3314, 1560 cm^{-1}; MS (ESI+) 398.1892 (398.1897 calcd for $C_{22}H_{27}N_3O_2S$, M + H^+).



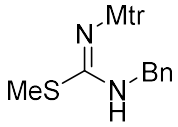
***N*-{[Benzyl(cinnamyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (3-7g).** The title compound was prepared from methyl *N*-benzyl-*N*'-tosylcarbamimidothioate **(3-S3)** (0.65 g, 1.94 mmol), ethanol (30 mL), mercuric oxide (0.65 g, 3.00 mmol), triethylamine (1.1 mL, 7.95 mmol), and (E)-*N*-benzyl-3-phenylprop-2-en-1-ylamine **(3-S9)** (0.70 g, 3.14 mmol) using a procedure analogous to that described above for the synthesis of **3-6a** except with a reaction time of 48 h. This procedure afforded 0.35 g (33%) of the title compound as a white solid, m.p. 120–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 2 H), 7.35–7.20 (m, 12 H), 7.17–7.11 (m, 5 H), 7.09 (t, *J* = 5.8 Hz, 1 H), 6.33 (d, *J* = 15.9 Hz, 1 H), 6.05 (dt, *J* = 15.9, 6.3 Hz, 1 H), 4.52 (s, 2 H), 4.41 (d, *J* = 5.8 Hz, 2 H), 3.98 (d, *J* = 6.3, 1.4 Hz, 2 H), 2.38 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.0, 141.7, 141.0, 136.8, 136.3, 136.0, 134.0, 129.1, 128.9, 128.8, 128.6, 128.1, 128.1, 128.0, 127.7, 127.5, 127.4, 126.5, 126.1, 123.6, 52.2, 51.5, 49.8, 21.5; IR (film) 3314, 1564 cm^{-1}; MS (ESI+) 510.2205 (510.2210 calcd for $C_{31}H_{31}N_3O_2S$, M + H^+).



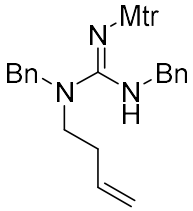
4-methoxy-2,3,6-trimethylbenzenesulfonamide (3-S10). A round bottom flask equipped was charged with ammonia in ethanol (10 mL, 20 mmol) and cooled on an ice bath. A solution of 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (2.48 g, 10 mmol) in ethanol (10 mL) was added, followed by triethylamine (1.4 mL, 10 mmol). The reaction was allowed to warm to rt and stir for 6 hours. Concentration of the reaction mixture *in vacuo* afforded the crude product that was purified via flash column chromatography to yield 1.26 g (55%) of the desired product as a tan solid.



Dimethyl [(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]carbonimidodithioate (3-S11). A flame dried flask was cooled under a stream of nitrogen and charged with 4-methoxy-2,3,6-trimethylbenzenesulfonamide **(3-S10)** (1.26 g, 5.5 mmol), carbon disulfide (0.5 mL, 8.8 mmol), and DMF (10 mL). The solution was then cooled on an ice bath. A solution of potassium hydroxide (0.73 g, 13 mmol) in water (5 mL) was added dropwise, and the reaction was stirred at 0 °C for 30 minutes. Iodidomethane (0.8 mL, 13 mmol) was added dropwise, and then the reaction was allowed to warm to rt and stirred for 30 minutes. Water (10 mL) was then added, and a light yellow solid precipitated from solution. The solid was isolated to afford 1.1 g (60%) of the desired product.

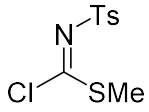


Methyl (*E*)-*N*-benzyl-*N′*-[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl] carbamimidothioate (3-S12). A flame dried flask was cooled under a stream of nitrogen and charged with Dimethyl {(4-methoxy-2,3,6-trimethylphenyl)sulfonyl}carbonimidodithioate **(3-S11)** (1.1 g, 3.3 mmol) in ethanol (20 mL). Benzylamine (0.55 mL, 4.95 mmol) was added slowly, and the reaction was then heated to reflux with stirring for 2 h. The solution was then cooled to rt, a stream of nitrogen was blown over the solution for 20 min, and then the solution was placed in the freezer overnight. The white precipitate that had formed was then isolated via filtration using a fritted glass funnel to yield 1.04 g (80%) of the title compound as a light tan solid.

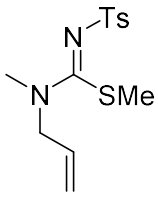


(*E*)-*N*-{[benzyl(but-3-en-1-yl)amino][benzylamino]methylene}-4-methoxy-2,3,6-trimethylbenzenesulfonamide (3-20). A round bottom flask was charged with Methyl (*E*)-*N*-benzyl-*N′*-[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]carbamimidothioate **(3-S12)** (1.04 g, 2.65 mmol), ethanol (26 mL), and mercuric oxide (0.86 g, 3.97 mmol), then purged with nitrogen. Triethylamine (1.5 mL, 10.6 mmol) was added followed by *N*-benzylbut-3-en-1-ylamine (0.64 g, 3.97 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column

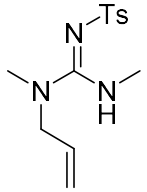
chromatography on silica gel (ethyl acetate:hexanes = 3:7) to yield 0.62 g (46%) of the title compound as a light tan solid, m.p. 96–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 6 H), 7.18–7.13 (m, 2 H), 7.11–7.03 (m, 2 H), 7.00 (t, *J* = 6.0 Hz, 1 H), 6.50 (s, 1 H), 5.60–5.51 (m, 1 H), 4.98–4.90 (m, 2 H), 4.47 (s, 3 H), 4.34 (d, *J* = 6.0 Hz, 2 H), 3.84 (s, 3 H), 3.25–3.15 (m, 2 H), 2.59 (s, 3 H), 2.57 (s, 3 H), 2.24 (q, *J* = 7.3 Hz, 2 H), 2.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 158.4, 138.6, 136.9, 136.7, 136.5, 134.5, 133.7, 128.8, 128.7, 127.9, 127.6, 127.3, 127.2, 124.7, 117.2, 111.7, 55.4, 52.6, 49.8, 48.2, 31.8, 24.0, 18.5, 11.9; IR (film) 3316, 1560, 1118 cm^{-1}; MS (ESI+) 506.2474 (506.2472 calcd for $C_{29}H_{35}N_3O_3S$, M + H^+).



Methyl tosylcarbonochloridoimidothioate (3-S13). A flame dried flask was cooled under a stream of nitrogen and charged with dimethyl tosylcarbonimidodithioate **(3-S2)** (4.00 g, 14.4 mmol) and dichloromethane (50 mL). Sulfonyl chloride (2.4 mL, 28.8 mmol) was added dropwise, and the reaction was refluxed for 3 hours. After cooling to rt, the reaction mixture was concentrated, and the crude product was purified via flash column chromatography (EtOAc/Hexanes) to afford 2.63 g (69%) of the title compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, *J* = 8.1 Hz, 2 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 2.45 (s, 3 H), 2.43 (s, 3 H).



Methyl-*N*-allyl-*N*-methyl-*N*'-tosylcarbamimidothioate (3-S14). A flame dried flask was cooled under a stream of nitrogen, charged with methyl tosylcarbonochloridoimidothioate **(3-S13)** (1.5 g, 5.69 mmol) and acetonitrile (38 mL), and cooled on an ice bath. Triethyl amine (0.95 mL, 6.83 mmol) was added dropwise, followed by dropwise addition of *N*-allylmethylamine in 9.5 mL acetonitrile. The reactionw as allowed to stir at rt for 48 h, then concentrated. The crude product was purified via flash column chromatography on silica gel (EtOAc:Hexanes = 30:70) to afford 1.568 g (92%) of the title compound as a yellow oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 5.61–5.70 (m, 1 H), 5.16 (dd, *J* = 10.3, 1.2 Hz, 1 H), 5.09 (dd, *J* = 17.1, 1.2 Hz, 1 H), 4.08 (d, *J* = 5.6 Hz, 2 H), 3.07 (s, 3 H), 2.45 (s, 3 H), 2.31 (s, 3 H).



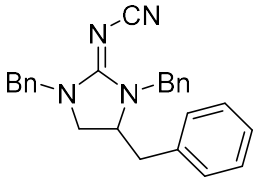
***N*-{[Allyl(methyl)amino](methylamino)methylene}-4-methylbenzenesulfonamide (3-23).** A round bottom flask was charged with Methyl-*N*-allyl-*N*-methyl-*N*'-tosylcarbamimidothioate **(3-S14)** (1.57 g, 5.25 mmol), ethanol (50 mL), and mercuric oxide (1.71 g, 7.88 mmol), then purged with nitrogen. Triethylamine (2.9 mL, 21 mmol) was added followed by methylamine (3.15 mL, 6.3 mmol) as a 2 M solution in methanol. The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite.

The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate:hexanes = 40:60) to yield 1.15 g (78%) of the title compound as a white solid, m.p. 63–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 5.79–5.71 (m, 1 H), 5.20–5.13 (m, 2 H), 3.81 (d, J = 5.6 Hz, 2 H), 2.82 (s, 3 H), 2.80 (d, J = 5.2 Hz, 3 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 141.8, 141.2, 132.5, 129.2, 125.9, 118.4, 53.9, 36.7, 32.4, 21.4; IR (film) 3356.1, 1590.3 cm^{-1}; MS (ESI+) 282.1271 (282.1271 calcd for $C_{13}H_{19}N_3O_2S$, M + H^+).

Preparation and Characterization of Products

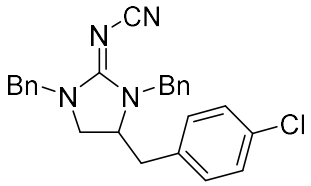
General Procedure A for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol%), XPhos or CPhos (4 mol%), and NaO^{t}Bu (2 equiv). The tube was purged with nitrogen and then a solution of the aryl bromide (1.5 equiv) in toluene was added, and the resulting solution was stirred at rt for 1 min. A solution of the *N*-protected guanidine substrate (1 equiv) in toluene (0.1 M) was added, and the solution was heated to 90 °C with stirring until the starting material had been consumed as judged by TLC or ^{1}H NMR analysis of the reaction mixture (ca 1 h). The mixture was then cooled to rt and saturated aqueous NH_4Cl (1 mL) was added. The resulting mixture was then extracted with ethyl acetate (3 x 2 mL), and the combined organic layers were filtered through a plug of silica gel. The organic layer was then concentrated *in vacuo*, and the crude product was purified via flash column chromatography on silica gel (methanol:dichloromethane = 1:99).

General Procedure B for Pd-Catalyzed Carboamination Reactions of Aryl Triflates. A flame dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol%), CPhos (4 mol%), and LiO^tBu (2 equiv). The tube was purged with nitrogen and then a solution of the aryl triflate (1.5 equiv) in $PhCF_3$ was added, and the resulting solution was stirred at rt for 1 min. A solution of the *N*-protected guanidine substrate (1 equiv) in CF_3Ph (0.2 M) was added, and the solution was heated to 100 ºC with stirring until the starting material had been consumed as judged by TLC or ^1H NMR analysis of the reaction mixture (ca 2 h). The mixture was then cooled to rt and saturated aqueous NH_4Cl (1 mL) was added. The resulting mixture was then extracted with ethyl acetate (3 x 2 mL), and the combined organic layers were filtered through a plug of silica gel. The organic layer was then concentrated *in vacuo*, and the crude product was purified via flash column chromatography on silica gel (methanol:dichloromethane = 1:99).

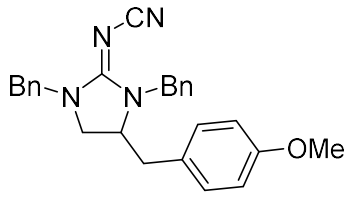


***N*-(1,3,4-Tribenzylimidazolidin-2-ylidene)cyanamide (3-8a).** The general procedure A was employed for the coupling of bromobenzene (47 mg, 0.30 mmol) with 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(3-6a)** (61 mg, 0.20 mmol). This procedure afforded 65 mg (86%) of the title compound as a white, viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.25 (m, 8 H), 7.25–7.15 (m, 5 H), 6.90 (dd, *J* = 7.3, 2.1 Hz, 2 H), 5.36 (d, *J* = 15.6

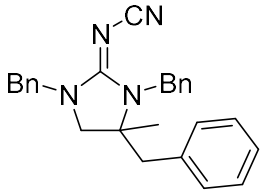
Hz, 1 H), 4.74–4.56 (m, 2 H), 4.19 (d, *J* = 15.6 Hz, 1 H), 3.70 (tdd, *J* = 9.1 Hz, 6.2 Hz, 4.4 Hz, 1 H), 3.20 (t, *J* = 9.6 Hz, 1 H), 3.04–2.93 (m, 2 H), 2.54 (dd, *J* = 13.6 Hz, 8.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 135.7, 135.4, 135.3, 129.0, 128.9, 128.2, 128.1, 128.1, 128.0, 127.2, 116.5, 55.8, 49.5, 49.4, 47.3, 38.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2171, 1595 cm^{-1}; MS (ESI+) 381.2074 (381.2074 calcd for $C_{25}H_{24}N_4$, M + H$^+$).



***N*-[1,3-Dibenzyl-4-(4-chlorobenzyl)imidazolidin-2-ylidene]cyanamide (3-8b).** The general procedure A was employed for the coupling of of 4-bromochlorobenzene (57.4 mg, 0.30 mmol) with 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(3-6a)** (61 mg, 0.20 mmol). This procedure afforded 68 mg (82%) of the title compound as a pale yellow, foamy solid, m.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.25 (m, 8 H), 7.18–7.15 (m, 4 H), 6.80 (d, *J* = 8.1 Hz, 2 H), 5.35 (d, *J* = 15.5 Hz, 1 H), 4.76 (d, *J* = 15.2 Hz, 1 H), 4.52 (d, *J* = 15.2 Hz, 1 H), 4.19 (d, *J* = 15.6 Hz, 1 H), 3.70–3.65 (m, 1 H), 3.20 (t, *J* = 9.6 Hz, 1 H), 2.96–2.88 (m, 2 H), 2.53 (dd, *J* = 13.7, 8.5, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 135.5, 135.2, 133.7, 133.2, 130.4, 129.0, 128.9, 128.2, 128.1, 128.0, 116.3, 55.4, 49.4, 49.2, 47.3, 37.3 (two carbon signals are absent due to incidental equivalence); IR (film) 2162, 1599 cm^{-1}; MS (ESI+) 415.1681 (415.1684 calcd for $C_{25}H_{23}ClN_4$, M + H$^+$).

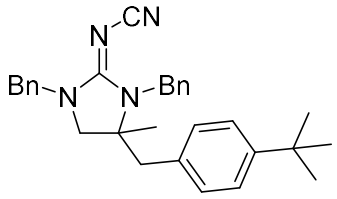


***N*-[1,3-Dibenzyl-4-(4-methoxybenzyl)imidazolidin-2-ylidene]cyanamide (3-8c).** The general procedure A was employed for the coupling of 4-bromoansole (56.1 mg, 0.30 mmol) with 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(3-6a)** (61 mg, 0.20 mmol). This procedure afforded 70 mg (85%) of the title compound as a pale yellow solid, m.p. 98–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.27 (m, 8 H), 7.22–7.16 (m, 2 H), 6.86–6.80 (m, 2 H), 6.80–6.74 (m, 2 H), 5.37 (d, *J* = 15.6 Hz, 1 H), 4.72 (d, *J* = 15.2 Hz, 1 H), 4.60 (d, *J* = 15.3 Hz, 1 H), 4.21 (d, *J* = 15.6 Hz, 1 H), 3.77 (s, 3 H), 3.72–3.65 (m, 1 H), 3.21 (t, *J* = 9.6 Hz, 1 H), 3.00 (dd, *J* = 9.8, 6.3 Hz, 1 H), 2.92 (dd, *J* = 13.8, 4.4 Hz, 1 H), 2.52 (dd, *J* = 13.8, 8.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 156.7, 136.4, 136.2, 130.0, 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 117.8, 114.3, 56.2, 55.3, 54.4, 53.7, 42.8, 37.4, 24.9 (one carbon signal is absent due to incidental equivalence); IR (film) 2170, 1595 cm^{-1}; MS (ESI+) 411.2179 (411.2179 calcd for $C_{26}H_{26}N_4O$, M + H^+).

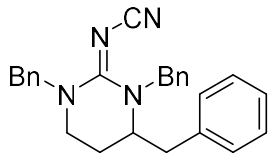


***N*-(1,3,4-Tribenzyl-4-methylimidazolidin-2-ylidene)cyanamide (3-8d).** The general procedure A was employed for the coupling of bromobenzene (35.3 mg, 0.225 mmol) with 1,3-dibenzyl-2-cyano-1-(2-methylallyl)guanidine **(3-6b)** (47.8 mg, 0.15 mmol). This procedure afforded 52 mg (88%) of the title compound as an off-white solid, m.p. 92–94

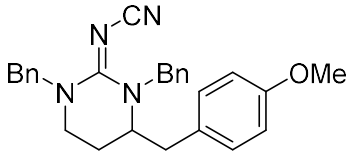
°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 7 H), 7.30–7.23 (m, 4 H), 7.20 (dd, *J* = 7.7, 1.8 Hz, 2 H), 6.94–6.87 (m, 2 H), 5.01 (d, *J* = 16.2 Hz, 1 H), 4.69–4.55 (m, 2 H), 4.40 (d, *J* = 16.2 Hz, 1 H), 3.30 (d, *J* = 9.8 Hz, 1 H), 2.92 (d, *J* = 9.8 Hz, 1 H), 2.77 (d, *J* = 13.6 Hz, 1 H), 2.59 (d, *J* = 13.6 Hz, 1 H), 1.16 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 138.2, 135.4, 135.0, 129.9, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.7, 127.5, 127.4, 127.3, 116.4, 62.4, 55.7, 49.4, 44.7, 43.5, 24.5; IR (film) 2167, 1593 cm^{-1}; MS (ESI+) 395.2227 (395.2230 calcd for $C_{26}H_{26}N_4$, M + H$^+$).



***N*-{1,3-Dibenzyl-4-[4-(*tert*-butyl)benzyl]-4-methylimidazolidin-2-ylidene}cyanamide (3-8e).** The general procedure A was employed for the coupling of 1-bromo-4-*tert*-butylbenzene (48 mg, 0.225 mmol) with 1,3-dibenzyl-2-cyano-1-(2-methylallyl)guanidine **(3-6b)** (47.8 mg, 0.15 mmol). This procedure afforded 58 mg (86%) of the title compound as a yellow solid, m.p. 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 7 H), 7.25–7.20 (m, 5 H), 6.82 (d, *J* = 8 Hz, 2 H), 4.97 (d, *J* = 16.2 Hz, 1 H), 4.70–4.54 (m, 2 H), 4.42 (d, *J* = 16.2 Hz, 1 H), 3.30 (d, *J* = 9.8 Hz, 1 H), 2.90 (d, *J* = 9.8 Hz, 1 H), 2.71 (d, *J* = 13.5 Hz, 1 H), 2.58 (d, *J* = 13.6 Hz, 1 H), 1.30 (s, 9 H), 1.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.2, 138.2, 135.5, 131.9, 130.0, 128.8, 128.6, 128.4, 128.0, 127.5, 127.4, 125.4, 116.4, 62.5, 55.7, 49.4, 44.7, 43.0, 34.5, 31.3, 24.2; IR (film) 2170, 1593 cm^{-1}; MS (ESI+) 451.2854 (451.2856 calcd for $C_{30}H_{34}N_4$, M + H$^+$).

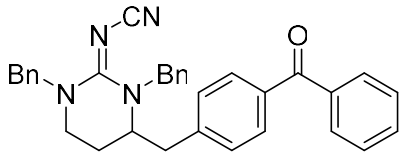


***N*-(1,3,4-Tribenzyltetrahydropyrimidin-2-[1*H*]-ylidene)cyanamide (3-8f).** The general procedure A was employed for the coupling of bromobenzene (35.3 mg, 0.225 mmol) with 1,3-dibenzyl-1-(but-3-en-1-yl)-2-cyanoguanidine **(3-6c)** (47.8 mg, 0.15 mmol). This procedure afforded 58 mg (98%) of the title compound as a pale yellow solid, m.p. 87–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.20 (m, 13 H), 7.00–6.93 (m, 2 H), 5.43 (d, *J* = 15.2 Hz, 1 H), 5.15 (d, *J* = 15.0 Hz, 1 H), 4.65 (d, *J* = 15.0 Hz, 1 H), 4.03 (d, *J* = 15.2 Hz, 1 H), 3.48–3.43 (m, 1 H), 3.60–3.12 (m, 2 h), 2.76 (dd, *J* = 13.6, 6.5 Hz, 1 H), 2.50 (dd, *J* = 13.5, 8.2 Hz, 1 H), 1.71–1.60 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 136.8, 136.3, 136.1, 129.0, 128.9, 128.8, 128.8, 128.3, 128.2, 128.1, 128.0, 127.0, 117.8, 56.1, 54.4, 53.7, 42.7, 38.2, 24.8; IR (film) 2165, 1526 cm^{-1}; MS (ESI+) 395.2231 (395.2230 calcd for $C_{26}H_{26}N_4$, M + H$^+$).

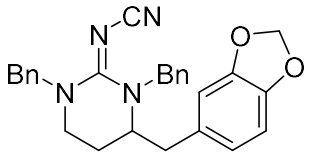


***N*-[1,3-Dibenzyl-4-(4-methoxybenzyl)tetrahydropyrimidin-2-[1*H*]-ylidene]cyanamide (3-8g).** The general procedure A was employed for the coupling of 4-bromoanisole (42.1 mg, 0.225 mmol) with 1,3-dibenzyl-1-(but-3-en-1-yl)-2-cyanoguanidine **(3-6c)** (47.8 mg, 0.15 mmol). This procedure afforded 60 mg (94%) of the title compound as a pale yellow solid, m.p. 43–46 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.21 (m, 11 H), 6.93–6.77 (m, 4 H), 5.43 (d, *J* = 15.3 Hz, 1 H), 5.14 (d, *J* = 15.0 Hz,

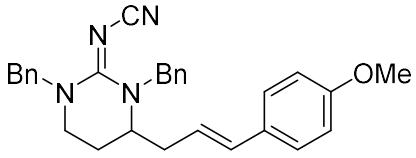
1 H), 4.63 (d, *J* = 15.1 Hz, 1 H), 4.02 (d, *J* = 15.3 Hz, 1 H), 3.78 (s, 3 H), 3.45–3.35 (m, 1 H), 3.29–3.11 (m, 2 H), 2.69 (dd, *J* = 13.7, 6.6 Hz, 1 H), 2.46 (dd, *J* = 13.7, 7.9 Hz, 1 H), 1.67–1.62 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 156.7, 136.4, 136.2, 130.0, 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 117.8, 114.3, 56.2, 55.3, 54.4, 53.7, 42.8, 37.4, 24.9 (one carbon signal is absent due to incidental equivalence); IR (film) 2164, 1511 cm^{-1}; MS (ESI+) 425.2337 (425.2336 calcd for $C_{27}H_{28}N_4O$, M + H^+).



***N*-[4-(4-Benzoylbenzyl)-1,3-dibenzyltetrahydropyrimidin-2-[1*H*]-ylidene]cyanamide (3-8h).** The general procedure A was employed for the coupling of 4-bromobenzophenone (78.3 mg, 0.30 mmol) with 1,3-dibenzyl-1-(but-3-en-1-yl)-2-cyanoguanidine **(3-6c)** (63.7 mg, 0.20 mmol). This procedure afforded 80.5 mg (81%) of the title compound as a pale yellow solid, m.p. 53–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.70 (m, 4 H), 7.63–7.56 (m, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.44–7.23 (m, 9 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 5.41 (d, *J* = 15.2 Hz, 1 H), 5.17 (d, *J* = 15.0 Hz, 1 H), 4.64 (d, *J* = 15.0 Hz, 1 H), 4.13 (d, *J* = 15.3 Hz, 1 H), 3.55–3.45 (m, 1 H), 3.31–3.15 (m, 2 H), 2.83 (dd, *J* = 13.5, 6.4 Hz, 1 H), 2.59 (dd, *J* = 13.5, 8.2 Hz, 1 H), 1.79–1.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 156.8, 141.6, 137.4, 136.4, 136.1, 136.0, 132.5, 130.7, 129.9, 129.0, 128.9, 128.8, 128.3, 128.2, 128.1, 117.6, 55.8, 54.4, 53.9, 42.7, 38.2, 25.0 (one carbon signal is absent due to incidental equivalence); IR (film) 2164, 1523 cm^{-1}; MS (ESI+) 499.2490 (499.2490 calcd for $C_{33}H_{30}N_4O$, M + H^+).

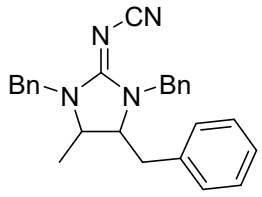


***N*-[4-(Benzo[d][1,3]dioxol-5-ylmethyl]-1,3-dibenzyltetrahydropyrimidin-2-[1*H*]-ylidene)cyanamide (3-8i).** The general procedure A was employed for the coupling of 1-bromo-3,4-(methylenedioxy)benzene (45.2 mg, 0.225 mmol) with 1,3-dibenzyl-1-(but-3-en-1-yl)-2-cyanoguanidine **(3-6c)** (47.8 mg, 0.15 mmol). This procedure afforded 64 mg (97%) of the title compound as a pale yellow, viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.26 (m, 10 H), 6.75–6.68 (m, 1 H), 6.39 (d, *J* = 6.9 Hz, 2 H), 5.93 (s, 2 H), 5.40 (d, *J* = 15.2 Hz, 1 H), 5.16 (d, *J* = 15.0 Hz, 1 H), 4.64 (d, *J* = 15.0 Hz, 1 H), 4.12 (d, *J* = 15.2 Hz, 1 H), 3.39 (ddt, *J* = 8.4, 6.1, 4.2 Hz, 1 H), 3.27–3.11 (m, 2 H), 2.66 (dd, *J* = 13.7, 6.4 Hz, 1 H), 2.39 (dd, *J* = 13.7, 8.4 Hz, 1 H), 1.68–1.62 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 147.9, 146.6, 136.3, 136.2, 130.4, 128.9, 128.3, 128.2, 128.1, 128.0, 122.0, 117.7, 109.1, 108.6, 101.1, 56.2, 54.5, 53.7, 42.8, 37.9, 24.6; IR (film) 2162, 1525 cm^{-1}; MS (ESI+) 439.2124 (439.2129 calcd for $C_{27}H_{26}N_4O_2$, M + H$^+$).



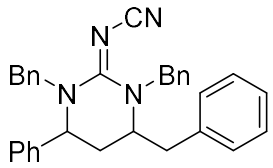
(*E*)-*N*-{1,3-Dibenzyl-4-[3-(4-methoxyphenyl)allyl]tetrahydropyrimidin-2-[1*H*]-ylidene}cyanamide (3-8j). The general procedure A was employed for the coupling of (*E*)-1-(2-bromovinyl)-4-methoxybenzene (47.9 mg, 0.225 mmol) with 1,3-dibenzyl-1-(but-3-en-1-yl)-2-cyanoguanidine **(3-6c)** (47.8 mg, 0.15 mmol). This procedure afforded 64 mg

(95%) of the title compound as a pale yellow, viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.28 (m, 10 H), 7.25–7.20 (m, 2 H), 6.86–6.81 (m, 2 H), 6.22 (d, *J* = 15.7 Hz, 1 H), 5.86–5.76 (m, 1 H), 5.51 (d, *J* = 15.3 Hz, 1 H), 5.09 (d, *J* = 15.0 Hz, 1 H), 4.67 (d, *J* = 15.1 Hz, 1 H), 4.36 (d, *J* = 15.3 Hz, 1 H), 3.80 (s, 3 H), 3.39–3.35 (m, 1 H), 3.21–3.13 (m, 2 H), 2.42–2.37 (m, 1 H), 2.25–2.14 (m, 1 H), 1.83–1.68 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 157.0, 136.5, 136.2, 133.4, 129.4, 128.9, 128.8, 128.3, 128.1, 128.0, 127.9, 127.3, 117.8, 55.3, 54.8, 54.4, 53.5, 24.7, 35.5, 25.2; IR (film) 2933, 2164, 1510 cm^{-1}; MS (ESI+) 451.2490 (451.2492 calcd for $C_{29}H_{30}N_4O$, M + H^+).



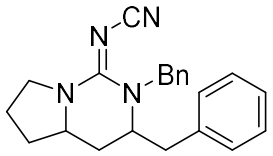
***N*-(1,3,4-Tribenzyl-5-methylimidazolidin-2-ylidene)cyanamide (3-8k).** The general procedure A was employed for the coupling of bromobenzene (47.1 mg, 0.30 mmol) with 1,3-dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine **(3-6d)** (63.7 mg, 0.20 mmol). This procedure afforded 56 mg (71%) of the title compound as a pale yellow, viscous oil. This compound was obtained as a 1.5:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.17 (m, 24 H), 7.11 (dd, *J* = 7.4,2.0 Hz, 2 H), 7.07–7.01 (m, 2 H), 6.86–6.79 (m, 2 H), 5.41 (d, *J* = 15.5 Hz, 1 H), 5.39–5.32 (m, 2 H), 5.24 (d, *J* = 15.4 Hz, 1 H), 4.19–4.03 (M, 3 H), 3.88–3.74 (m, 2 H), 3.60–3.46 (m, 1 H), 3.26–3.13 (m, 1 H), 3.00 (dd, *J* = 14.2, 6.7 Hz, 1 H), 2.87 (dd, *J* = 13.6, 4.3 Hz, 1 H), 2.76 (dd, *J* = 14.2, 7.9 Hz, 1 H), 2.42 (dd, *J* = 13.6, 7.9 Hz, 1 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 0.76 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 157.6,

136.7, 136.0, 135.8, 135.7, 135.3, 129.2, 129.0, 128.9, 128.8, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.82, 127.8, 127.0, 116.8, 116.5, 63.2, 59.6, 55.3, 54.4, 47.7, 47.4, 46.8, 46.2, 38.2, 33.7, 18.6, 12.3; IR (film) 2171, 1592 cm^{-1}; MS (ESI+) 395.2228 (395.2230 calcd for $C_{26}H_{26}N_4$, M + H^+).

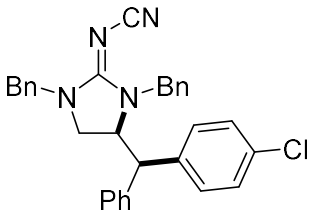


***N*-(1,3,4-Tribenzyl-6-phenyltetrahydropyrimidin-2-[1*H*]-ylidene)cyanamide (3-8l).** The general procedure A was employed for the coupling of bromobenzene (35.3 mg, 0.225 mmmol) with 1,3-dibenzyl-2-cyano-1-(1-phenylbut-3-en-1-yl)guanidine **(3-6e)** (59.2 mg, 0.15 mmol). This procedure afforded 60 mg (85%) of the title compound as a pale yellow solid, m.p. 68–75 °C. This compound was obtained as a 1.7:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.25 (m, 10 H), 7.25–7.11 (m, 6 H), 6.90–6.84 (d, *J* = 6.8 Hz, 2 H), 6.68–6.60 (m, 2 H), 5.85–5.67 (m, 3 H), 5.36 (d, *J* = 14.9 Hz, 1 H), 4.55–4.40 (m, 2 H), 4.34 (dd, *J* = 11.4, 6.6 Hz, 1 H), 3.97 (d, *J* = 15.7 Hz, 1 H), 3.85 (t, *J* = 15.4 Hz, 1 H), 3.57 (dq, *J* = 10.2, 5.1 Hz, 1 H), 3.36 (dp, *J* = 11.0, 3.8 Hz, 1 H), 2.58 (dd, *J* = 13.5, 7.6 Hz, 1 H), 2.39–2.33 (m, 2 H), 2.06–1.92 (m, 3 H), 1.88 (ddd, *J* = 14.0, 6.7, 3.1 Hz, 1 H), 1.67 (ddd, *J* = 14.0, 11.4, 4.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.3, 139.6, 139.5, 137.0, 136.9, 136.6, 136.0, 135.8, 129.4, 129.3, 129.2, 129.0, 128.91, 128.86, 128.84, 128.77, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.84, 127.78, 127.7, 127.4, 127.0, 126.83, 126.80, 126.3, 117.8, 117.1, 58.2, 56.6, 56.5, 55.2, 54.2, 52.1, 51.8, 51.5,

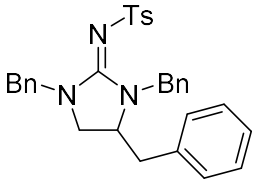
38.3, 36.1, 33.2; IR (film) 2165, 1515 cm^{-1}; MS (ESI+) 471.2542 (471.2543 calcd for $C_{32}H_{30}N_4$, M + H^+).



***N*-(2,3-Dibenzylhexahydropyrrolo[1,2-c]pyrimidin-1-[2*H*]-ylidene)cyanamide (3-8m).** The general procedure A was employed for the coupling of bromobenzene (47.1 mg, 0.30 mmol) with 2-allyl-*N*-benzyl-*N*'-cyanopyrrolidine-1-carboximidamide **(3-6f)** (58.0 mg, 0.22 mmol). This procedure afforded 72 mg (97%) of the title compound as a pale yellow solid, m.p. 52–55 °C. This compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.17 (m, 7 H), 7.09–7.05 (m, 1 H), 6.97–6.91 (m, 2 H), 5.53–5.44 (m, 2 H), 4.44–4.32 (m, 2 H), 4.15–4.13 (m, 2 H), 3.95 (td, *J* = 10.4, 7.4 Hz, 1 H), 3.75–3.66 (m, 2 H), 3.53 (dtd, *J* = 10.1, 5.0, 1.6 Hz, 1 H), 3.44–3.35 (m, 3 H), 3.24 (dd, *J* = 13.2, 3.9 Hz, 1 H), 3.12 (dd, *J* = 13.8, 4.8 Hz, 1 H), 2.62 (dd, *J* = 13.7, 9.9 Hz, 1 H), 2.43 (dd, *J* = 13.2, 9.6 Hz, 1 H), 2.14 (dtd, *J* = 12.1, 6.2, 2.2 Hz, 1 H), 2.11–2.06 (m, 2 H), 1.98–1.82 (m, 2 H), 1.53 (dq, *J* = 13.1, 6.8 Hz, 1 H), 1.50–1.42 (m, 1 H), 1.37 (dt, *J* = 13.3, 11.2 Hz, 1 H), 1.30–1.17 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 154.1, 137.3, 137.0, 136.9, 136.8, 129.0, 128.9, 128.8, 128.7, 128.6, 127.9, 127.8, 127.7, 127.6, 127.0, 126.9, 118.4, 55.4, 55.2, 54.8, 54.0, 51.2, 50.9, 49.1, 49.0, 39.8, 38.9, 35.3, 32.4, 31.5, 29.1, 23.8, 23.3; IR (film) 2163, 1512 cm^{-1}; MS (ESI+) 345.2072 (345.2074 calcd for $C_{22}H_{24}N_4$, M + H^+).

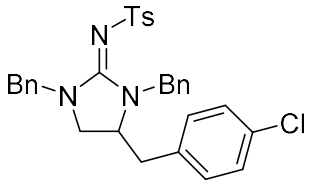


(4*S*,4'*R*)-*N*-{1,3-dibenzyl-4-[(4-chlorophenyl)(phenyl)methyl]imidazolidin-2-ylidene}cyanamide (3-8n). The general procedure A was employed for the coupling of 4-bromochlorobenzene (43 mg, 0.225 mmol) with 1,3-dibenzyl-1-cinnamyl-2-cyanoguanidine **(3-6g)** (57.1 mg, 0.15 mmol). This procedure afforded 18 mg (24%) of the title compound as a pale yellow solid, m.p. 59–63 °C. This compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 9 H), 7.22–7.17 (m, 2 H), 7.17–7.07 (m, 4 H), 7.05–6.98 (m, 2 H), 6.93–6.86 (m, 2 H), 5.27 (d, *J* = 16.0 Hz, 1 H), 4.65–4.49 (m, 2 H), 4.22–4.17 (m, 1 H), 4.03 (d, *J* = 7.9 Hz, 1 H), 3.45 (t, *J* = 9.9 Hz 1 H), 3.32 (d, *J* = 16.0 Hz, 1 H), 3.01 (dd, *J* = 10.2, 4.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 139.7, 138.1, 135.9, 135.1, 133.3, 129.6, 129.2, 129.0, 128.9, 128.4, 128.1, 128.1, 128.0, 127.8, 127.7, 116.4, 57.6, 54.2, 49.2, 49.1, 48.4 (one carbon signal is absent due to incidental equivalence); IR (film) 2172, 1598 cm^{-1}; MS (ESI+) 491.1992 (491.1997 calcd for $C_{31}H_{27}ClN_4$, M + H$^+$).



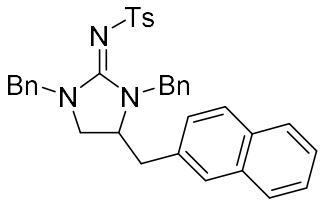
4-Methyl-*N*-(1,3,4-tribenzylimidazolidin-2-ylidene)benzenesulfonamide (3-9a). The general procedure B was employed for the coupling of phenyl trifluoromethanesulfonate

(101.8 mg, 0.45 mmol) with *N*-{[allyl(benzyl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7a)** (134.3 mg, 0.30 mmol). This procedure afforded 140 mg (92%) of the title compound as a pale yellow solid, m.p. 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.83 (m, 2 H), 7.39–7.28 (m, 6 H), 7.28–7.14 (m, 9 H), 6.89–6.81 (m, 2 H), 5.29 (d, *J* = 15.3 Hz, 1 H), 4.77 (d, *J* = 15.1 Hz, 1 H), 4.53 (d, *J* = 15.1 Hz, 1 H), 4.17 (d, *J* = 15.3 Hz, 1 H), 3.71–3.65 (m, 1 H), 3.23 (t, *J* = 9.9 Hz, 1 H), 3.03–2.89 (m, 2 H), 2.51 (dd, *J* = 13.6, 8.8 Hz, 1 H), 2.36 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 142.9, 141.1, 136.0, 135.5, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9, 127.8, 127.0, 125.8, 55.5, 50.8, 48.8, 48.7, 38.3, 21.4; IR (film) 2922, 1562 cm^{-1}; MS (ESI+) 510.2204 (510.2210 calcd for $C_{31}H_{31}N_3O_2S$, M + H^+).

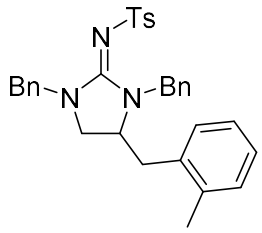


***N*-[1,3-Dibenzyl-4-(4-chlorobenzyl)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (3-9b).** The general procedure B was employed for the coupling of 4-chlorophenyl trifluoromethanesulfonate (78.2 mg, 0.30 mmol) with *N*-{[allyl(benzyl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7a)** (86.7 mg, 0.20 mmol). This procedure afforded 76.2 mg (70%) of the title compound as a pale yellow solid, m.p. 151–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2 H), 7.39–7.10 (m, 14 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.33 (d, *J* = 15.4 Hz, 1 H), 4.80 (d, *J* = 15.0 Hz, 1 H), 4.40 (d, *J* = 15.0 Hz, 1 H), 4.19 (d, *J* = 15.4 Hz, 1 H), 3.65 (tt, *J* = 9.5, 4.8 Hz, 1 H), 3.23 (t, *J* = 9.9 Hz, 1 H), 2.93 (dd, *J* = 10.3, 5.1 Hz, 1 H), 2.83 (dd, *J* = 13.7, 4.5 Hz, 1 H), 2.53 (dd, *J* = 13.7, 8.1 Hz, 1 H), 2.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1,

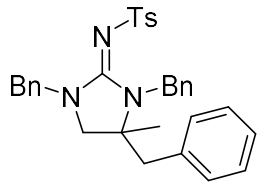
142.8, 141.2, 135.8, 135.5, 133.7, 133.0, 130.6, 129.0, 128.9, 128.7, 128.2, 128.0, 127.9, 125.8, 55.1, 50.5, 49.0, 48.3, 37.4, 21.3 (two carbon signals are absent due to incidental equivalence); IR (film) 2923, 1561 cm^{-1}; MS (ESI+) 544.1814 (544.1820 calcd for $C_{31}H_{30}ClN_3O_2S$, M + H^+).



***N*-[1,3-Dibenzyl-4-(naphthalen-2-ylmethyl)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (3-9c).** The general procedure B was employed for the coupling of naphthalen-2-yl trifluoromethanesulfonate (139 mg, 0.50 mmol) with *N*-{[allyl(benzyl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7a)** (145.7 mg, 0.34 mmol). This procedure afforded 151.6 mg (80%) of the title compound as a pale yellow solid, m.p. 149–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2 H), 7.82–7.75 (m, 1 H), 7.69 (dd, *J* = 9.0, 2.6 Hz, 2 H), 7.48–7.43 (m, 2 H), 7.40–7.30 (m, 3 H), 7.0–7.19 (m, 6 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.14–7.08 (m, 2 H), 6.98 (dd, *J* = 8.4, 1.7 Hz, 1 H), 5.34 (d, *J* = 15.4 Hz, 1 H), 4.83 (d, *J* = 15.0 Hz, 1 H), 4.42 (d, *J* = 15.1 Hz, 1 H), 4.26 (d, *J* = 15.4 Hz, 1 H), 3.78 (tt, *J* = 9.3, 4.7 Hz, 1 H), 3.22 (t, *J* = 9.9 Hz, 1 H), 3.21–2.99 (m, 2 H), 2.68 (dd, *J* = 13.6, 8.7 Hz, 1 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 142.9, 141.1, 136.0, 135.7, 133.3, 132.8, 132.3, 128.9, 129.0, 128.9, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.1, 126.3, 125.9, 125.8, 55.3, 50.6, 48.8, 48.4, 38.2, 21.3; IR (film) 2921, 1559 cm^{-1}; MS (ESI+) 560.2358 (560.2366 calcd for $C_{35}H_{33}N_3O_2S$, M + H^+).

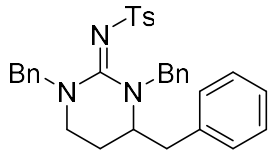


***N*-[1,3-dibenzyl-4-(2-methylbenzyl)imidazolidin-2-ylidene]-4-methylbenzenesulfonamide (3-9d).** The general procedure B was employed for the coupling of *o*-tolyl trifluoromethanesulfonate (108.1 mg, 0.45 mmol) with *N*-{[allyl(benzyl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7a)** (130 mg, 0.30 mmol). This procedure afforded 122 mg of the title compound as a pale yellow solid, m.p. 130–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8 Hz, 2 H), 7.35–7.24 (m, 8 H), 7.18 (d, *J* = 7.6 Hz, 4 H), 7.09–6.97 (m, 3 H), 6.64 (d, *J* = 7.6 Hz, 1 H), 5.26 (d, *J* = 15.2 Hz, 1 H), 4.90 (d, *J* = 14.8 Hz, 1 H), 4.51 (d, *J* = 15.2 Hz, 1 H), 4.09 (d, *J* = 15.2 Hz, 1 H), 3.65 (tt, 9.6, 4.9 Hz, 1 H), 3.21 (t, 9.8 Hz, 1 H), 3.00 (m, 2 H), 2.42 (dd, *J* = 13.6, 9.6 Hz, 1 H), 2.34 (s, 3 H), 1.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 142.9, 141.2, 136.3, 136.0, 135.9, 134.0, 130.6, 130.0, 129.0, 128.8, 128.5, 128.2, 128.0, 127.9, 127.1, 126.2, 125.8, 54.1, 50..8, 48.9, 48.8, 36.0, 21.4, 19.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2922, 1562 cm^{-1}; MS (ESI+) 524.2365 (524.2366 calcd for $C_{32}H_{33}N_3O_2S$, M + H^+).



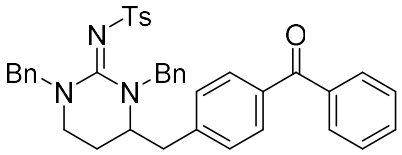
4-Methyl-*N*-(1,3,4-tribenzyl-4-methylimidazolidin-2-ylidene)benzenesulfonamide (3-9e). The general procedure B was employed for the coupling of phenyl

trifluoromethanesulfonate (67.9 mg, 0.30 mmol) with *N*-{[benzyl(2-methylallyl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7b)** (89.5 mg, 0.20) except using 1 mL benzotrifluoride (0.1 M) as solvent. This procedure afforded 89.8 mg (86%) of the title compound as a pale yellow solid, m.p. 129–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 2 H), 7.39–7.31 (m, 5 H), 7.31–7.15 (m, 8 H), 7.11 (d, *J* = 7.9 Hz, 2 H), 6.74 (dd, *J* = 7.3, 1.9 Hz, 2 H), 5.02 (d, *J* = 14.8 Hz, 1 H), 4.75 (d, *J* = 16.0 Hz, 1 H), 4.64 (d, *J* = 14.9 Hz, 1 H), 4.31 (d, *J* = 16.0 Hz, 1 H), 3.32 (d, *J* = 10.3 Hz, 1 H), 2.93 (d, *J* = 10.3 Hz, 1 H), 2.61 (q, *J* = 13.4 Hz, 2 H), 2.33 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 142.8, 141.0, 138.3, 133.0, 135.1, 130.1, 129.0, 128.9, 128.8, 128.5, 128.4, 127.9, 127.4, 27.2, 127.1, 125.8, 61.0, 55.1, 51.7, 45.0, 43.4, 24.0, 21.3; IR (film) 2927, 1564 cm^{-1}; MS (ESI+) 524.2362 (524.2366 calcd for $C_{32}H_{33}N_3O_2S$, M + H^+).

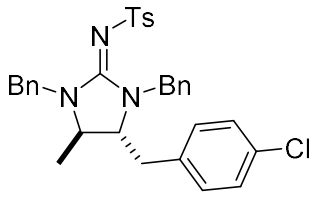


4-Methyl-*N*-[1,3,4-tribenzyltetrahydropyrimidin-2(1*H*)-ylidene]benzenesulfonamide (3-9f). The general procedure B was employed for the coupling of phenyl trifluoromethanesulfonate (101.8 mg, 0.45 mmol) with *N*-[(benzyl(but-3-en-1-yl)amino](benzylamino)methylene)-4-methylbenzenesulfonamide **(3-7c)** (134.3 mg, 0.30 mmol). This procedure afforded 133.2 mg (85%) of the title compound as a pale yellow solid, m.p. 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2 H), 7.40–7.16 (m, 11 H), 7.12 (dd, *J* = 7.5, 1.9 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 5.40 (d, *J* = 15.2 Hz, 1 H), 5.19 (d, *J* = 14.8 Hz, 1 H), 4.52 (d, *J* = 14.8 Hz, 1 H), 3.95

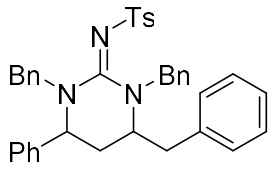
(d, *J* = 15.2 Hz, 1 h), 3.48–3.37 (m, 1 H), 3.23–3.11 (m, 2 H), 2.91 (dd, *J* = 13.6, 6.2 Hz, 1 H), 2.48 (dd, *J* = 13.6, 8.8 Hz, 1 H), 2.27 (s, 3 H), 1.67–1.47 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 143.5, 140.5, 137.0, 136.3, 136.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.8, 126.9, 125.5, 56.1, 54.9, 54.3, 42.2, 38.0, 24.4, 21.3; IR (film) 3028, 1537 cm^{-1}; MS (ESI+) 524.2360 (524.2366 calcd for $C_{32}H_{33}N_3O_2S$, M + H^+).



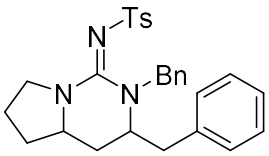
***N*-[4-(4-Benzoylbenzyl)-1,3-dibenzyltetrahydropyrimidin-2-[1*H*]-ylidene]-4-methylbenzenesulfonamide (3-9g).** The general procedure B was employed for the coupling of 4-benzoylphenyl trifluoromethanesulfonate (148.6 mg, 0.45 mmol) with *N*-[(benzyl(but-3-en-1-yl)amino](benzylamino)methylene)-4-methylbenzenesulfonamide **(7c)** (134.3 mg, 0.30 mmol). This procedure afforded 183.0 mg (96%) of the title compound as a pale yellow solid, m.p. 70–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 2 H), 7.76–7.65 (m, 4 H), 7.56 (t, *J* = 7.7 Hz, 2 H), 7.39–7.20 (m, 8 H), 7.19–7.11 (m, 2 H), 7.07 (dd, *J* = 8.3, 2.6 Hz, 4 H), 5.41 (d, *J* = 15.1 Hz, 1 H), 5.15 (d, *J* = 14.8 Hz, 1 H), 4.50 (d, *J* = 14.8 Hz, 1 H), 4.01 (d, *J* = 15.2 Hz, 1 H), 3.51–3.41 (m, 1 H), 3.25–3.10 (m, 2 H), 2.98 (dd, *J* = 13.6, 6.3 Hz, 1 H), 2.56 (dd, *J* = 13.5, 8.5 Hz, 1 H), 2.26 (s, 3 H), 1.71–1.49 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 155.2, 143.4, 141.9, 140.7, 137.4, 136.3, 136.2, 136.1, 132.5, 130.6, 129., 129.0, 128.9, 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 125.5, 56.0, 54.7, 54.6, 42.1, 38.1, 24.7, 21.3; IR (film) 2922, 1536 cm^{-1}; MS (ESI+) 628.2622 (628.2628 calcd for $C_{39}H_{37}N_3O_3S$, M + H^+).



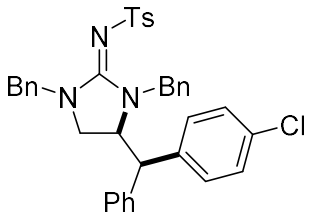
***N*-[1,3-Dibenzyl-4-(4-chlorobenzyl)-5-methylimidazolidin-2-ylidene]-4-methylbenzenesulfonamide (3-9h).** The general procedure B was employed for the coupling of 4-chlorophenyl trifluoromethanesulfonate (117.3 mg, 0.45 mmol) with *N*-{[benzyl(but-3-en-2-yl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(7d)** (134.3 mg, 0.30 mmol). This procedure afforded 106 mg (63%) of the title compound as a pale yellow solid, m.p. 47–50 °C. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; ^{1}H data are for the major diastereomer, ^{13}C data are for the mixture. ^{1}H NMR (400 MHz, C_6D_6) δ 8.21 (d, *J* = 8.4 Hz, 2 H), 7.15–7.05 (m, 6 H), 7.04–6.98 (m, 4 H), 6.94–6.90 (m, 2 H), 6.80–6.75 (m, 2 H), 6.37 (d, *J* = 8.4 Hz, 2 H), 5.72 (d, *J* = 15.6 Hz, 1 H), 5.29 (d, *J* = 15.3 Hz, 1 H), 3.85 (d, *J* = 15.4 Hz, 1 H), 3.69 (d, *J* = 15.3 Hz, 1 H), 2.79 (dt, *J* = 7.6, 4.4 Hz, 1 H), 2.71 (qd, *J* = 6.2, 3.7 Hz, 1 H), 2.40 (dd, *J* = 14.0, 7.8 Hz, 1 H), 2.18–1.96 (m, 1 H), 1.82 (s, 3 H), 0.33 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 155.1, 143.0, 141.2, 141.1, 136.2, 136.0, 135.9, 135.8, 135.4, 133.8, 132.9, 132.8, 130.8, 130.6, 129.1, 129.0, 128.9, 128.9, 128.9, 128.8, 128.7, 128.7, 128.5, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 125.8, 125.7, 62.3, 59.3, 54.2, 53.6, 20.4, 19.3, 47.8, 47.0, 37.2, 33.5, 21.4, 18.6, 12.4; IR (film) 2924, 1557 cm^{-1}; MS (ESI+) 558.1977 (558.1977 calcd for $C_{32}H_{32}ClN_3O_2S$, M + H$^+$).



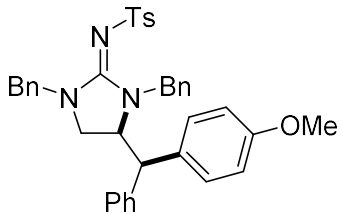
4-Methyl-*N*-[1,3,4-tribenzyl-6-phenyltetrahydropyrimidin-2(1*H*)-ylidene]enzenesulfonamide (3-9i). The general procedure B was employed for the coupling of phenyl trifluoromethanesulfonate (101.8 mg, 0.45 mmol) with *N*-{[benzyl(1-phenylbut-3-en-1-yl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7e)** (157 mg, 0.30 mmol). This procedure afforded 150.7 mg (84%) of the title compound as a pale yellow solid, m.p. 76–80 °C. This compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.87 (m, 4 H), 7.51–7.14 (m, 33 H), 7.14–7.03 (m, 7 H), 6.90–6.84 (m, 2 H), 6.53–6.43 (m, 2 H), 5.89 (d, *J* = 15.3 Hz, 1 H), 5.84 (d, *J* = 14.8 Hz, 1 H), 5.71 (d, *J* = 15.4 Hz 1 H), 5.23 (d, *J* = 15.0 Hz, 1 H), 4.47 (dd, *J* = 6.4, 4.5 Hz, 1 H), 4.27 (dd, *J* = 11.7, 6.7 Hz, 1 H), 4.09 (d, *J* = 15.5 Hz, 1 H), 3.98 (d, *J* = 14.8 Hz, 1 H), 3.92 (d, *J* = 15.3 Hz, 1 H), 3.83 (d, *J* = 15.0 Hz, 1 H), 3.53–3.43 (m, 1 H), 3.36 (tq, *J* = 7.6, 4.1, 3.5 Hz, 1 H), 3.00 (dd, *J* = 13.6, 4.6 Hz, 1 H), 2.74 (dd, *J* = 13.5, 7.2 Hz, 1 H), 2.43 (dd, *J* = 13.6, 8.2 Hz, 1 H), 2.37 (s, 3 H), 2.33-2.28 (m, 1 H), 2.27 (s, 3 H), 1.95 (dt, *J* = 14.1, 4.2 Hz, 1 H), 1.86–1.78 (m, 2 H), 1.71–1.62 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 155.6, 143.7, 143.4, 140.7, 139.2, 137.0, 136.8, 136.6, 136.0, 135.99, 129.4, 129.3, 129.2, 129.1, 129.0, 128.94, 128.87, 128.85, 128.79, 128.71, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.0, 126.9, 126.8, 126.7, 125.6, 56.8, 56.4, 55.2, 54.5, 54.4, 54.0, 52.7, 38.1, 36.0, 31.4, 21.4, 21.3; IR (film) cm^{-1}; MS (ESI+) 600.2673 (600.2679 calcd for $C_{38}H_{37}N_3O_2S$, M + H^+).



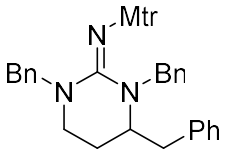
***N*-[2,3-Dibenzylhexahydropyrrolo(1,2-*c*)pyrimidin-1(2*H*)-ylidene]4-methylbenzenesulfonamide (3-9j).** The general procedure B was employed for the coupling of phenyl trifluoromethanesulfonate (101.8 mg, 0.45 mmol) with 2-allyl-*N*-benzyl-*N*'-tosylpyrrolidine-1-carboximidamide **(3-7f)** (119.3 mg, 0.30 mmol). This procedure afforded 141 mg (99%) of the title compound as a pale yellow solid, m.p. 55–57 °C. This compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.73 (m, 4 H), 7.40–7.17 (m, 15 H), 7.17–7.09 (m, 5 H), 7.09–7.03 (m, 1 H), 6.93–6.87 (m, 3 H), 5.34 (d, *J* = 15.6 Hz, 1 H), 5.15 (d, *J* = 15.3 Hz, 1 H), 4.25 (d, *J* = 15.6 Hz, 1 H), 4.21–4.06 (m, 2 H), 4.01 (dt, *J* = 11.8, 7.2 Hz, 1 H), 3.88–3.68 (m, 2 H), 3.55–3.45 (m, 1 H), 3.40–3.28 (m, 2 H), 3.10 (dd, *J* = 13.7, 5.3 Hz, 1 H), 2.65 (dd, *J* = 13.7, 9.5 Hz, 1 H), 2.44–2.35 (m, 1 H), 2.33 (s, 6 H), 2.25–2.16 (m, 1 H), 2.16–2.06 (m, 1 H), 2.03–1.72 (m, 8 H), 1.63–1.47 (m, 2 H), 1.40 (q, *J* = 12.3, 11.9 Hz, 1 H), 1.20 (td, *J* = 12.9, 5.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 144.1, 143.7, 140.6, 140.3, 137.2, 137.0, 136.9, 129.1, 128.9, 128.89, 128.87, 128.79, 128.65, 128.6, 127.9, 127.8, 127.63, 127.6, 127.0, 126.8, 125.5, 125.4, 55.2, 55.0, 54.5, 53.6, 51.5, 51.48, 51.5, 51.2, 39.7, 39.1, 35.5, 32.5, 31.5, 28.8, 23.1, 23.08, 21.3; IR (film) 2922, 1538 cm^{-1}; MS (ESI+) 474.2204 (474.2210 calcd for $C_{28}H_{31}N_3O_2S$, M + H$^+$).



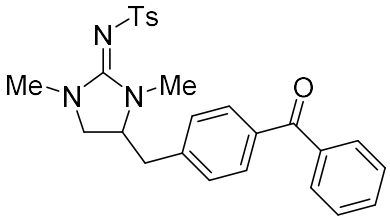
(4*S*,4'*R*)-*N*-{1,3-Dibenzyl-4-[(4-chlorophenyl)(phenyl)methyl]imidazolidin-2-ylidene}-4-methylbenzenesulfonamide (3-9k). The general procedure B was employed for the coupling of 4-chlorophenyltrifluoromethanesulfonate (78.2 mg, 0.30 mmol) with *N*-{-[benzyl(cinnamyl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7g)** (101.9 mg, 0.20 mmol). This procedure afforded 94 mg (76%) of the title compound as a pale yellow solid, m.p. 70–75 °C. This compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.80 (m, 2 H), 7.37–7.23 (m, 9 H), 7.20–7.05 (m, 8 H), 7.03–6.96 (m, 2 H), 6.91–6.83 (m, 2 H), 5.23 (d, *J* = 15.7 H, 1 H), 4.69 (d, *J* = 15.0 Hz, 1 H), 4.34 (d, *J* = 15.0 Hz, 1 H), 4.15-4.10 (m, 1 H), 3.96 (d, *J* = 8 Hz, 1 H), 3.44 (t, *J* = 10.1 Hz, 1 H), 3.32 (d, *J* = 15.7 Hz, 1 H), 2.96 (dd, *J* = 10.6, 3.6 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 142.8, 141.2, 139.8, 138.1, 136.3, 135.5, 133.1, 129.9, 129.0, 128.8, 128.7, 128.6, 128.3, 127.9, 127.8, 127.6, 125.8, 57.3, 54.1, 50.4, 50.3, 48.3, 21.4; IR (film) 2922, 1564 cm^{-1}; MS (ESI+) 620.2128 (620.2133 calcd for $C_{37}H_{34}ClN_3O_2S$, M + H^+).



(4*S*,4'*R*)-*N*-(1,3-Dibenzyl-4-[(4-methoxyphenyl)(phenyl)methyl]imidazolidin-2-ylidene)-4-methylbenzenesulfonamide (3-9l). The general procedure B was employed for the coupling of 4-methoxyphenyltrifluoromethanesulfonate (77 mg, 0.30 mmol) with *N*-{-[benzyl(cinnamyl)amino][benzylamino]methylene}-4-methylbenzenesulfonamide **(3-7g)** (101.9 mg, 0.20 mmol). This procedure afforded 101 mg (82%) of the title compound as a pale yellow solid, m.p. 65–69 °C. This compound was obtained as a 10:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2 H), 7.35–7.20 (m, 9 H), 7.20–7.08 (m, 6 H), 7.00–6.94 (m, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.73 (d, *J* = 8.8 Hz, 2 H), 5.17 (d, *J* = 16 Hz, 1 H), 4.64 (d, *J* = 15 Hz, 1 H), 4.44 (d, *J* = 15.0 Hz, 1 H), 4.10 (ddd, *J* = 9.6, 8.3, 3.6 Hz, 1 H), 3.91 (d, *J* = 8.5 Hz, 1 H), 3.74 (s, 3 H), 3.42 (t, *J* = 10 Hz, 1 H), 3.2 (d, *J* = 15.5 Hz, 1 H), 2.99 (dd, *J* = 10.6, 3.7 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 17.0, 142.9, 141.1, 140.7, 136.5, 135.7, 131.8, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.3, 125.8, 114.1, 57.6, 55.2, 54.4, 50.4, 50.2, 48.7, 21.3; IR (film) 3027, 2248, 1561 cm^{-1}; MS (ESI+) 616.2624 (616.2628 calcd for $C_{38}H_{37}N_3O_3S$, M + H^+).



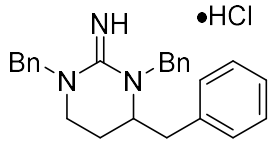
(*Z*)-4-methoxy-2,3,6-trimethyl-*N*-[1,3,4-tribenzyltetrahydropyrimidin-2(1*H*)-ylidene]benzenesulfonamide (3-21). The general procedure B was employed for the coupling of phenyltrifluoromethanesulfonate (68 mg, 0.30 mmol) with (*E*)-*N*-[{benzyl(but-3-en-1-yl)amino}{benzylamino}methylene]-4-methoxy-2,3,6-trimethylbenzenesulfonamide **(3-20)** (101.1 mg, 0.20 mmol). This procedure afforded 110 mg (95%) of the title compound as a pale yellow solid, m.p. 62–65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.17 (m, 11 H), 7.12 (d, *J* = 6.5 Hz, 2 H), 6.95 (d, *J* = 6.5 Hz, 2 H), 6.41 (s, 1 H), 5.34 (d, *J* = 15.1 Hz, 1 H), 5.05 (d, *J* = 14.8 Hz, 1 H), 4.55 (d, *J* = 14.8 Hz, 1 H), 4.06 (d, *J* = 15.2 Hz, 1 H), 3.75 (s, 3 H), 3.50–3.37 (m, 1 H), 3.25–3.14 (m, 2 H), 2.96 (dd, *J* = 13.6, 5.8 Hz, 1 H), 2.73 (s, 3 H), 2.67 (s, 3 H), 2.50 (dd, *J* = 13.6, 9.1 Hz, 1 H), 2.06 (s, 3 H), 1.68–1.50 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 155.0, 137.4, 137.1, 137.0, 136.7, 136.5, 135.0, 129.0, 128.8, 128.6, 128.5, 125.4, 128.1, 127.8, 127.7, 126.9, 124.2, 111.5, 55.8, 55.3, 55.1, 54.4, 42.2, 38.1, 24.4, 24.2, 18.5, 11.9; IR (film) 2936, 1494, 1113 cm^{-1}; MS (ESI+) 582.283 (582.2785 calcd for $C_{35}H_{39}N_3O_3S$, M + H$^+$).



***N*-[4-(4-Benzoylbenzyl)-1,3-dimethylimidazolidin-2-ylidene]-4-methylbenzenesulfonamide (3-24).** The general procedure B was employed for the

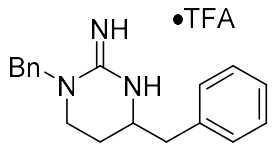
coupling of 4-benzoylphenyl trifluoromethanesulfonate (148.6 mg, 0.45 mmol) with *N*-{[allyl(methyl)amino](methylamino)methylene}-4-methylbenzenesulfonamide **(3-23)** (84.4 mg, 0.3 mmol). This procedure afforded 96 mg (69%) of the title compound as a pale yellow solid, m.p. 53–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2 H), 7.78–7.76 (m, 4 H), 7.60–7.57 (m, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 3.95–3.85 (m, 1 H), 3.51 (t, *J* = 9.7 Hz, 1 H), 3.19–3.13 (m, 2 H), 3.05 (s, 3 H), 2.95 (s, 3 H), 2.92–2.80 (m, 1 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 157.1, 142.9, 141.2, 140.5, 137.4, 136.6, 132.5, 130.6, 129.9, 129.2, 128.9, 128.3, 125.7, 59.4, 52.8, 38.7, 34.4, 33.2, 21.4; IR (film) 2922.5, 1652.6, 1568.5 cm^{-1}; MS (ESI+) 462.1848 (462.1846 calcd for $C_{26}H_{27}N_3O_3S$, M + H$^+$).

Deprotection of Cyclic Guanidine Products



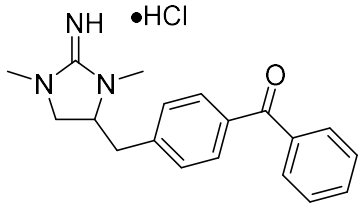
1,3,4-Tribenzyltetrahydropyrimidin-2(*1H*)-imine hydrochloride (3-19). A scintillation vial containing *N*-[1,3,4-tribenzyltetrahydropyrimidin-2(1*H*)-ylidene]cyanamide **(3-7f)** (57 mg, 0.145 mmol) was charged with a stir bar and purged with nitrogen. Concentrated hydrochloric acid (1.5 mL) was added via syringe, and the mixture was heated to 90 °C overnight. The reaction mixture was then cooled to rt, and was extracted with dichloromethane (3 x 3 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate then dried, filtered, and concentrated *in vacuo* to afford the title compound as a light brown foam (95%), m.p. 48–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.12 (m, 13 H), 6.98 (d, *J* = 7.2 Hz, 2 H), 6.30 (s, br, 2 H), 5.27 (d, *J* = 16.0 Hz, 1

H), 5.05 (d, *J* = 15.9 Hz, 1 H), 4.54 (d, *J* = 15.9 Hz, 1 H), 4.12 (d, *J* = 16.0 Hz, 1 H), 3.50–3.39 (m, 1 H), 3.36–3.29 (m, 1 H), 3.18–3.12 (m, 1 H), 2.93 (dd, *J* = 13.5, 5.6 Hz, 1 H), 2.57 (dd, *J* = 13.5, 9.2 Hz, 1 H), 1.83–1.75 (m, 1 H), 1.67–1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 137.5, 137.0, 136.8, 129.0, 128.8, 128.7, 127.6, 127.58, 127.55, 126.8, 56.0, 54.2, 52.9, 24.6, 38.2, 24.8 (two carbon signals are absent due to incidental equivalence); IR (film) 3062, 1572 cm^{-1}; MS (ESI+) 370.2277 (370.2278 calcd for $C_{32}H_{33}N_3O_2S$, M + H$^+$).



1,4-Dibenzyltetrahydropyrimidin-2(1*H*)-imine 2,2,2-trifluoroacetate (3-22). A sample of (*Z*)-4-methoxy-2,3,6-trimethyl-*N*-[1,3,4-tribenzyltetrahydropyrimidin-2(1*H*)-ylidene]benzenesulfonamide **(3-21)** (53 mg, 0.092 mmol) was dissolved in trifluoroacetic acid (5 mL). Methanesulfonic acid (0.27 mL, 4.2 mmol) was added slowly, followed by thioanisole (65 µL, 0.55 mmol). The reaction solution was stirred at 50 °C for 24 hours. After cooling to rt the trifluoroacetic acid was azeotroped off with toluene (3 x 5 mL). The crude material was dissolved in DCM (10 mL) and washed with sat. sodium bicarbonate solution. The organic layer was dried, filtered, and concentrated *in vacuo* to afford crude product. Purification via flash column chromatography afforded 17 mg (47%) of the desired product as a tan, viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1 H), 7.39 (s, 2 H), 7.37–7.27 (m, 5 H), 7.26–7.13 (m, 5 H), 4.75–4.52 (m, 2 H), 3.65–3.60 (m, 1 H), 3.29–3.20 (m, 2 H), 3.14 (dd, *J* = 13.5, 4.3 Hz, 1 H), 2.70 (dd, *J* = 13.5, 9.3 Hz, 1 H), 2.05 (s, br, 1 H), 1.86–1.82 (m, 1 H), 1.66–1.60 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3,

136.0, 134.1, 129.4, 129.2, 128.7, 128.4, 127.4, 127.0, 53.3, 50.5, 44.9, 41.2, 25.4; IR (film) 3144, 1630, 1593 cm^{-1}; MS (ESI+) 280.1817 (280.1808 calcd for $C_{18}H_{21}N_3$, M + H^+).

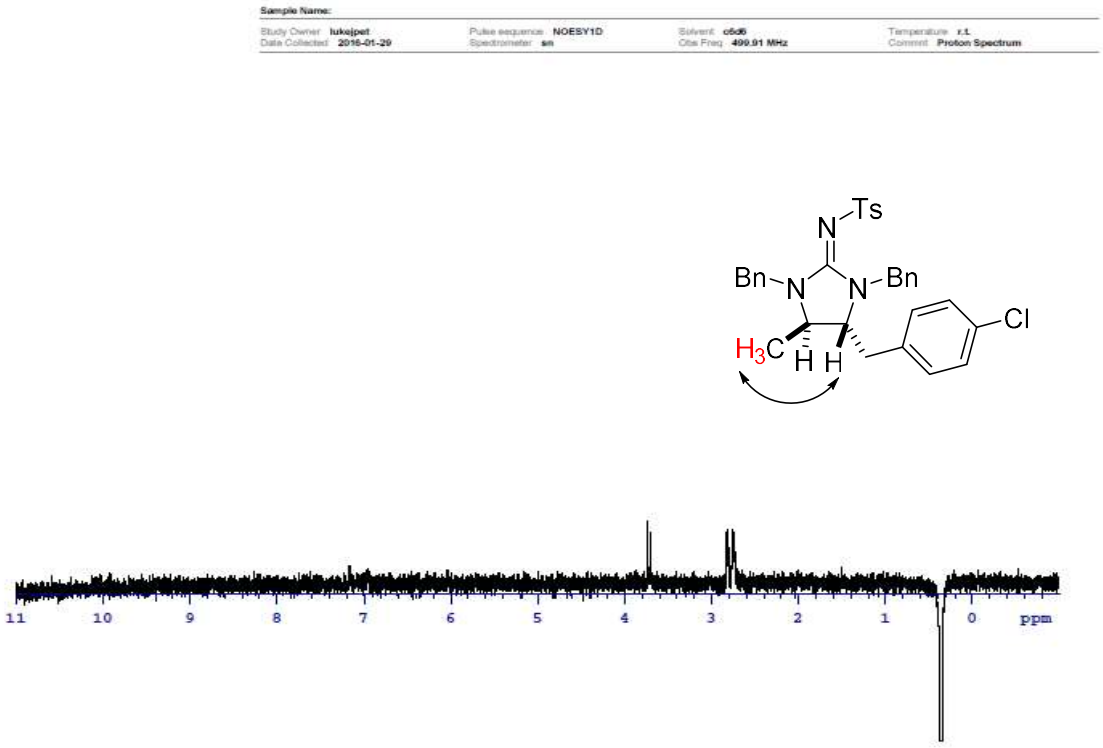


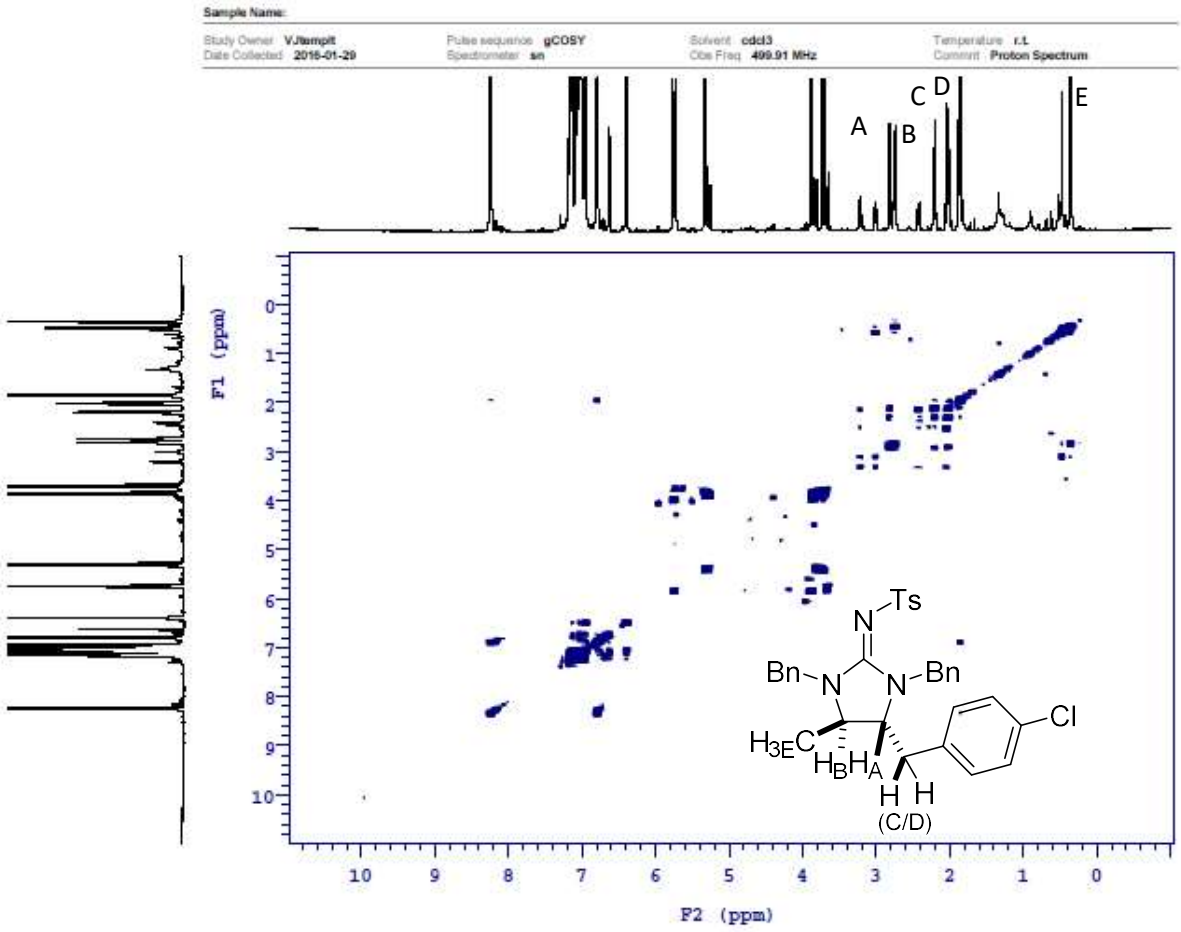
{4-[(2-Imino-1,3-dimethylimidazolidin-4-yl)methyl]phenyl}(phenyl)methanone hydrochloride (3-25). A sample of *N*-[4-(4-benzoylbenzyl)-1,3-dimethylimidazolidin-2-ylidene]-4-methylbenzenesulfonamide **(3-24)** (95 mg, 0.206 mmol) was dissolved in trifluoroacetic acid (13 mL). Methanesulfonic acid (0.6 mL, 9.5 mmol) was added slowly, followed by thioanisole (146 µL, 1.24 mmol). The reaction solution was stirred at rt for 16 hours. The trifluoroacetic acid was azeotroped off with toluene (3 x 5 mL). The crude material was dissolved in DCM (10 mL) and washed with HCl (6 M), followed by sat. sodium bicarbonate solution. The organic layer was dried, filtered, and concentrated *in vacuo* to afford crude product. Purification via flash column chromatography (methanol:dichloromethane = 9:91) afforded 50 mg (70%) of the desired product as a tan solid, m.p. 252–255 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.76–7.72 (m, 4 H), 7.65–7.62 (m, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.43 (d, *J* = 7.9 Hz, 2 H), 4.20–4.12 (m, 1 H), 3.64 (t, *J* = 9.6 Hz, 1 H), 3.37 (dd, *J* = 9.8, 6.0 Hz, 1 H), 3.29 (s, 3 H), 3.21 (dd, *J* = 13.7, 4.4 Hz, 1 H), 3.01 (s, 3 H), 2.96 (dd, *J* = 13.6, 7.8 Hz, 1 H), 2.81 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 196.6, 158.1, 141.1, 137.4, 136.3, 132.5, 130.1, 129.5, 129.3, 128.1, 59.9, 52.5, 37.0, 30.7, 29.8; IR (film) 3376, 1684 cm^{-1}; MS (ESI+) 308.1760 (308.1757 calcd for $C_{19}H_{21}N_3O$, M + H^+).

Assignment of relative stereochemistry for 9h

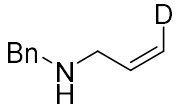
The relative stereochemistry of **3-9h** was assigned using COSY and 1D NOESY analysis.

The coupling found in the 1D NOESY can be seen below.



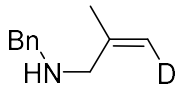


Synthesis of deuterated substrates and products



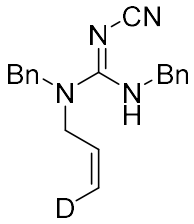
(Z)-*N*-benzylprop-2-en-3-d-1-amine (3-S13): A flame dried flask was cooled under a stream of nitrogen and charged with *N*-benzylprop-2-en-1-ylamine (1.00 g, 6.84 mmol) and diethyl ether (12 mL). The solution was cooled to -42 °C, and then n-butyl lithium (8.2 mmol, 2.5 M) was added slowly. After 30 minutes tert-butyl lithium (15 mmol, 1.7 M) was added slowly. After stirring at -42 °C for 30 minutes the reaction was transferred to

an ice-water bath and allowed to stir for 1 hour. The reaction was then cooled to -78 °C, and deuterium oxide was added (2.5 mL, 136.8 mmol). After stirring overnight the reaction was cooled on an ice-water bath, and then quenched with water (15 mL). The mixture was extracted with diethyl ether (2 x 20 mL) and separated. The combined organic layers were then dried, filtered, and evaporated. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes) to afford 0.568 g (56%) of the title compound as a pale yellow oil, with 84% deuterium incorporation as determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 4.5 Hz, 4 H), 7.2–7.18 (m, 1 H), 6.03–5.79 (m, 1 H), 5.22–5.15 (m, 1 H), 5.12–5.06 (m, 1 H), 3.78 (s, 3 H), 3.27 (d, 6 Hz, 2 H).

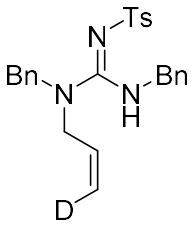


(*Z*)-*N*-benzyl-2-methylprop-2-en-3-d-1-amine (3-S14). A flame dried flask was cooled under a stream of nitrogen and charged with *N*-benzylbut-3-en-2-ylamine **(3-S5)** (1.00 g, 6.62 mmol) and diethyl ether (13 mL). The solution was cooled to -42 °C, and then n-butyl lithium (7.95 mmol, 2.5 M) was added slowly. After 30 minutes tert-butyl lithium (14.59 mmol, 1.7 M) was added slowly. After stirring at -42 °C for 30 minutes the reaction was transferred to an ice-water bath and allowed to stir for 1 hour. The reaction was then cooled to -78 °C, and deuterium oxide was added (2.4 mL, 132.4 mmol). After stirring overnight the reaction was cooled on an ice-water bath, and then quenched with water (15 mL). The mixture was extracted with diethyl ether (2 x 20 mL) and separated. The combined organic layers were then dried, filtered, and evaporated. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes) to afford 0.60 g (56%) of the title compound as a pale yellow oil, with 83% deuterium

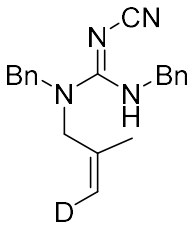
incorporation as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$) δ 7.39–7.28 (m, 4 H), 7.28–7.18 (m, 1 H), 4.90 (s, 1 H), 4.84 (s, 1 H), 3.76 (s, 2 H), 3.18 (s, 2 H), 1.76 (s, 3 H).



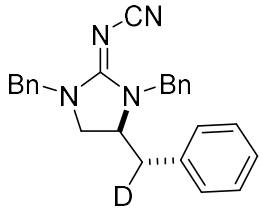
1-[(*Z*)-allyl-3-d]-1,3-dibenzyl-2-cyanoguanidine (3-10). A round bottom flask was charged with methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.196 g, 0.96 mmol), ethanol (10 mL), and mercuric oxide (0.312 g, 1.44 mmol), then purged with nitrogen. Triethylamine (0.5 mL, 3.84 mmol) was added followed by (Z)-*N*-benzylprop-2-en-3-d-1-amine **(S13)** (0.170 g, 1.15 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes to yield 0.153 g (52%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 6 H), 7.24-7.18 (m, 4 H), 5.80–5.72 (m, 1 H), 5.23 (d, *J* = 10.4 Hz, 1 H), 5.15 (d, *J* = 17.2 Hz, 1 H), 4.98 (br, 1 H), 4.74 (d, *J* = 5.2 Hz, 2 H), 4.58 (s, 2 H), 3.95 (d, *J* = 5.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.1, 135.8, 129.0, 128.9, 128.0, 127.9, 127.7, 127.3, 118.2 (t, *J* = 23.5 Hz, 117.2, 52.2, 51.4, 47.5; IR (film) 3249, 2162, 1536 cm^{-1}; MS (ESI+) 306.1827 (306.1823 calcd for $C_{19}H_{19}DN_4$, M + H^+).



***N*-{[(*Z*)-allyl-3-d](benzyl)amino}-benzylaminomethylene-4-methylbenzenesulfonamide (3-11).** A round bottom flask was charged with dimethyl tosylcarbonimidodithioate **(3-S3)** (0.569 g, 1.70 mmol), ethanol (17 mL), and mercuric oxide (0.548 g, 2.53 mmol), then purged with nitrogen. Triethylamine (0.95 mL, 6.75 mmol) was added followed by (Z)-*N*-benzylprop-2-en-3-d-1-amine **(3-S13)** (0.300 g, 2.0 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes) to yield 0.363 g (49%) of the title compound as a white solid, m.p. 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2 H), 7.33–7.20 (m, 6 H), 7.18–7.06 (m, 6 H), 6.96 (br, 1 H), 5.75–5.67 (m, 1 H), 5.16 (d, J = 10.4 Hz, 1 H), 5.08 (d, J = 17.3 Hz, 1 H), 4.47 (s, 2 H), 4.37 (d, J = 5.9 Hz, 2 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 141.7, 141.0, 136.9, 136.4, 132.3, 129.1, 128.9, 128.7, 128.0, 127.61, 127.6, 127.58, 127.4, 126.0, 118.6 (t, J = 25 Hz), 51.8, 51.75, 49.7; IR (film) 3322, 1564 cm^{-1}; MS (ESI+) 435.1965 (435.1960 calcd for $C_{25}H_{26}DN_3O_2S$, M + H$^+$).

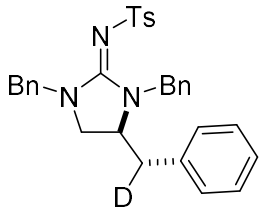


1,3-dibenzyl-2-cyano-1-[(Z)-2-methylallyl-3-d]guanidine (3-12). A round bottom flask was charged with methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(3-S1)** (0.60 g, 2.91 mmol), ethanol (30 mL), and mercuric oxide (0.95 g, 4.37 mmol), then purged with nitrogen. Triethylamine (1.6 mL, 11.64 mmol) was added followed by (Z)-*N*-benzyl-2-methylprop-2-en-3-d-1-amine **(3-S14)** (0.57 g, 3.49 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes) to yield 0.39 g (42%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 6 H), 7.24–7.18 (m, 4 H), 5.09 (s, br, 1 H), 4.93 (s, 1 H), 4.80 (s, 1 H), 4.77 (d, *J* = 5.3 Hz, 2 H), 4.60 (s, 2 H), 3.80 (s, 2 H), 1.65 (s, 3 H); ^{13}C NMR (125 MHz, CDCl3) δ 159.2, 139.5, 137.1, 135.9, 129.0, 128.9, 128.8, 128.1, 128.0, 127.7, 127.5, 117.1, 112.6 (t, *J* = 33.1 Hz), 54.2, 52.5, 47.7, 19.8; IR (film) 3256, 2162, 1539 cm^{-1}; MS (ESI+) 320.1986 (320.1980 calcd for $C_{20}H_{21}DN_4$, M + H$^+$).



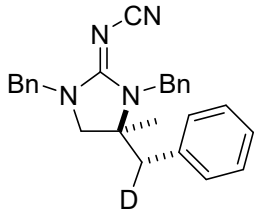
***N*-{(±)-1,3-dibenzyl-4-[(±)-phenylmethyl-d]imidazolidin-2-ylidene}cyanamide (3-13).** The general procedure A was employed for the coupling of bromobenzene (35.3 mg,

0.225 mmol) with 1-((Z)-allyl-3-d)-1,3-dibenzyl-2-cyanoguanidine **(3-10)** (45.8 mg, 0.15 mmol). This procedure afforded 33.3 mg (58%) of the title compound as a white, viscous oil. This compound was obtained as a 9:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 8 H), 7.25–7.15 (m, 5 H), 6.95–6.84 (m, 2 H), 5.36 (d, *J* = 15.6 Hz, 1 H), 4.79–4.51 (m, 2 H), 4.19 (d, *J* = 15.6 Hz, 1 H), 3.78–3.60 (m, 1 H), 3.19 (t, *J* = 9.6 Hz, 1 H), 3.05–2.90 (m, 2 H), 2.54 (dd, *J* = 13.4, 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 135.7, 135.34 135.2, 129.1, 129.0, 128.88, 128.82 128.2, 128.13, 128.11, 128.0, 127.2, 116.5, 55.8, 49.5, 47.3, 38.2, 37.8 (t, *J* = 19.3 Hz); IR (film) 2169, 1596 cm^{-1}; MS (ESI+) 382.2132 (382.2136 calcd for $C_{25}H_{23}DN_4$, M + H$^+$).



***N*-{(±)-1,3-dibenzyl-4-[(±)-phenylmethyl-d]imidazolidin-2-ylidene}-4-methylbenzenesulfonamide (3-14).** The general procedure B was empoyed for the coupling of phenyl trifluoromethanesulfonate (101.8 mg, 0.45 mmol) with *N*-{[(Z)-allyl-3-d](benzyl)amino}-benzylaminomethylene-4-methylbenzenesulfonamide **(3-11)** (134.3 mg, 0.30 mmol). This procedure afforded 140 mg (92%) of the title compound as a pale yellow solid, m.p. 106–108 °C. This compound was obtained as a >20:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2 H), 7.36–7.26 (m, 5 H), 7.25–7.14 (m, 10 H), 6.87–6.80 (m, 2 H), 5.27 (d, *J* = 15.3 Hz, 1 H), 4.75 (d, *J* = 15.0 Hz, 1 H), 4.51 (d, *J* = 15.1

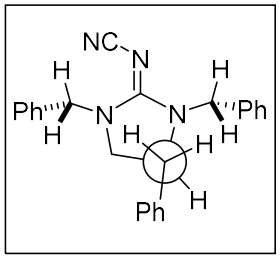
Hz, 1 H), 4.15 (d, *J* = 15.4 Hz, 1 H), 3.64 (dt, 9.7, 4.9 Hz, 1 H), 3.20 (t, *J* = 9.9 Hz, 1 H), 3.02–2.85 (m, 2 H), 2.49 (dd, *J* = 13.8, 8.3 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 143.0, 141.1, 135.9, 135.7, 135.5, 129.2, 128.9, 128.8, 128.74, 128.72, 128.3, 128.27, 127.9, 127.8, 127.0, 125.8, 55.4, 50.8, 48.76, 48.71, 37.9 (t, *J* = 19 Hz); IR (film) 1563 cm^{-1}, MS (ESI+) 511.2271 (511.2273 calcd for $C_{31}H_{30}DN_3O_2S$, M + H$^+$).

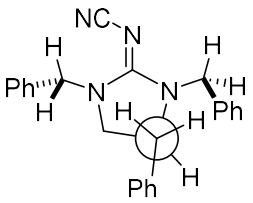


***N*-[(4S)-1,3-dibenzyl-4-methyl-4-(phenylmethyl-d)imidazolidin-2-ylidene]cyanamide (3-15).** The general procedure A was employed for the coupling of bromobenzene (35.3 mg, 0.225 mmol) with 1,3-dibenzyl-2-cyano-1-[(Z)-2-methylallyl-3-d]guanidine **(3-12)** (64 mg, 0.2 mmol). This procedure afforded 63 mg (80%) of the title compound as a white, viscous oil. This compound was obtained as a 15.5:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR ($CDCl_3$) δ 7.39–7.30 (m, 6 H), 7.28–7.22 (m, 4 H), 7.20 (dd, *J* = 7.7, 1.8 Hz, 2 H), 6.93–6.86 (m, 2 H), 5.00 (d, *J* = 16.2 Hz, 1 H), 4.69–4.52 (m, 2 H), 4.41 (d, *J* = 16.2 Hz, 1 H), 3.29 (d, *J* = 9.8 Hz, 1 H), 2.91 (d, *J* = 9.8 Hz, 1 H), 2.77 (d, *J* = 13.7 Hz, 1 H), 2.59 (d, *J* = 12.2 Hz, 1 H), 1.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 138.2, 135.4, 135.0, 129.9, 128.9, 128.8, 128.7, 128.6, 128.4, 128.0, 127.5, 127.4, 127.3, 62.3, 55.6, 49.4, 44.7, 43.5, 43.2 (t, *J* = 20 Hz), 24.5; IR (film) 2167, 1593 cm^{-1}; MS (ESI+) 396.2300 (296.2293 calcd for $C_{26}H_{25}DN_4$, M + H$^+$).

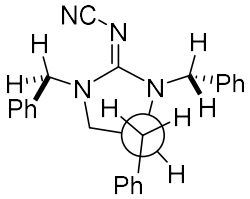
Computational Details

All geometries were optimized using the spin-restricted B3LYP[66] density functional and the 6-31G* basis set. All density functional calculations were performed using Spartan'14[67]. The calculations are meant to be used for qualitative purposes only.

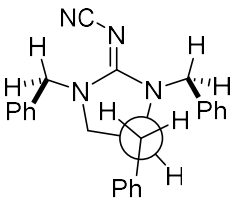




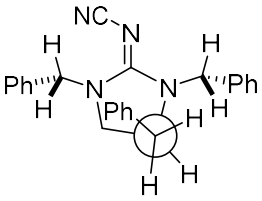
+0.93 kcal/mol



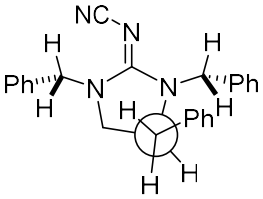
+0.42 kcal/mol



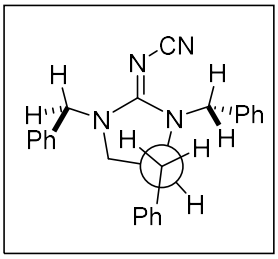
+1.27 kcal/mol

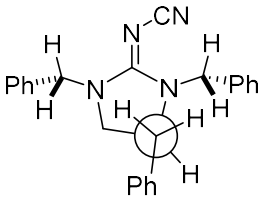


+1.35 kcal/mol

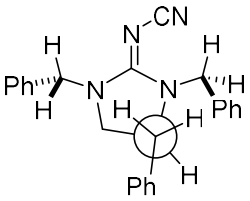


+1.28 kcal/mol

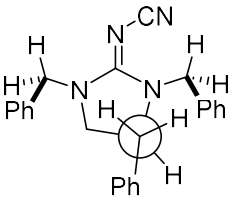




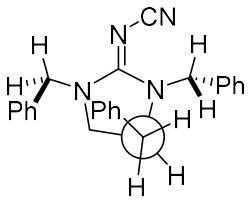
+0.20 kcal/mol



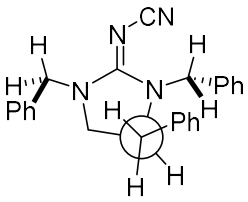
+0.40 kcal/mol



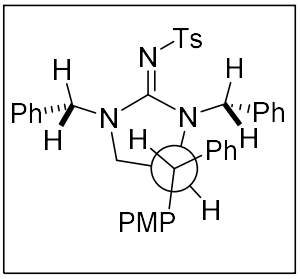
+0.52 kcal/mol

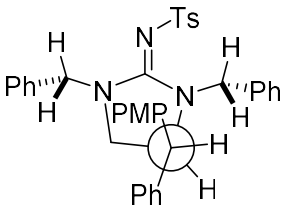


+1.34 kcal/mol

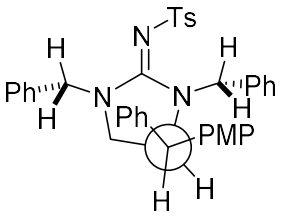


+0.91 kcal/mol

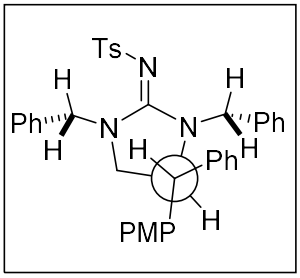


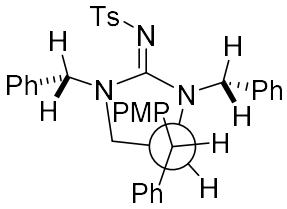


+0.57 kcal/mol

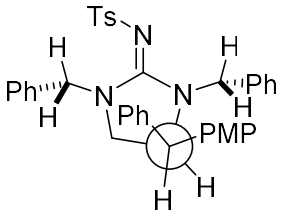


+0.73 kcal/mol



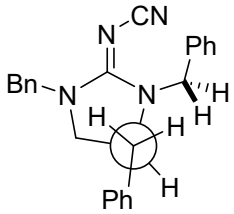


+0.81 kcal/mol

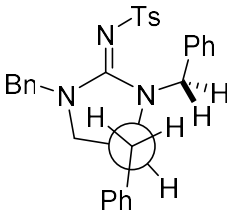


+0.77 kcal/mol

Deuterium Labeling Studies

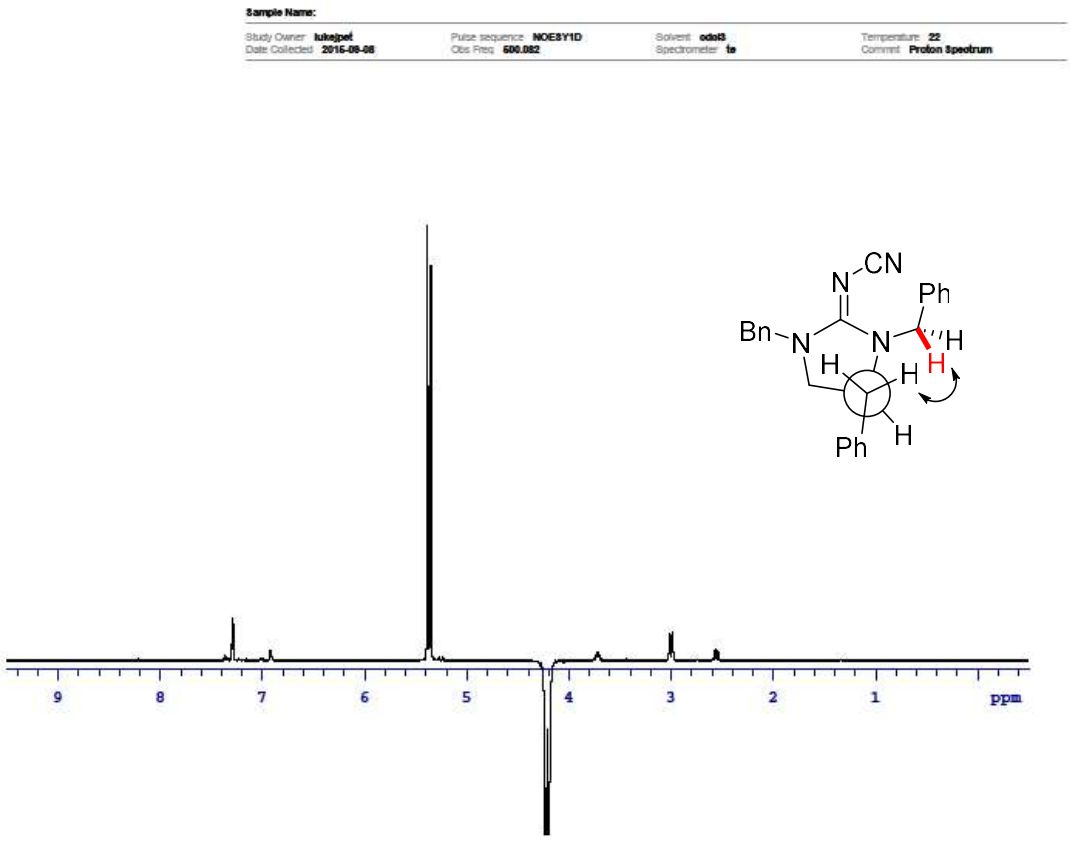


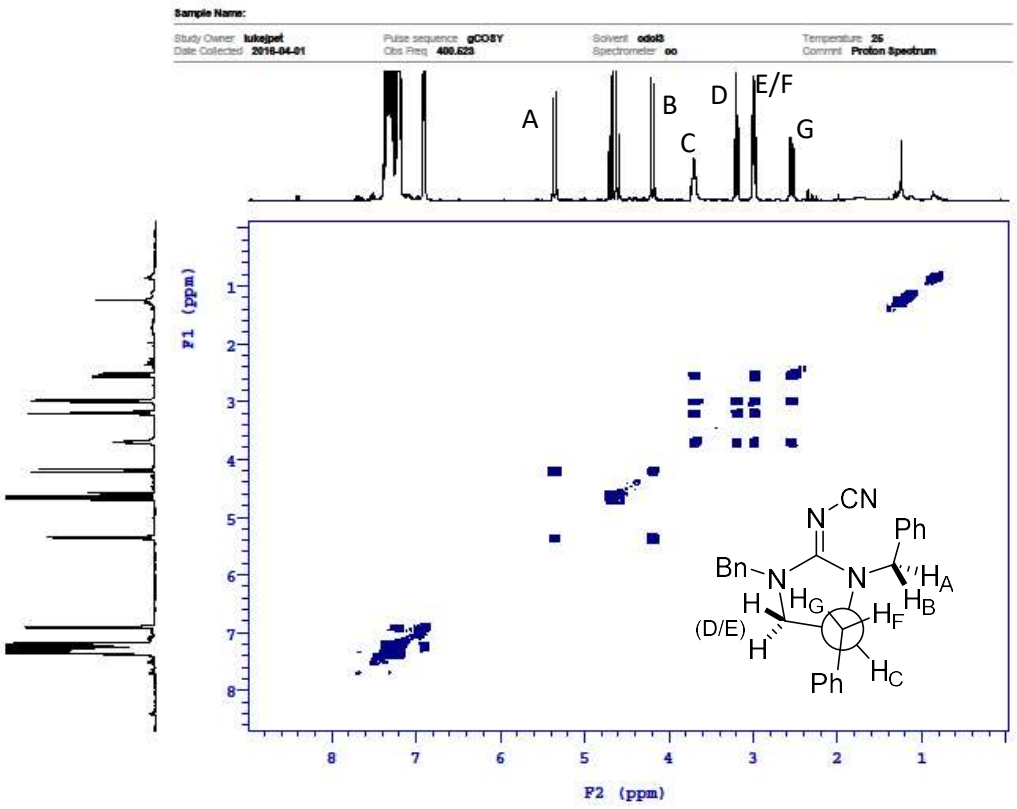
13

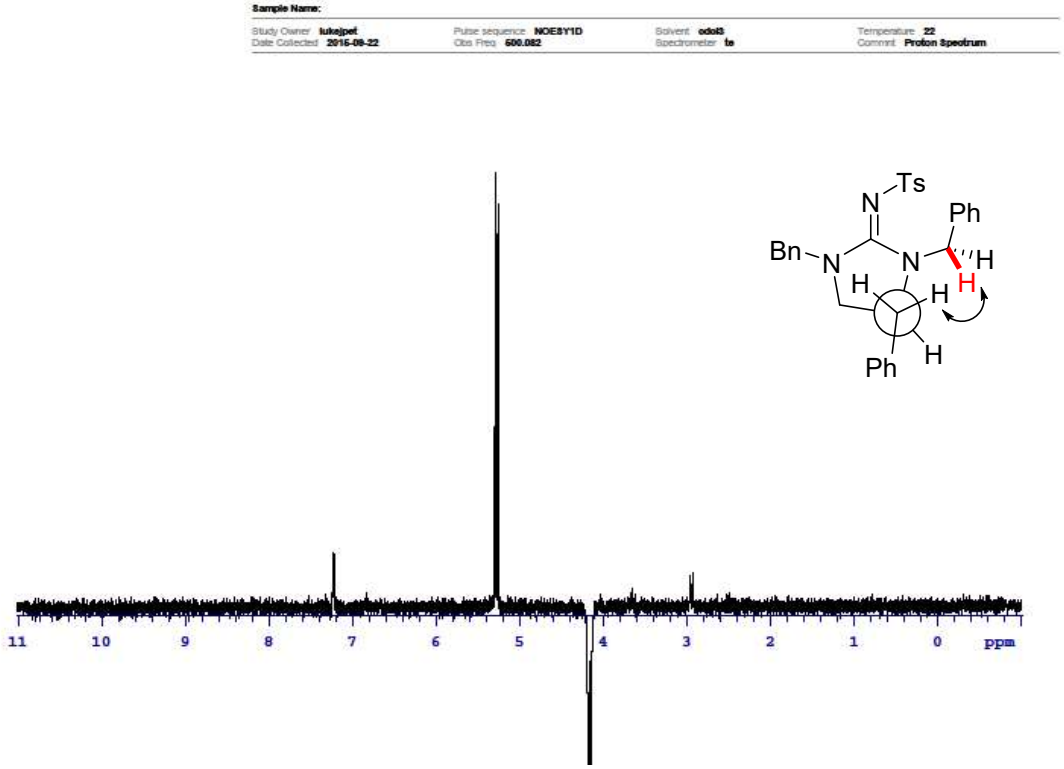


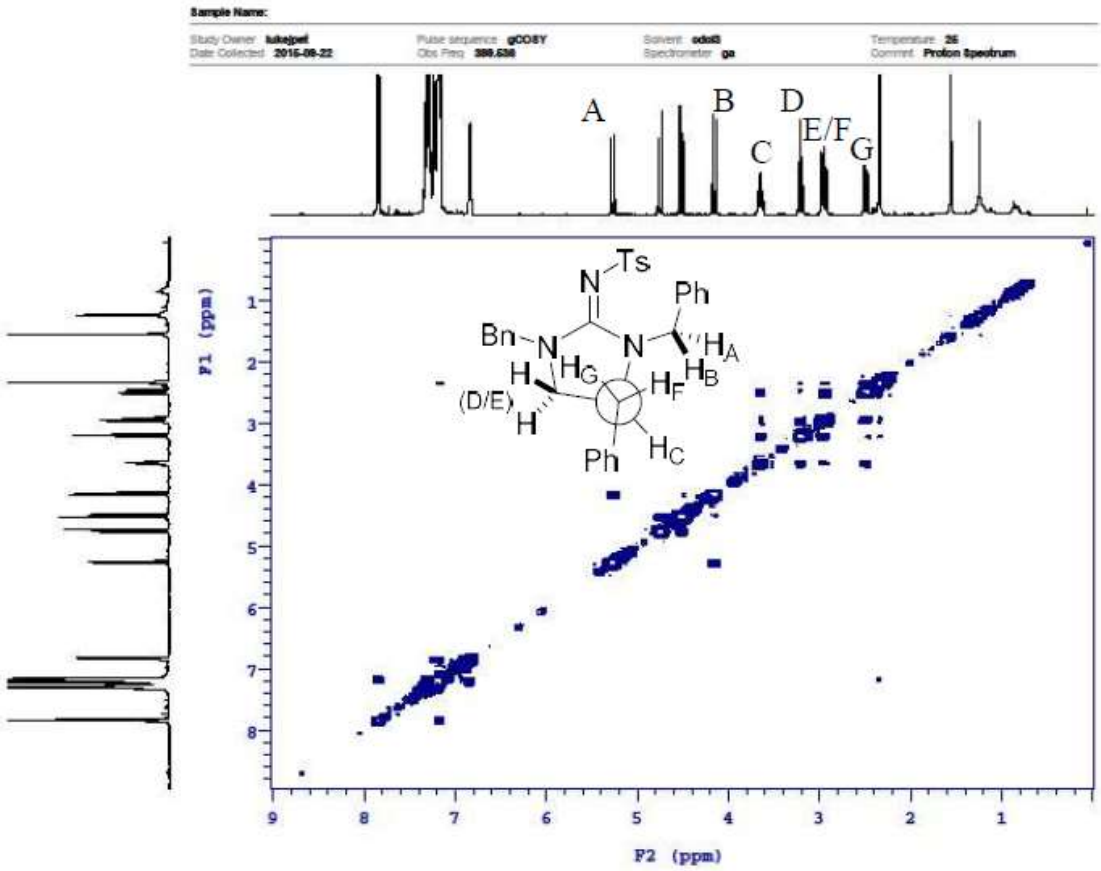
14

In order to determine the relative stereochemical configuration of the deuterium labelled compounds **3-13** and **3-14**, the hypothesized ground state energy conformations shown above were used in conjunction with 1D ^{1}H nOe analysis of the all-proteo analogs of these compounds. The key nOe signals are shown below.

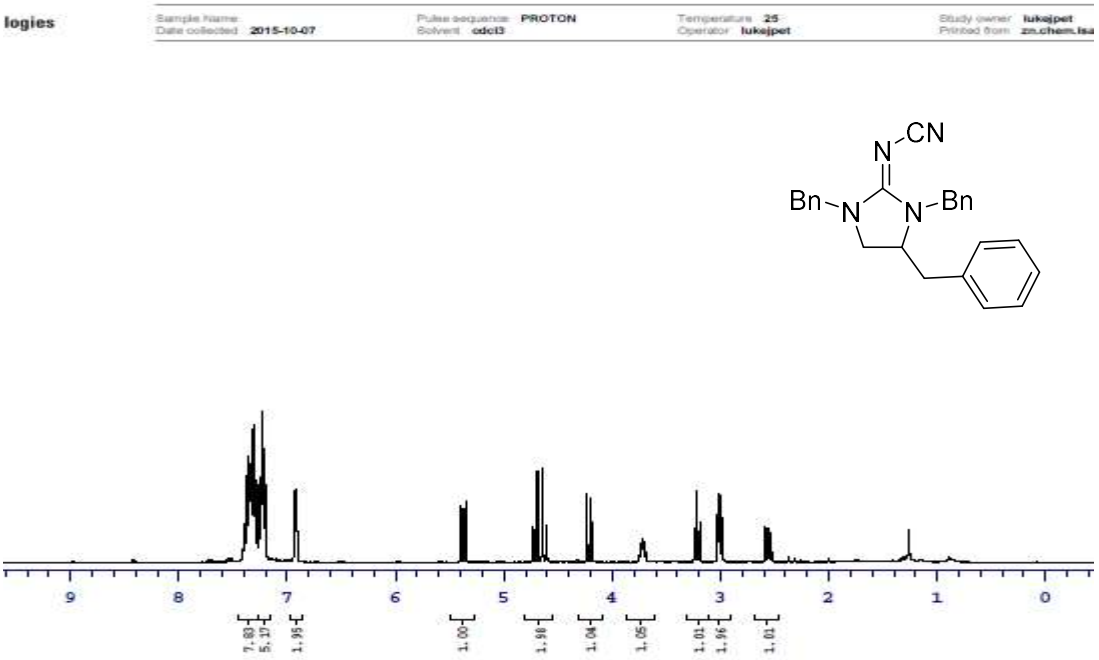

Sample Name:
Study Owner lukejpet
Date Collected 2016-08-08
Pulse sequence NOESY1D
Obs Freq 600.082
Solvent cdcl3
Spectrometer fe
Temperature 22
Comment Proton Spectrum
N
CN
Ph
Bn
N
N
H
H
H
H
Ph
H
9
8
7
6
5
4
3
2
1
ppm

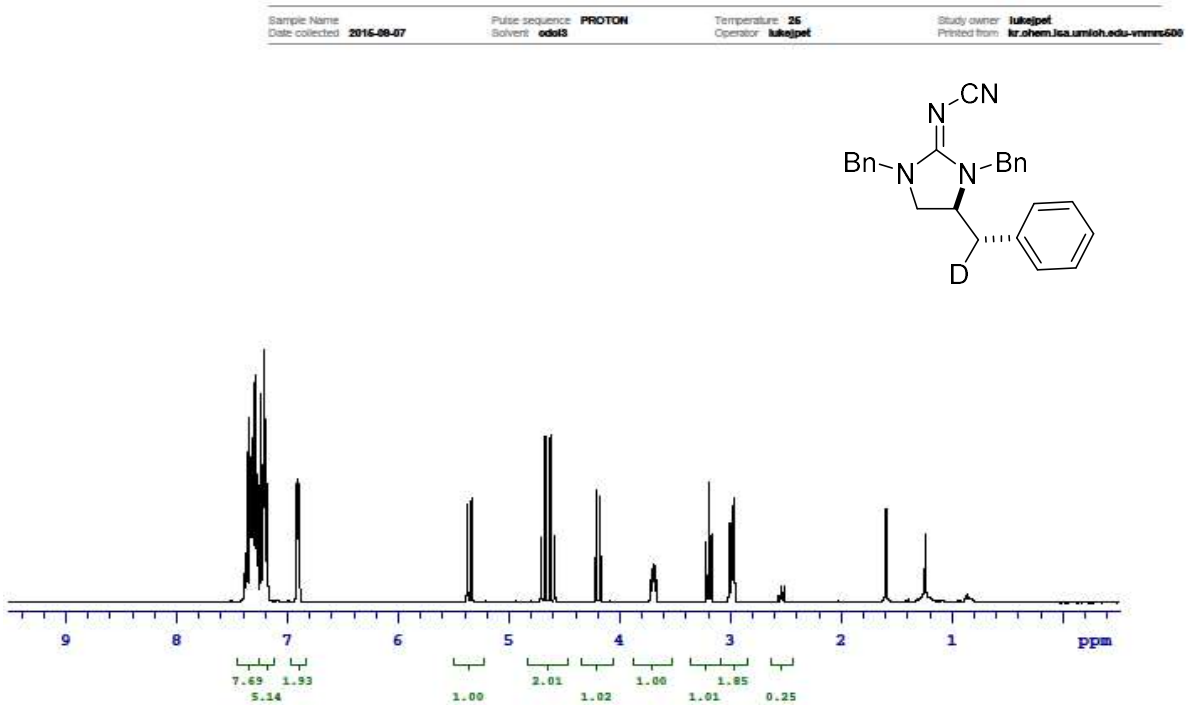

Sample Name:
Study Owner lukejpet
Date Collected 2018-04-01
Pulse sequence gCOSY
Obs Freq 400.623
Solvent cdcl3
Spectrometer oo
Temperature 25
Comment Proton Spectrum
A
B
C
D
E/F
G
F1 (ppm)
F2 (ppm)
N
CN
Ph
Bn
N
N
H
HA
HB
HG
HF
(D/E)
H
Ph
HC

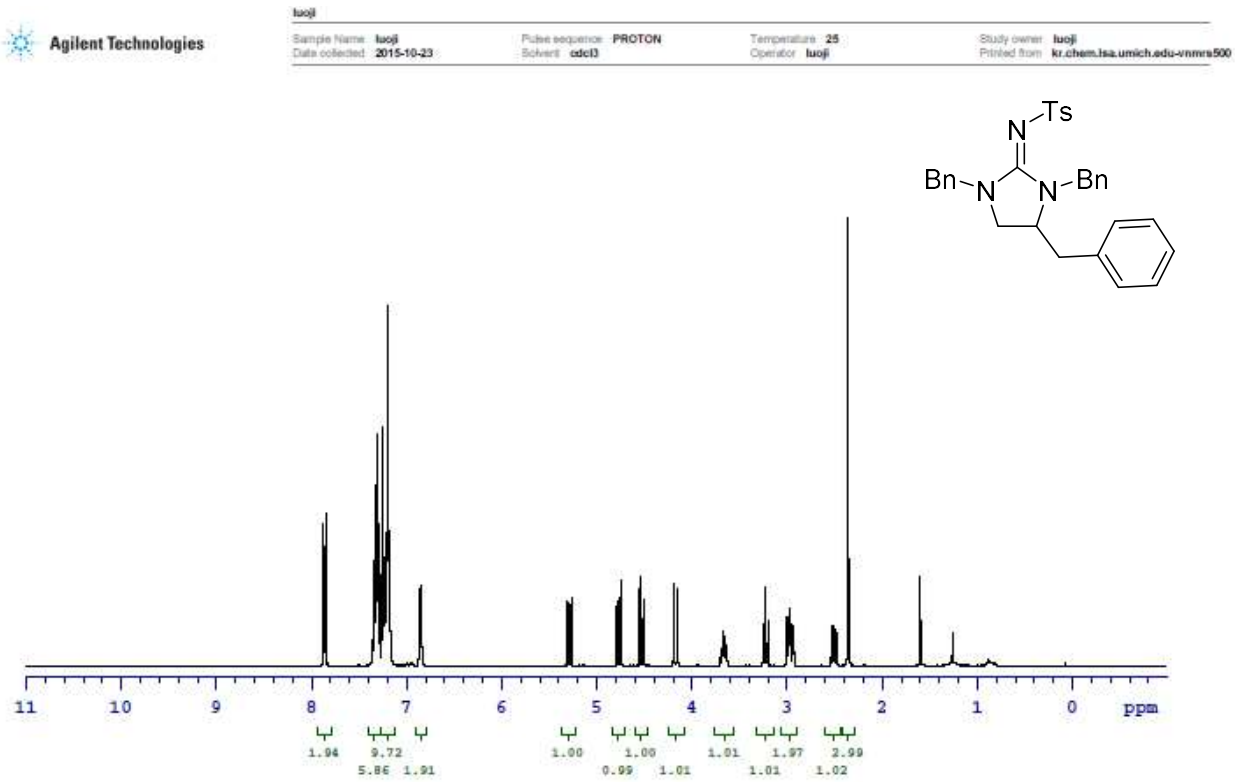

Sample Name:
Study Owner lukejpel
Date Collected 2016-09-22
Pulse sequence NOESY1D
Obs Freq 600.082
Solvent cdcl3
Spectrometer fa
Temperature 22
Comment Proton Spectrum
Ts
N
Ph
Bn
N
N
H
H
H
H
Ph
H
11
10
9
8
7
6
5
4
3
2
1
0
ppm

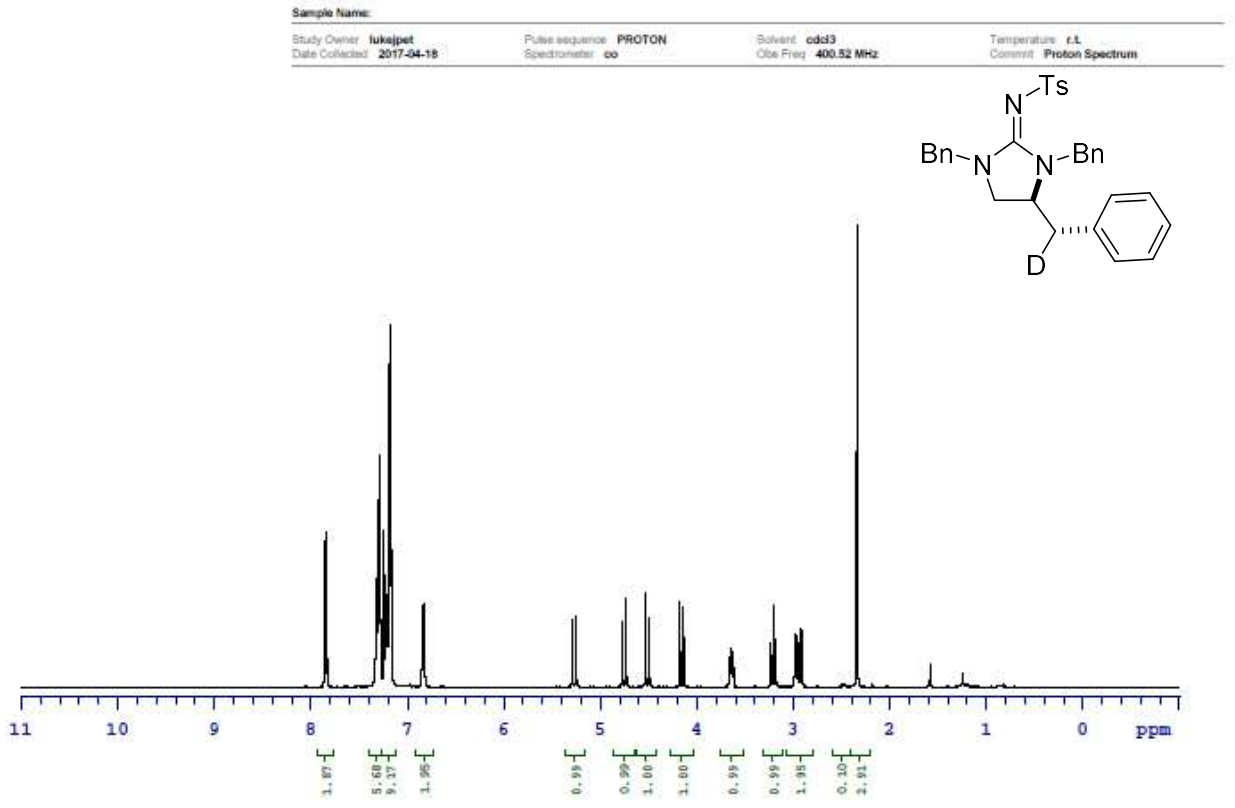

Sample Name:
Study Owner lukejpel
Date Collected 2016-09-22
Pulse sequence gCOSY
Obs Freq 399.638
Solvent cdcl3
Spectrometer ga
Temperature 25
Comment Proton Spectrum
A
B
C
D
E/F
G
Ts
N
Ph
Bn
N
N
H
HA
HG
HB
HF
(D/E)
H
Ph
HC
F1 (ppm)
F2 (ppm)

The configuration of the deuterated products was then assigned by examining which signal was absent from the ^{1}H NMR.



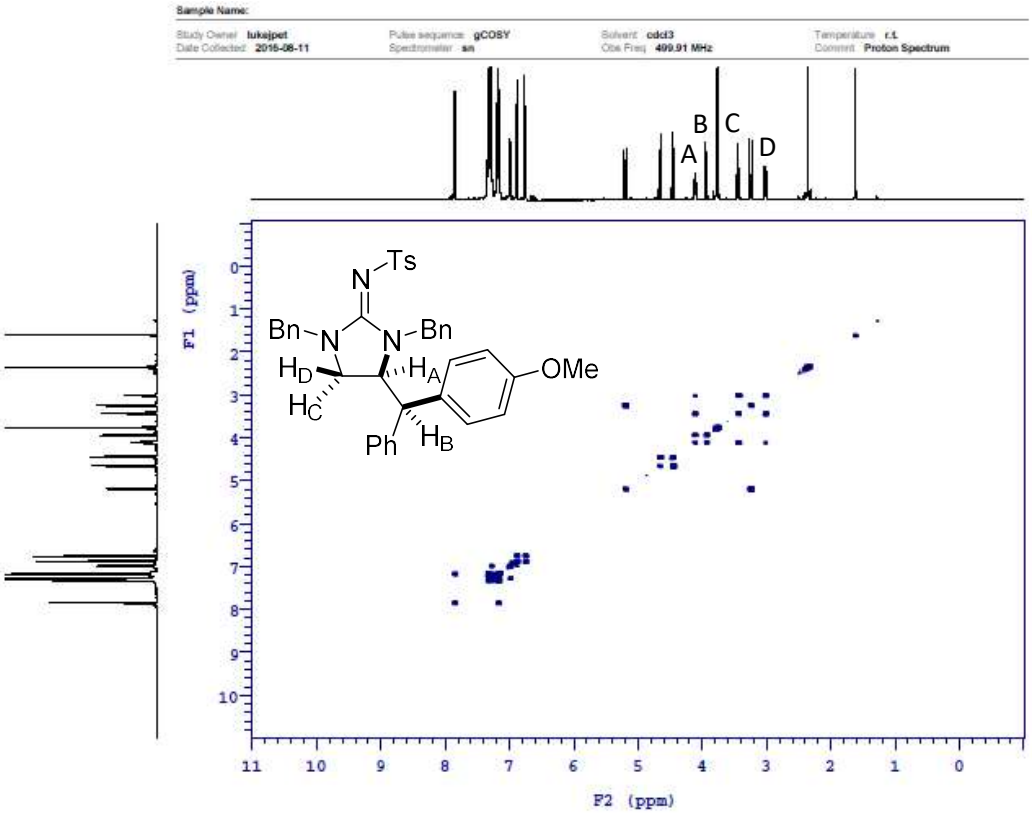



luoji
Sample Name luoji
Date collected 2015-10-23
Pulse sequence PROTON
Solvent cdcl3
Temperature 25
Operator luoji
Study owner luoji
Printed from kr.chem.lsa.umich.edu-vnmrs500
Ts
N
Bn
N
N
Bn
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.94
9.72
5.86
1.91
1.00
1.00
0.99
1.01
1.01
1.97
1.01
2.99
1.02


Sample Name:
Study Owner lukejpet
Date Collected 2017-04-18
Pulse sequence PROTON
Spectrometer co
Solvent cdcl3
Obs Freq 400.52 MHz
Temperature r.t.
Comment Proton Spectrum
Ts
N
Bn
N
N
Bn
D
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.87
5.68
9.37
1.96
0.99
0.99
1.00
1.00
0.99
0.99
1.95
0.10
2.91

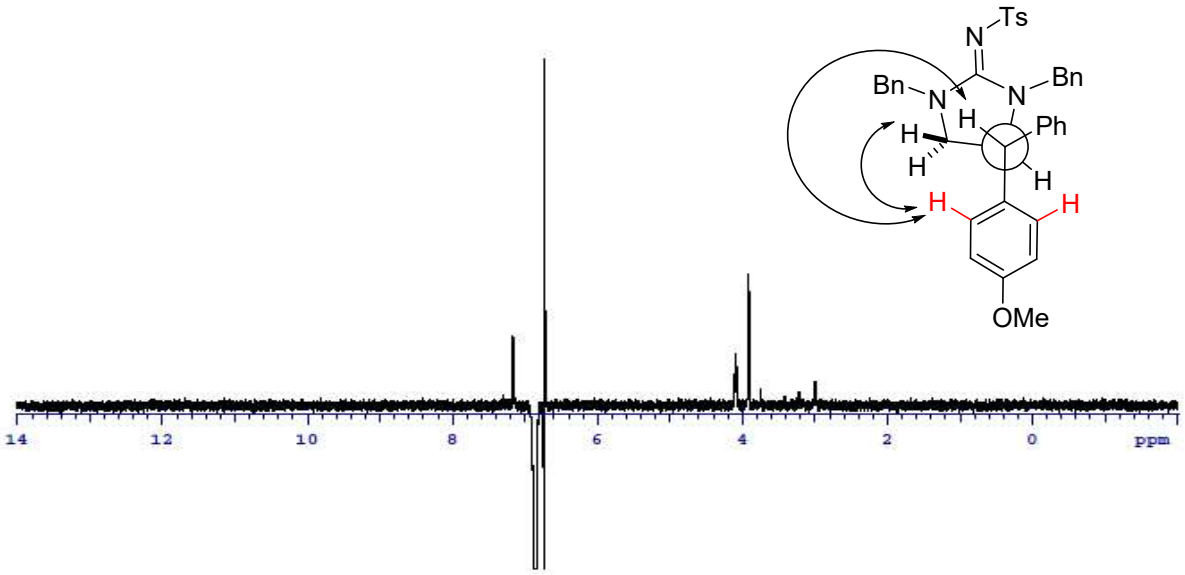
Assignment of Stereochemistry for 3-8n, 3-9k, and 3-9l.

The stereochemistry for compound **3-9l** was determined through use of 1D ^{1}H nOe analysis. The key nOe signals are shown below. The stereochemistry for compounds **3-8n** and **3-9k** were assumed based on the results for compound **3-9l**.



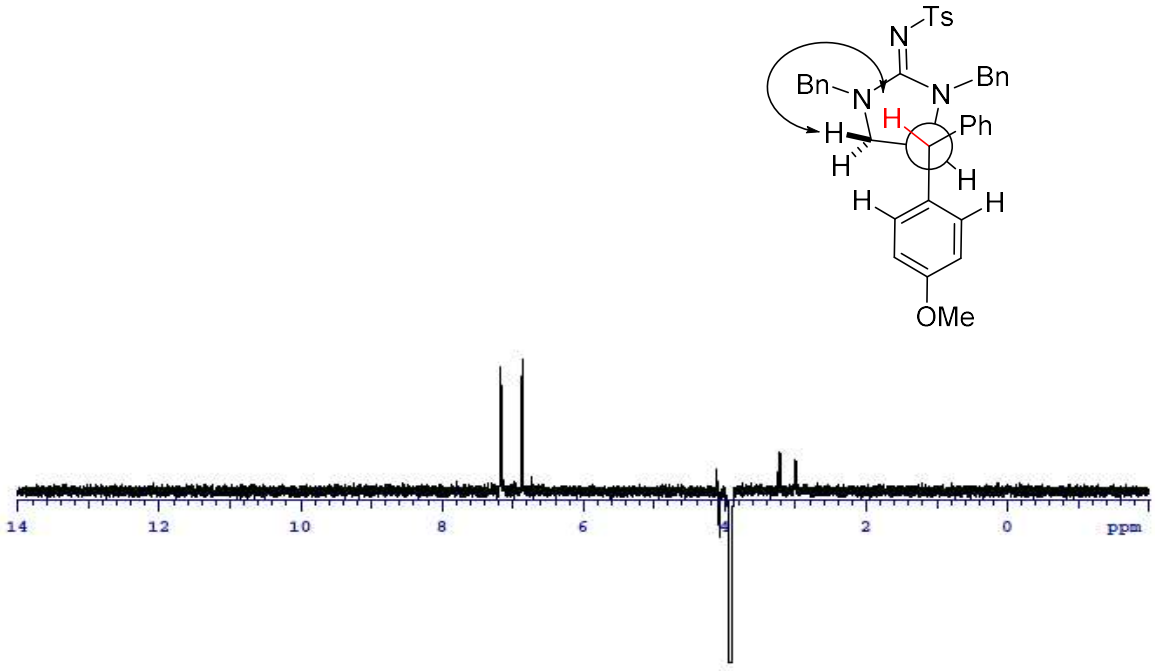
Sample Name:

Study Owner lukejpet | Pulse sequence NOESY1D | Solvent cdcl3 | Temperature r.t.
Date Collected 2016-08-11 | Spectrometer te | Obs Freq 500.08 MHz | Comment Proton Spectrum



Sample Name:

Study Owner lukejpet | Pulse sequence NOESY1D | Solvent cdcl3 | Temperature r.t.
Date Collected 2016-08-11 | Spectrometer te | Obs Freq 500.08 MHz | Comment Proton Spectrum



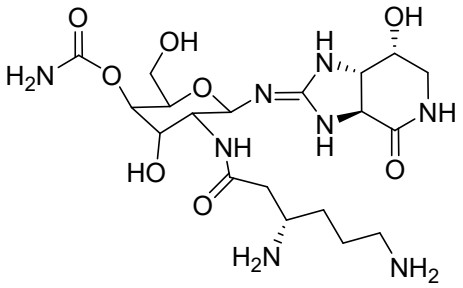
Chapter 4

Palladium-Catalyzed Couplings of *N*-Allyl Guanidine Substrates with Amine Electrophiles to Synthesize Amino-Substituted Cyclic Guanidines

4-1 Introduction

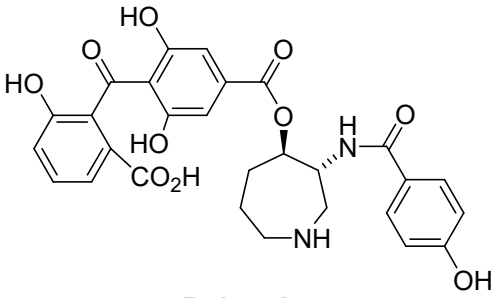
Diamamination reactions have become increasingly sought after in synthetic chemistry, as the 1,2-diamine moiety is prevalent in a wide variety of biologically active and pharmaceutically interesting scaffolds **(Scheme 4-1)**.[68]

Scheme 4-1. Biologically Active Compounds Containing Cyclic Guanidines and/or 1,2-Diamines.



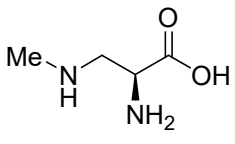
Streptothricin F

antiobiotic activity



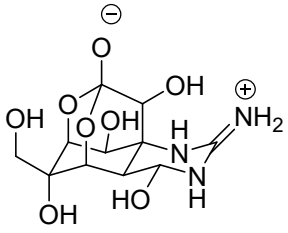
Balanol

protein kinase C inhibitor



L-β-methylaminoalanine

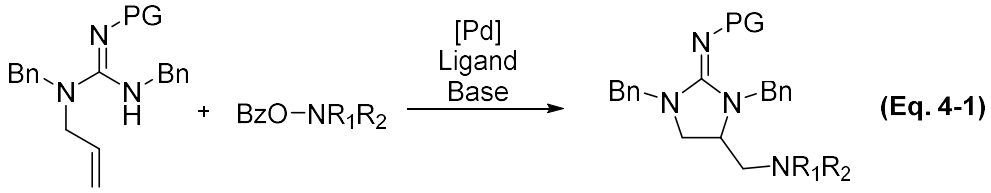
neurotoxin



Tetrodotoxin

neurotoxin

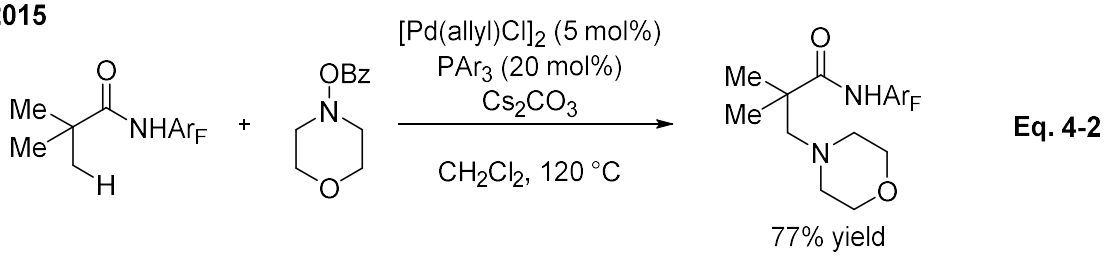
Furthermore, the cyclic guanidine motif is an attractive synthetic target, as it is present in a number of biologically active natural products including antiobiotics, protein kinase inhibitors, and neurotoxins.[69] Having just recently published a method to construct cyclic guanidines via a carboamination reaction, wherein *N*-allyl guanidine substrates were coupled with aryl halides or aryl triflates to concurrently form the C-C bond, the C-N bond, and the ring in the same reaction,[70] we hypothesized that an analogous transformation could be utilized with *O*-benzoyl protected amine electrophiles in a variation on a 1,2-diamination reaction **(Eq. 4-1).**



(Eq. 4-1)

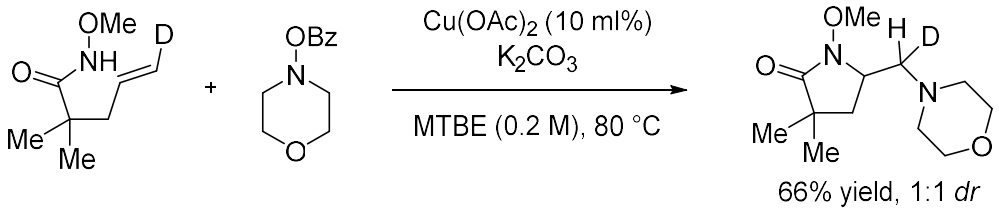
The oxidative addition of a palladium catalyst into the N-O bond of a benzoyl-protected amine electrophile has been previously established in the literature for the C-H activation of sp^3 C-H bonds in substrates bearing pendant amide directing groups.[new71] Furthermore, the use of these electrophiles in alkene difunctionalization reactions has been established by the Wang group, who has successfully reacted amide substrates bearing pendant alkenes with the aforementioned *O*-benzoyl protected amine electrophiles in the presence of a Cu(II) catalyst to accomplish 1,2-diaminations (**Eq. 4-2 and 4-3**).[new72]

Yu, 2015



Eq. 4-2

Wang, 2015



Eq. 4-3

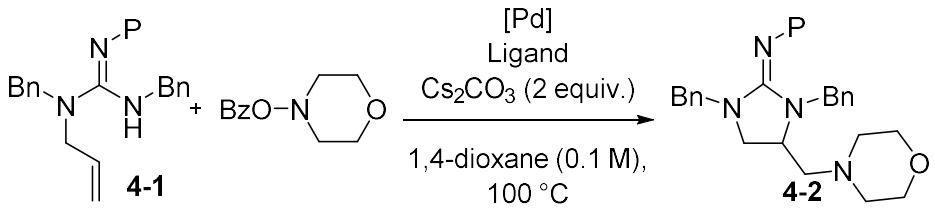
Although the efforts by Wang and coworkers to afford the cyclized amide product (**Eq. 4-3**) were successful, the reaction afforded the deuterated product in a 1:1 mixture of diastereomers. We hypothesize that our proposed palladium catalyzed transformation shown in **Eq. 4-1** provides an opportunity for diastereoselective addition across the alkene functionality. Furthermore, the guanidine and urea substrates used in our methodology provide a complementary scope to the established results from the Wang group.

4-2 Optimization Studies

To test this hypothesis we examined the Pd-catalyzed coupling of **4-1** with morpholino benzoate **(Table 4-1)** to afford cyclic guanidine product **4-2**. A series of phosphine ligands was surveyed, as we have seen success with a variety of phosphine ligands (both monodentate and bidentate) in our previous carboamination studies.[7,73] As can be seen from **Table 4-1**, electron poor aryl phosphine ligands, such as $P(C_6F_5)$ afforded the desired product in modest yields, and the $P(3,5\text{-}CF_3C_6H_3)_3$ ligand afforded the desired product **4-2** in an 80% NMR yield. With this knowledge in hand we hypothesized that the biaryl, Buchwald-type ligand JackiePhos would be an ideal ligand to effect the desired transformation due to the fact that and we have utilized Buchwald-

type ligands in carboamination reactions with success in the past,[73] as well as the fact that this ligand contains two (3,5-$CF_3C_6H_3$) aryl groups, similar to our initial hit. Gratifyingly, the use of JackiePhos as the ligand afforded **4-2** in a 95% NMR yield, and a decrease in the equivalents of amine electrophile used did not cause a decrease in the observed NMR yield.

Table 4-1. Optimization Studies.



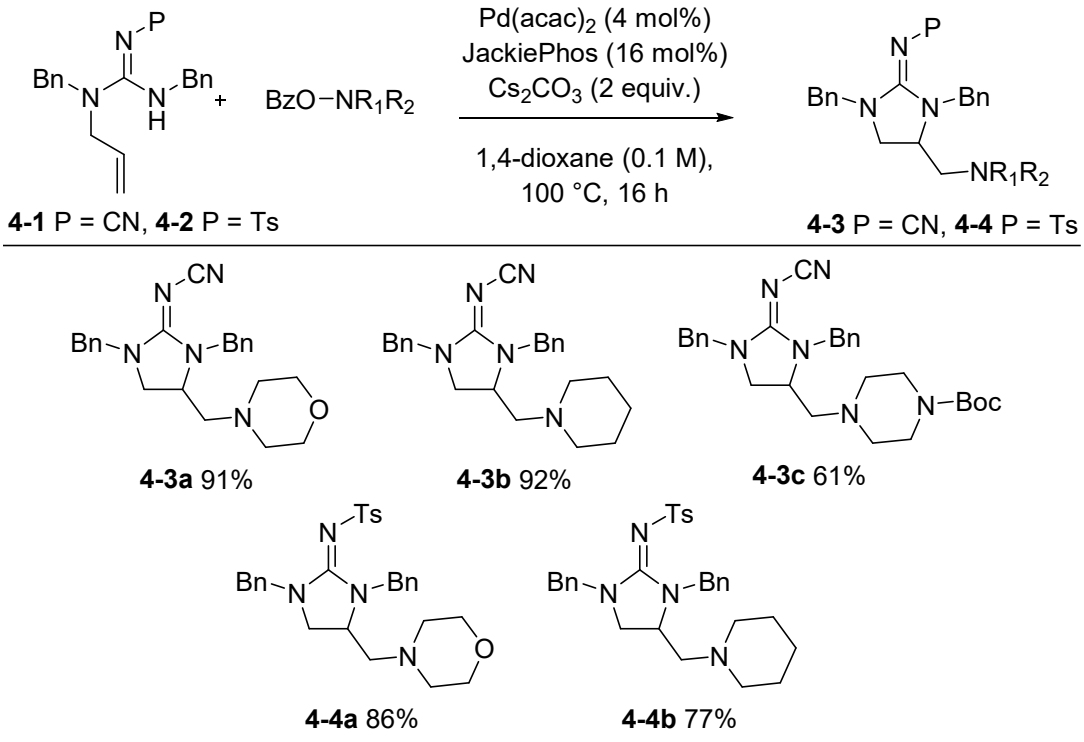
[Pd]	Ligand	4-2 [%][e]
$Pd(OAc)_2$	DPEPhos[a]	13
$Pd(OAc)_2$	CPhos[b]	0
$Pd(OAc)_2$	XantPhos[b]	0
$Pd(OAc)_2$	$P(C_6F_5)$[b]	30
$Pd_2(dba)_3$	$P(C_6F_5)$[c]	0
$Pd(TFA)_2$	$P(C_6F_5)$[c]	40
$Pd(acac)_2$	$P(C_6F_5)$[c]	60
$Pd(acac)_2$	$P(3,5\text{-}CF_3C_6H_3)_3$[c]	80
$Pd(acac)_2$	JackiePhos[c]	95
$Pd(acac)_2$	JackiePhos[d]	95

[a] *Conditions*: 1.0 equiv. 4-1, 4 equiv. $BzONR_1R_2$, 2 equiv. Cs_2CO_3, 2 mol% [Pd], 4 mol% ligand.
[b] *Conditions*: 1.0 equiv. 4-1, 4 equiv. $BzONR_1R_2$, 2 equiv. Cs_2CO_3, 2 mol% [Pd], 8 mol% ligand.
[c] *Conditions*: 1.0 equiv. 4-1, 4 equiv. $BzONR_1R_2$, 2 equiv. Cs_2CO_3, 4 mol% [Pd], 16 mol% ligand.
[d] *Conditions*: 1.0 equiv. 4-1, 3 equiv. $BzONR_1R_2$, 2 equiv. Cs_2CO_3, 4 mol% [Pd], 16 mol% ligand.
[e] Yield determined by ^1H NMR using 1,10-phenanthrene as an internal standard. In most instances the mass balance consisted of unreacted starting material 4-1.

4-3 Scope

We then explored the scope of the Pd-catalyzed coupling reactions of *N*-cyano and *N*-tosylguanidine substrates with OBz-protected amine electrohpiles. As shown in **Table 4-2**, these transformations are effective with morpholino benzoate, as well as piperidinyl and piperizinyl benzoate derivatives.

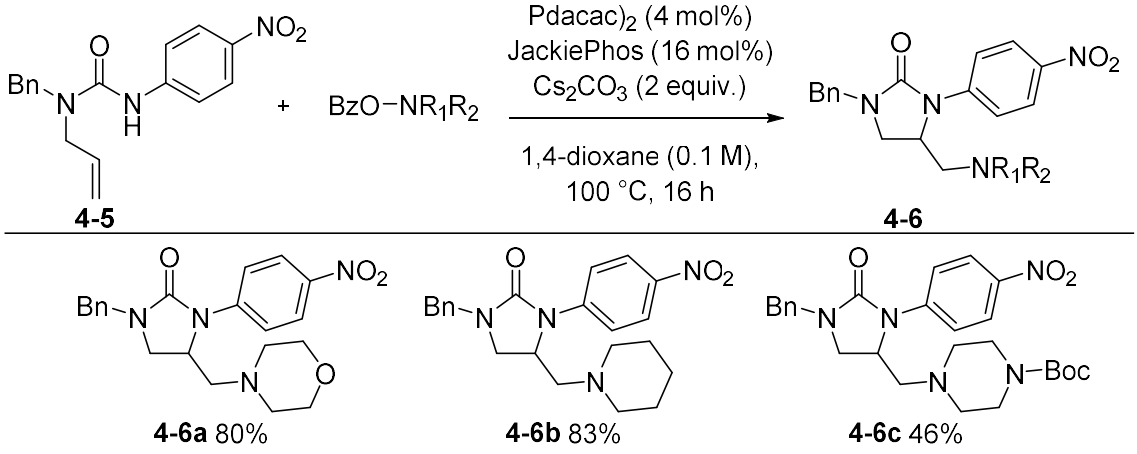
Table 4-2. Electrophile Scope with *N*-Cyano and *N*-Tosyl Guanidine Substrates.[a]



[a] *Conditions*: 1.0 equiv. of **4-1** or **4-2**, 3 equiv. of R_1-Br, 2.0 equiv. of Cs_2CO_3, $Pd(acac)_2$ (4 mol%), JackiePhos (16 mol%), 1,4-dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale.

We also explored the coupling of *N*-allyl urea substrate **4-5** with the previously determined conditions **(Table 4-3)**. Comparable yields were obtained when **4-5** was coupled with the same $BzONR_1R_2$ electrophile as **4-1**.

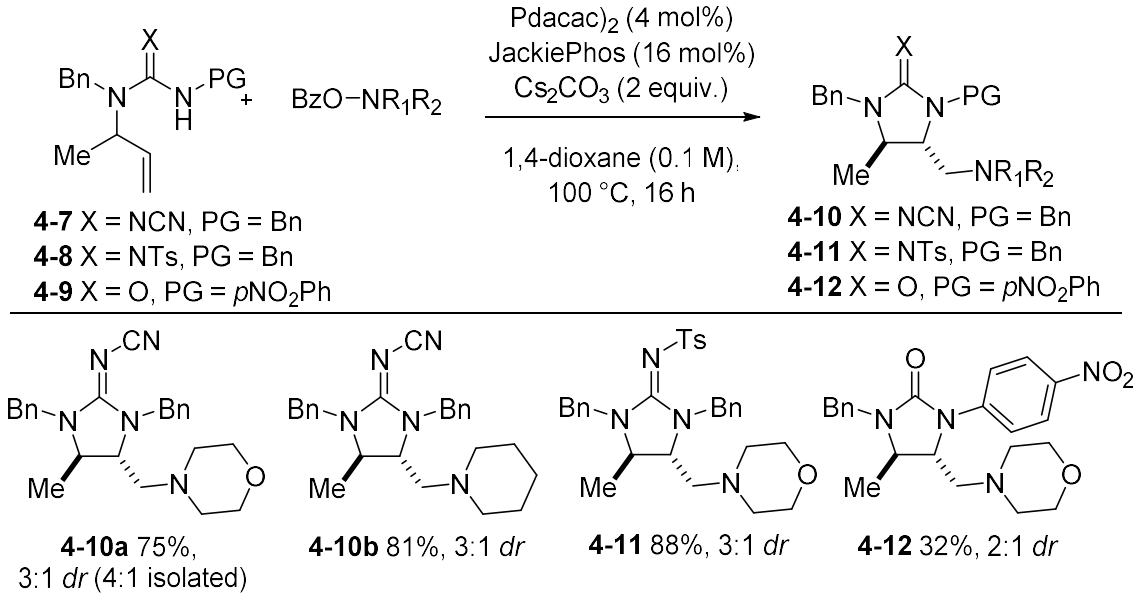
Table 4-3. Electrophile Scope with Urea Substrate **4-5.**[a]



[a] *Conditions*: 1.0 equiv. of **4-5**, 3 equiv. of R_1-Br, 2.0 equiv. of Cs_2CO_3, $Pd(acac)_2$ (4 mol%), JackiePhos (16 mol%), 1,4-dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale.

As was the case with our previously described couplings of *N*-cyano and *N*-tosylguanidine substrates with aryl halide and aryl triflate electrophiles, the observed diastereoselectivity for these reactions was quite low (2:1–4:1).

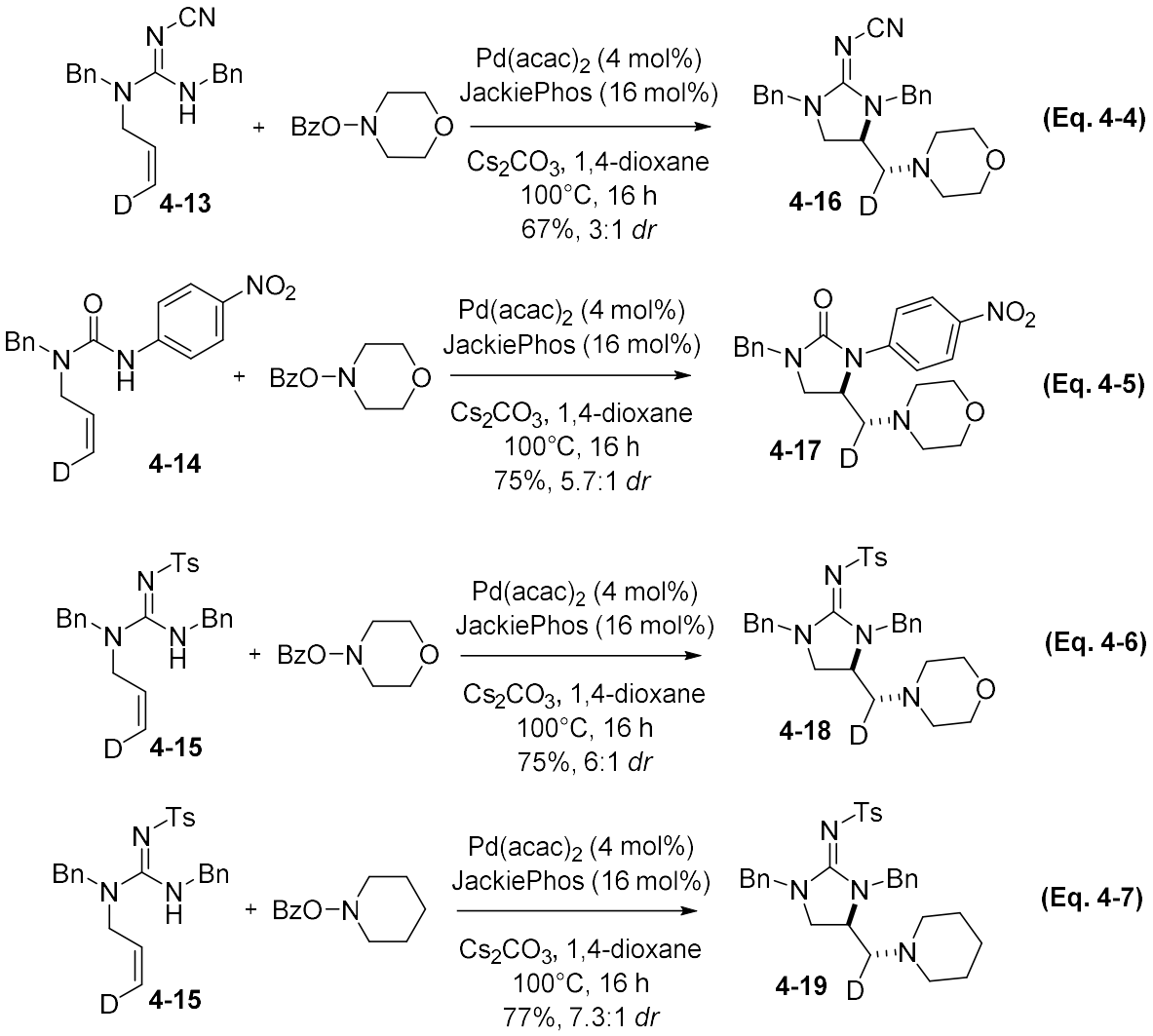
Table 4-4. Diastereoselectivity Studies.[a]



[a] *Conditions*: 1.0 equiv. of **4-7** or **4-8**, 3 equiv. of BzO-NR_1R_2, 2.0 equiv. of Cs_2CO_3, $Pd(acac)_2$ (4 mol%), JackiePhos (16 mol%), 1,4-dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale.

4-4 Mechanistic Studies via Deuterium Labelling

The low diastereoselectivity observed for these reactions led us to explore *syn*- vs *anti*-addition pathways in transformations of deuterated substrates **4-13**–**4-15**. As shown in **Eq. 2-5**, the coupling of **4-13** with morpholino benzoate afforded *anti*-addition product **4-16** in 67% yield and 3:1 *dr*. The reaction of urea substrate **4-14** with morpholino benzoate also proceeded via *anti*-addition with a 3:1 *dr*. Furthermore, the reaction of *N*-tosyl substrate **4-15** with morpholino benzoate to yield **4-18** also proceeded via *anti*-addition to the double bond, but with 6:1 *dr*. The low diastereomeric ratios observed for these experiments may be a result of slow reductive elimination of the palladium complex to form the C(sp3)-N(sp3) bond.[74] To test this hypothesis, substrate **4-15** was coupled with piperidin-1-yl benzoate to afforded deuterium-labelled product **4-19**. This reaction proceeded via *anti*-addition with a 7.3:1 *dr*. Based on these results, we cannot make any conclusions about the effect of the electronics of the amine electrophile on the diastereoselectivity of the coupling reaction.



4-5 Conclusion

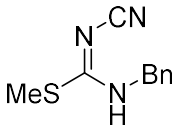
In conclusion, we have developed a new approach to the coupling of guanidine substrates with amine electrophiles in a modular alkene diamination. This reaction simultaneously creates a ring system, and two C-N bonds from two distinct nitrogen sources. The Pd-catalyzed coupling reactions proceed in generally good chemical yields and provide products resulting from *anti*-addition to the alkene. Furthermore, these reactions improved upon existing methodology by accomplishing the alkene functionalization with some, albeit limited, diastereoselectivity. Also, the C-N bond forming

reductive elimination step is accomplished in the presence of β-hydrogens, which cannot be said for other methodologies that utilize these *O*-benzoyl protected amine electrophiles.[71] Future studies will be directed toward improving diastereoselectivities in these reactions and improving the scope of the coupling reaction.

4-6 Experimental

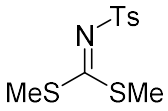
General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium(0) and palladium(II) acetate were purchased from Strem Chemical Co. and used without purification, and C-Phos and X-Phos were purchased from Sigma-Aldrich Co. and was used without further purification. Aryl triflates were prepared according to a procedure published by Frantz and coworkers,[62] except the products were purified by column chromatography. Bulk quantities of lithium *tert*-butoxide and sodium *tert*-butoxide were stored in nitrogen-filled glove box and small amounts were removed shortly before use. Toluene, THF, dichloromethane 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 ^{1}H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted.

Preparation and Characterization of Substrates

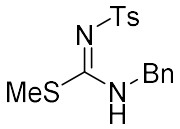


Methyl *N*-benzyl-*N*'-cyanocarbamimidothioate (4-S1). A flame dried flask was cooled under a stream of nitrogen and charged with dimethyl cyanocarbonimidodithioate (2 g,

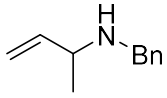
13.6 mmol) and ethanol (40 mL). Benzylamine (2.2 mL, 20.6 mmol) was then added via syringe, and the solution was heated to reflux with stirring for 2 h. The solution was then cooled to rt, a stream of nitrogen was blown over the solution for 20 min, and then the solution was placed in the freezer overnight. The white precipitate that had formed was then isolated via filtration using a fritted glass funnel to yield 2.61g (94%) of the desired product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 5 H), 6.60 (s, br, 1 H), 4.50 (s, br, 2 H), 2.48 (s, br, 3 H).



Dimethyl tosylcarbonimidodithioate (4-S2). A flame dried flask was cooled under a stream of nitrogen and charged with 4-methylbenzenesulfonamide (25.68 g, 150 mmol), carbon disulfide (14.2 mL, 240 mmol), and DMF (200 mL). The mixture was cooled to 0 °C in an ice bath, and then a solution of KOH (19.9 g, 354 mmol) in water (60 mL) was added dropwise at a rate sufficiently slow that the reaction temperature remained below 10 °C at all times. The reaction mixture was then stirred at 0 °C for 30 min, and then methyl iodide (21.7 mL, 348 mmol) was added dropwise at a rate sufficiently slow that the reaction temperature remained below 10 °C at all times. The reaction mixture was then warmed to rt and stirred for 30 min. Water was then added (150 mL), and the white precipitate that had formed was then isolated via filtration using a fritted glass funnel. The white solid was washed with water followed by ethanol, then was dried *in vacuo* to afford 31.27 g (75%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 2.53 (s, 6 H), 2.43 (s, 3 H).

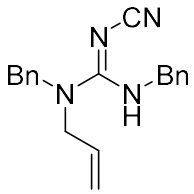


Methyl *N*-benzyl-*N'*-tosylcarbamimidothioate (4-S3). A flame dried flask was cooled under a stream of nitrogen and charged with dimethyl tosylcarbonimidodithioate **(4-S2)** (2.00 g, 7.26 mmol) and ethanol (40 mL). Benzylamine (1.2 mL, 10.89 mmol) was then added slowly, and the reaction was then heated to reflux with stirring for 2 h. The solution was then cooled to rt, a stream of nitrogen was blown over the solution for 20 min, and then the solution was placed in the freezer overnight. The white precipitate that had formed was then isolated via filtration using a fritted glass funnel to yield 2.19 g (90%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, br, 1 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.41–7.31 (m, 3 H), 7.31–7.17 (m, 4 H), 4.48 (d, *J* = 5.9 Hz, 2 H), 2.42 (s, 3 H), 2.38 (s, 3 H).

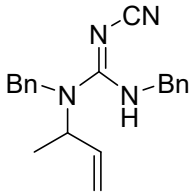


***N*-Benzylbut-3-en-2-ylamine (4-S4).** A flame dried flask was cooled under a stream of nitrogen and charged with *N*-(but-3-en-2-yl)benzamide[63] (1.32 g, 7.53 mmol) in diethyl ether (30 mL). The solution was cooled on an ice bath, and a solution of $LiAlH_4$ (30 mL, 30 mmol, 1 M in THF) was added slowly. The reaction mixture was then heated to reflux with stirring overnight. The mixture was then cooled in an ice bath, and water (7.53 mL) was slowly added followed by 1 M NaOH (7.5 mL). The miture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 10 mL). The organic laywers were combined, dried, filtered, and concentrated *in vacuo* to afford 1.2 g (99%) of the title

compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 4 H), 7.28–7.21 (m, 1 H), 5.80–5.64 (m, 1 H), 5.19–5.02 (m, 2 H), 3.80 (d, *J* = 13.1 Hz, 1 H), 3.68 (d, *J* = 13.1 Hz, 1 H), 3.28–3.16 (m, 1 H), 1.50 (s, br, 1 H), 1.18 (d, *J* = 6.5 Hz, 3 H).

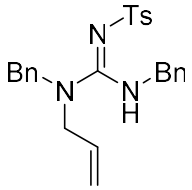


1-Allyl-1,3-dibenzyl-2-cyanoguanidine (4-1).[70] A round bottom flask was charged with methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(4-S1)** (0.93 g, 4.53 mmol), ethanol (45 mL), and mercuric oxide (1.47 g, 6.80 mmol), then purged with nitrogen. Triethylamine (2.5 mL, 18.12 mmol) was added followed by *N*-benzylprop-2-en-1-ylamine (1.00 g, 6.80 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate:hexanes 4:6) to yield 1.00 g (72%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 6 H), 7.23–7.18 (m, 4 H), 5.81–5.71 (m, 1 H), 5.28–5.08 (m, 3 H), 4.72 (d, *J* = 5.3 Hz, 2 H), 4.58 (s, 2 H), 3.94 (dt, *J* = 5.6, 1.6 Hz, 2 H).

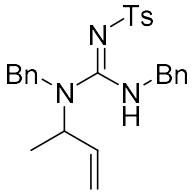


1,3-Dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine (4-7).[70] The title compound was prepared from methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(4-S1)** (0.888 g, 4.53 mmol),

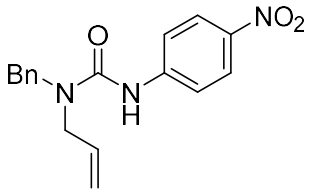
ethanol (40 mL), mercuric oxide (1.40 g, 6.5 mmol), triethylamine (2.4 mL, 17.3 mmol) and *N*-benzylbut-3-en-2-ylamine **(4-S4)** (0.837 g, 5.2 mmol) using a procedure analogous to that described above for the synthesis of **4-1**. This procedure afforded 0.316 g (23%) of an off white solid, m.p. 104–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 3 H), 7.26–7.19 (m, 3 H), 7.18–7.16 (m, 2 H), 6.97–6.95 (m, 2 H), 5.92–5.86 (m, 1 H), 5.25–5.15 (m, 2 H), 5.11–5.09 (m, 1 H), 4.97 (d, *J* = 5.3 Hz, 1 H), 4.70–4.58 (m, 2 H), 4.46–4.28 (m, 2 H),1.31 (d, *J* = 6.5 Hz, 3 H).



***N*-{[Allyl(benzyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (4-2).**[70] The title compound was prepared from methyl *N*-benzyl-*N*'-tosylcarbamimidothioate **(4-S3)** (1.06 g, 3.17 mmol), ethanol (30 mL), mercuric oxide (1.03 g, 4.75 mmol), triethylamine (1.8 mL, 12.68 mmol), and *N*-benzylprop-2-en-1-ylamine (0.70 g, 4.75 mmol) using a procedure analogous to that described above for the synthesis of **4-1** except with a reaction time of 48 h. This procedure afforded 1.06 g (77%) of the title compound as a white solid, m.p. 91–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2 H), 7.34–7.22 (m, 6 H), 7.20–7.08 (m, 6 H), 6.99 (t, *J* = 5.7 Hz, 1 H), 5.74 (ddt, *J* = 16.4, 9.8, 5.8 Hz, 1 H), 5.24–5.05 (m, 2 H), 4.48 (s, 2 H), 4.39 (d, *J* = 5.7 Hz, 2 H), 3.82 (d, *J* = 5.7 Hz, 2 H), 2.39 (s, 3 H).

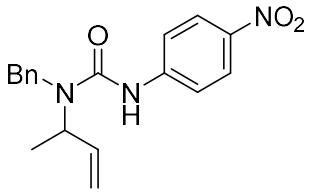


***N*-{[Benzyl(but-3-en-2-yl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (4-8).**[70] The title compound was prepared from methyl *N*-benzyl-*N*'-tosylcarbamimidothioate **(4-S3)** (1.018 g, 3.05 mmol), ethanol (30 mL), mercuric oxide (0.991 g, 4.58 mmol), triethyl amine (1.7 mL, 12.2 mmol), and *N*-benzylbut-3-en-2-ylamine **(4-S4)** (0.590 g, 3.66 mmol) using a procedure analogous to that described above for the synthesis of **4-1** except with a reaction time of 48 h. This procedure afforded 1.21 g (89%) of the title compound as an off white solid, m.p. 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2 H), 7.27–7.11 (m, 6 H), 7.10–7.02 (m, 2 H), 6.97 (dd, *J* = 7.9, 1.9 Hz, 4 H), 6.87 (t, *J* = 5.7 Hz, 1 H), 5.95–5.86 (m, 1 H), 5.24–5.11 (m, 2 H), 4.55–4.50 (m, 1 H), 4.38 (t, *J* = 5.5 Hz, 2 H), 4.31 (s, 2 H), 2.33 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 3 H).

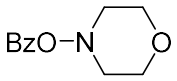


1-allyl-1-benzyl-3-(4-nitrophenyl)urea (4-5). A flame dried flask was cooled under a stream of nitrogen and charged with *p*-nitrophenyl isocyanate (0.500 g, 3.05 mmol) in DCM (3 mL). *N*-benzylprop-2-en-1-ylamine (0.450 g, 3.05 mmol) was then added, and the reaction stirred at rt overnight. The reaction mixture was then concentrated *en vacuo*, and the crude product was purified via flash column chromatography on silica gel to afford 0.845 g (90%) of the title compound as a yellow solid, m.p. ^{1}H NMR (500 MHz, $CDCl_3$) δ

8.16–8.13 (m, 2 H), 7.47–7.43 (m, 2 H), 7.41–7.37 (m, 2 H), 7.35–7.31 (m, 3 H), 6.79 (br s, 1 H), 5.93–5.84 (m, 1 H), 5.38–5.34 (m, 2 H), 4.61 (s, 2 H), 4.01 (d, J = 5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 145.3, 142.5, 136.8, 133.4, 129.0, 128.0, 127.5, 125.0, 118.3, 118.0, 50.8, 50.2; IR (film) 3332, 1654 cm^{-1}; MS (ESI+) 312.1345 (312.1343 calcd for $C_{17}H_{17}N_3O_3$, M + H+).

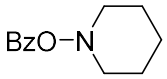


1-Benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (4-9): A flame dried flask was cooled under a stream of nitrogen and charged with *p*-nitrophenyl isocyanate (0.356 g, 2.17 mmol) in DCM (2.2 mL). *N*-benzylbut-3-en-2-amine (0.350 g, 2.17 mmol) was then added, and the reaction stirred at rt overnight. The reaction mixture was then concentrated *en vacuo*, and the crude product was purified via flash column chromatography on silica gel to afford 0.563 g (80%) of the title compound as a yellow solid, m.p. 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.2 Hz, 2 H), 7.42–7.28 (m, 7 H), 6.74 (br s, 1 H), 6.03–5.95 (m, 1 H), 5.32–5.27 (m, 2 H), 4.95 (br s, 1 H), 4.56 (d, J = 16.8 Hz, 1 H), 4.39 (d, J = 17.2 Hz, 1 H), 1.35 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 145.2, 142.4, 138.7, 137.2, 127.3, 128.2, 126.8, 124.9, 118.2, 116.9, 52.8, 47.8, 16.5; IR (film) 3384, 1653; MS (ESI+) 326.1502 (326.1499 calcd for $C_{18}H_{19}N_3O_3$, M + H+).

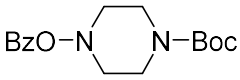


Morpholino benzoate (4-S5).[73] A flame dried 100 mL flask was cooled under a stream of nitrogen and charged with morphiline (1.0 g, 11.5 mmol) in THF (34 mL), and then

Na_2HPO_4 (8.149 g, 57.4 mmol). Benzoyl peroxide (2.969 g, 12.3 mmol) in THF (12 mL) was then added slowly, and the reaction as refluxed overnight. Once the reaction had cooled to rt it was filtered through celite, and then concentrated. The crude product was then purified via flash column chromatography on silica gel (EtOAc:Hexanes = 15:85) to yield 1.28 g (54%) of the product as a white solid, m.p. 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.41 (t, *J* = 7.2 H, 2 H), 3.98–3.82 (m, 4 H), 3.45 (d, *J* = 10 Hz, 2 H), 3.08–3.00 (m, 2 H).



Piperidin-1-yl benzoate (4-S6).[73] A flame dried 100 mL flask was cooled under a stream of nitrogen and charged with piperidine (1.25 g, 14.7 mmol) in THF (35 mL), and then Na_2HPO_4 (9.39 g, 66.2 mmol). Benzoyl peroxide (3.91 g, 16.2 mmol) in THF (15 mL) was then added slowly, and the reaction as refluxed overnight. Once the reaction had cooled to rt it was filtered through celite, and then concentrated. The crude product was then purified via flash column chromatography on silica gel (EtOAc:Hexanes = 15:85) to yield 2.06 g (68%) of the product as a white solid, m.p. 62–64 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.99 (d, *J* = 8.4 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.41 (t, *J* = 7.2 H, 2 H), 3.54–3.45 (m, 2 H), 2.80–2.71 (m, 2 H), 1.83–1.77 (m, 4 H), 1.65 (br s, 1H), 1.28–1.26 (m, 1H).

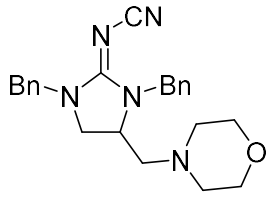


tert-Butyl 4-(benzoyloxy)piperazine-1-carboxylate (4-S7). A flame dried flask was cooled under a stream of nitrogen and charged with 1-Boc-piperizine (2.328 g, 12.5 mmol) in THF (30 mL), and then Na_2HPO_4 (8.873 g, 62.5 mmol). Benzoyl peroxide (3.33 g, 13.75

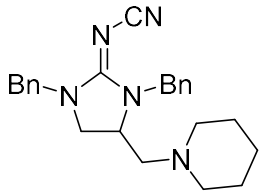
mmol) in THF (10 mL) was then added slowly, and the reaction as refluxed overnight. Once the reaction had cooled to rt it was filtered through celite, and then concentrated. The crude product was then purified via flash column chromatography on silica gel (EtOAc:Hexanes = 15:85) to yield 2.50 g (65%) of the product as a white solid, m.p. 104–106 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.98 (d, *J* = 7.2 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 4.02 (br s, 2 H), 3.44–3.25 (m, 4 H), 2.90 (br s, 2 H), 1.40 (s, 9 H).

Preparation and Characterization of Products

General Procedure A for Pd-Catalyzed Carboamination Reactions of Aryl Bromides. A flame dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (4 mol%), JackiePhos (16 mol%), OBz-protected amine electrophile (3 equiv.), and Cs_2CO_3 (2 equiv). The tube was purged with nitrogen and then a solution of the *N*-protected guanidine or urea substrate (1 equiv) in 1,4-dioxane (0.1 M) was added, and the solution was heated to 100 °C with stirring until the starting material had been consumed as judged by TLC or ^{1}H NMR analysis of the reaction mixture (ca 16 h). The mixture was then cooled to rt and diluted with diethyl ether (2 mL). The resulting mixture was then filtered through cotton, and this procedure was repeated once more. The solution was then concentrated *in vacuo*, and the crude product was purified via flash column chromatography on silica gel (methanol:dichloromethane = 1:99).

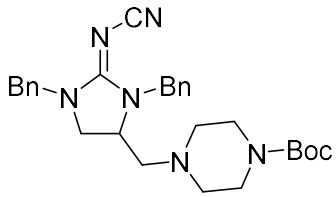


***N*-(1,3-dibenzyl-4-(morpholinomethyl)imidazolidin-2-ylidene)cyanamide (4-3a)**. The general procedure was followed for the coupling of 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(4-1)** (30.4 mg, 0.1 mmol) with morpholino benzoate **(4-S5)** (62.2 mg, 0.3 mmol). This procedure afforded 36 mg (92%) of the title compound as a tan, viscous oil. ^{1}H NMR (500 MHz, C_6H_6) δ 7.29–6.95 (m, 10 H), 5.24 (d, *J* = 15.5 Hz, 1 H), 4.56–4.46 (m, 2 H) 4.05 (d, *J* = 15.5 Hz, 1 H), 3.33–3.24 (m, 4 H), 3.01 (m, 1 H), 2.64 (appt, *J* = 9.5 Hz, 1 H), 2.52 (dd, *J* = 9.6, 7.1 Hz, 1 H), 1.87 (dd, *J* = 12.8, 5.6 Hz, 1 H), 1.77–1.66 (m, 4 H), 1.53 (dd, *J* = 12.8. 6.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 135.9, 135.4, 128.9, 128.8, 128.2, 128.1, 128.0, 127.9, 116.5, 66.7, 61.0, 54.1, 51.9, 49.5, 49.3, 47.8; IR (film) 2919, 2171, 1596 cm^{-1}; MS (ESI+) 390.2292 (390.2288 calcd for $C_{23}H_{27}N_5O$, M + H$^+$).

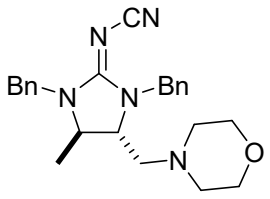


***N*-(1,3-dibenzyl-4-(piperidin-1-ylmethyl)imidazolidin-2-ylidene)cyanamide (4-3b)**. The general procedure was followed for the coupling of 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(4-1)** (30.4 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-S6)** (61.5 mg, 0.3 mmol). This procedure afforded 36 mg (93%) of the title compound as a tan, viscous oil. ^{1}H NMR (500 MHz, C_6H_6) δ 7.26 (d, *J* = 7.5 Hz, 2 H), 7.17–7.03 (m, 8 H), 5.31 (d, *J* = 16 Hz, 1 H), 4.51 (s, 2 H), 4.12 (d, *J* = 15.4 Hz, 1 H), 3.10 (dt, *J* = 13.1, 6.6 Hz, 1 H), 2.66

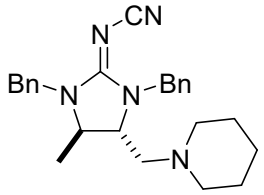
(t, *J* = 9.5 Hz, 1 H), 2.57 (dd, *J* = 9.6, 7.1 Hz, 1 H), 1.97 (dd, *J* = 12.7, 5.6 Hz, 1 H), 1.83 (br s, 4 H), 1.61 (dd, *J* = 12.8, 7.1 Hz, 1 H), 1.24 (h, *J* = 5.6 Hz, 4 H), 1.15 (q, *J* = 5.8 Hz, 2 H). ^{13}C NMR (100 MHz, C_6H_6) δ 158.3, 136.8, 136.0, 128.6, 128.5, 128.4, 128.3, 115.9, 61.2, 54.8, 51.9, 49.1, 47.4, 25.8, 24.0; IR (film) 2933, 2171, 1595 cm^{-1}; MS (ESI+) 388.2496 (388.496 calcd for $C_{24}H_{29}N_5$, M + H+).



tert-Butyl 4-((1,3-dibenzyl-2-(cyanoimino)imidazolidin-4-yl)methyl)piperazine-1-carboxylate (4-3c). The general procedure was followed for the coupling of 1-allyl-1,3-dibenzyl-2-cyanoguanidine **(4-1)** (30.4 mg, 0.1 mmol) with tert-butyl 4-(benzoyloxy)piperazine-1-carboxylate **(4-S7)** (91.9 mg, 0.3 mmol). This procedure afforded 30 mg (61%) of the title comound as a pale yellow, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.11 (m, 10 H), 5.28 (d, *J* = 15.6 Hz, 1 H), 4.83–4.61 (m, 2 H), 4.33 (d, *J* = 15.6 Hz, 1 H), 3.58 (dt, *J* = 12.4, 6.3 Hz, 1 H), 3.38 (t, *J* = 9.7 Hz, 1 H), 3.28 (br s, 4 H), 3.09 (dd, *J* = 9.8, 6.5 Hz, 1 H), 2.49 (dd, *J* = 12.9, 5.6 Hz, 1 H), 2.29–2.13 (m, 5H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 154.5, 135.8, 135., 128.8, 128.2, 128.0, 127.9, 127.8, 116.4, 79.7, 60.6, 53.4, 51.9, 49.4, 49.2, 47.7; IR (film) 2927, 2170, 1685, 1595 cm^{-1}; MS (ESI+) 489.2970 (489.2973 calcd for $C_{28}H_{36}N_6O_2$, M + H$^+$).

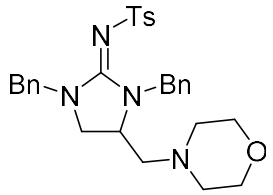


***N*-((4R,5R)-1,3-dibenzyl-4-methyl-5-(morpholinomethyl)imidazolidin-2-ylidene)cyanamide (4-10a)**. The general procedure was followed for the coupling of 1,3-dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine **(4-7)** (31.8 mg, 0.1 mmol) with morpholino benzoate **(4-S5)** (62.1 mg, 0.3 mmol). This procedure afforded 32.3 mg (80%) of the title compound as a tan, viscous oil. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; ^{1}H NMR data are for the major diastereomer, ^{13}C NMR data are for the mixture. ^{1}H NMR (400 MHz, C_6H_6) δ 7.22–7.17 (m, 5 H), 7.15–7.02 (m, 5 H), 5.42 (d, *J* = 15.5 Hz, 1 H), 5.35 (d, *J* = 15.5 Hz, 1 H), 4.07 (d, *J* = 16.0 Hz, 1 H), 3.85 (d, *J* = 16.0 Hz, 1 H), 3.33–3.27 (m, 4 H), 2.92 (p, *J* = 6.5 Hz, 1 H), 2.72 (q, *J* = 6.0 Hz, 1 H), 1.84 (dd, *J* = 13.0 Hz, 6 Hz, 1 H), 1.80–1.72 (m, 4 H), 1.50 (dd, *J* = 13.0, 6.5 Hz, 1 H), 0.57 (d, *J* = 5.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 136.0, 135.8, 128.9, 128.8, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 116.7, 66.8, 66.7, 60.7, 59.2, 56.7, 55.1, 54.3, 54.1, 54.0, 53.9, 47.8, 47.7, 56.8, 56.2, 18.6, 12.0; IR (film) 2925, 2170, 1591 cm^{-1}; MS (ESI+) 404.2446 (404.2445 cacld for $C_{24}H_{29}N_5O$, M + H+).



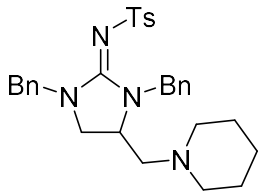
***N*-((4R,5R)-1,3-dibenzyl-4-methyl-5-(piperidin-1-ylmethyl)imidazolidin-2-ylidene)cyanamide (4-10b)**. The general procedure was followed for the coupling of 1,3-dibenzyl-1-(but-3-en-2-yl)-2-cyanoguanidine **(4-7)** (31.8 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-S6)** (61.5 mg, 0.3 mmol). This procedure afforded 31 mg (76%) of the title compound as a tan, viscous oil. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; ^{1}H NMR data are for the major

diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 6.8 Hz, 2 H), 7.15–7.00 (m, 8 H), 5.45 (d, *J* = 15.6 Hz, 1 H), 5.30 (d, *J* = 15.6 Hz, 1 H), 4.11 (d, *J* = 15.2 Hz, 1 H), 3.83 (d, *J* = 15.6 Hz, 1 H), 2.96–2.90 (m, 1 H), 2.79 (q, *J* = 6.0 Hz, 1 H), 1.91 (dd, *J* = 13.4, 4.8 Hz, 1 H), 1.83 (br s, 4 H), 1.55 (dd, *J* = 12.4 Hz, 6.4 Hz, 1 H), 1.20 (br s, 4 H), 1.18–1.12 (m, 2 H), 0.57 (d, *J* = 6 Hz, 3 H); ^{13}C NMR (125 MHz, C_6H_6) δ 158.1, 137.1 136.7, 136.5, 136.4, 128.6, 128.56, 128.51, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 116.0, 60.9, 59.3, 56.4, 55.3, 54.8, 54.6, 54.5, 53.6, 47.4, 47.2, 46.5, 45.9, 25.8, 25.7, 24.1, 24.0, 17.8, 11.3; IR (film) 2933, 2173, 1585 cm^{-1}; MS (ESI+) 402.2650 (402.2652 calcd for $C_{25}H_{31}N_5$, M + H+).

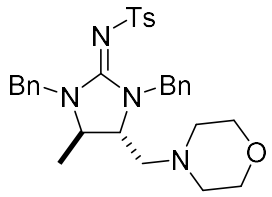


***N*-(1,3-dibenzyl-4-(morpholinomethyl)imidazolidin-2-ylidene)-4-methylbenzenesulfonamide (4-4a)**. The general procedure was followed for the coupling of *N*-{[allyl(benzyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (XX) (43.3 mg, 0.1 mmol) with morpholino benzoate **(4-S5)** (62.2 mg, 0.3 mmol). This procedure afforded 42.5 mg (82%) of the title compound as a tan, viscous oil. ^{1}H NMR (500 MHz, C_6H_6) δ 8.27 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 7 Hz, 4 H), 7.19–7.09 (m, 4 H), 7.05 (td, *J* = 7.3, 4.8 Hz, 2 H), 6.82 (d, *J* = 7.9 Hz, 2 H), 5.48 (d, *J* = 15.3 Hz, 1 H), 4.84 (d, *J* = 15.0 Hz, 1 H), 4.68 (d, *J* = 15.0 Hz, 1 H), 4.15 (d, *J* = 15.3 Hz, 1 H), 3.37–3.30 (m, 4 H), 3.14–3.07 (m, 1 H), 2.76 (t, *J* = 9.7 Hz, 1 H), 2.67 (dd, *J* = 9.8, 6.4 Hz, 1 H), 1.91 (dd, *J* = 12.5, 5 Hz, 1 H), 1.89 (s, 3 H), 1.86–1.83 (m, 2 H), 1.79–1.74 (m, 2 H), 1.67 (dd, *J* = 12.8, 6.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 142.9,

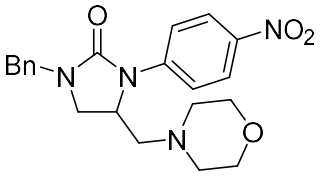
141.1, 136.2, 135.8, 129.0, 128.8, 128.7, 128.4, 128.1, 127.9, 127.8, 125.8, 66.7, 60.7, 54.1, 51.7, 50.8, 49.1, 48.7, 21.3; iR (film) 2921, 1559 cm^{-1}; MS (ESI+) 519.2422 (519.2424 calcd for $C_{29}H_{34}N_4O_3S$, M + H+).



***N*-(1,3-dibenzyl-4-(piperidin-1-ylmethyl)imidazolidin-2-ylidene)-4-methylbenzenesulfonamide (4-4b)**. The general procedure was followed for the coupling of *N*-{[Allyl(benzyl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide (43.3 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-S6)** (61.5 mg, 0.3 mmol). This procedure afforded 39 mg (76%) of the title compound as a tan, viscous oil. ^{1}H NMR (400 MHz, C_6H_6) δ 8.26 (d, *J* = 8.0 Hz, 2 H), 7.34–7.27 (m, 4 H), 7.14–6.96 (m, 6 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 5.46 (d, *J* = 15.2 Hz, 1 H), 4.82 (d, *J* = 15.0 Hz, 1 H), 4.70 (d, *J* = 15.0 Hz, 1 H), 4.22 (d, *J* = 15.3 Hz, 1 H), 3.22–3.14 (m, 1 H), 2.79 (t, *J* = 9.7 Hz, 1 H), 2.70 (dd, *J* = 9.8, 6.3 Hz, 1 H), 2.04 (dd, *J* = 12.8, 5.5 Hz, 1 H), 1.89 (s, 3H), 1.88–1.83 (m, 4 H), 1.73 (dd, *J* = 12.8, 7.1 Hz, 1 H), 1.23 (br s, 4 H), 1.17–1.12 (m, 2 H); ^{13}C NMR (100 MHz, C_6H_6) δ 156.2, 144.3, 140.4, 137.1, 136.4, 128.8, 128.6, 128.5, 128.45, 128.41, 127.4 126.2, 61.1, 54.8, 51.7, 50.8, 48.8, 48.7, 25.8, 24.0, 20.7; IR (film) 2932, 1578 cm^{-1}; MS (ESI+) 517.2633 (517.2632 calcd for $C_{30}H_{36}N_4O_2S$, M + H+).

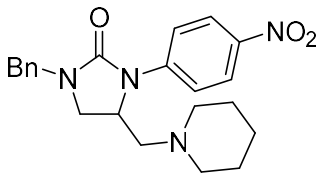


***N*-((4R,5R)-1,3-dibenzyl-4-methyl-5-(morpholinomethyl)imidazolidin-2-ylidene)-4-methylbenzenesulfonamide (4-11)**. The general procedure was followed for the coupling of *N*-{[benzyl(but-3-en-2-yl)amino](benzylamino)methylene}-4-methylbenzenesulfonamide **(4-8)** (44.8 mg, 0.1 mmol) with morpholino benzoate **(4-S5)** (62.2 mg, 0.3 mmol). This procedure afforded 46 mg (86%) of the title compound as a tan, viscous oil. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; ^{1}H NMRdata are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2 H), 7.32–7.11 (m, 12 H), 5.34–5.22 (m, 2 H), 4.23 (d, *J* = 15.2 Hz, 1 H), 4.07 (d, *J* = 15.2 Hz, 1 H), 3.55–3.50 (m, 4 H), 3.31–3.27 (m, 1 H), 3.00 (q, *J* = 4.8 Hz, 1 H), 2.37–2.32 (m, 1 H), 2.23–2.13 (m, 4 H), 2.04 (dd, *J* = 12.8, 7.6 Hz, 1 H), 0.98 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6H_6) δ 155.6, 144.2, 140.5, 136.9, 136.7, 128.8, 128.5, 128.48, 128.45, 128.3, 126.2, 66.4, 60.0, 58.8, 54.2, 54.0, 49.1, 48.0, 20.7, 18.2; IR (film) 2925, 1559 cm^{-1}; MS (ESI+) 533.2580 (533.2581 calcd for $C_{30}H_{36}N_4O_3S$, M + H+).

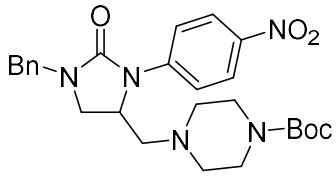


1-benzyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (4-6a). The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (31.1 mg, 0.1 mmol) with morpholino benzoate **(4-S5)** (62.2 mg, 0.3 mmol). This

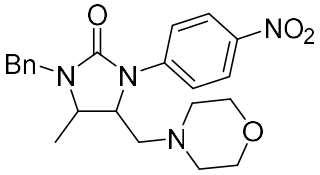
procedure afforded 46 mg (86%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, C_6H_6) δ 8.04 (d, *J* = 9.3 Hz, 2 H), 7.59 (d, *J* = 9.3 Hz, 2 H), 7.15–7.02 (m, 5 H), 4.30 –4.19 m, 2 H), 3.44–3.34 (m, 4 H), 2.85 (dd, *J* = 8.9, 2.8 Hz, 1 H), 2.75 (t, *J* = 8.7 Hz, 1 H), 1.98 (dd, *J* = 13.0, 3.1 Hz, 1 H), 1.97–1.88 (m, 2 H), 1.83–1.75 (m, 2 H), 1.71 (dd, *J* = 13.0, 9.3 Hz, 1 H); ^{13}C NMR (125 MHz, C_6H_6) δ 155.8, 145.0, 142.0, 136.6, 128.6, 128.2, 127.9, 124.6, 116.8, 66.4, 58.7, 53.8, 50.0, 47.5, 45.3; IR (film) 2921, 1709 cm^{-1}; MS (ESI+) 397.1868 (397.1870 calcd for $C_{21}H_{24}N_4O_4$, M + H+).



1-benzyl-3-(4-nitrophenyl)-4-(piperidin-1-ylmethyl)imidazolidin-2-one (4-6b). The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (31.1 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-S6)** (61.5 mg, 0.3 mmol). This procedure afforded 32.2 mg (82%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.3 Hz, 2 H), 7.75 (d, *J* = 9.3 Hz, 2 H), 7.41–7.26 (m, 5 H), 4.50–4.45 (m, 2 H), 4.30 (t, *J* = 8.8 Hz, 1 H), 3.46 (t, *J* = 8.8 Hz, 1 H), 3.33 (dd, *J* = 9.2, 2.8 Hz, 1 H), 2.54 (dd, *J* = 13.0, 3.2 Hz, 1 H), 2.43 (br s, 2 H), 2.37–2.20 (m, 3 H), 1.52–1.45 (m, 4 H), 1.40–1.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 145.5, 141.8, 136.2, 128.8, 128.2, 127.7, 124.9, 117.1, 59.8, 55.3, 51.4, 47.8, 46.2, 25.9, 23.9; IR (film) 2932, 1710 cm^{-1}; MS (ESI+) 395.2074 (395.2078 calcd for $C_{22}H_{26}N_4O_3$, M + H+).



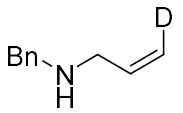
tert-Butyl 4-((1-benzyl-3-(4-nitrophenyl)-2-oxoimidazolidin-4-yl)methyl)piperazine-1-carboxylate (4-6c). The general procedure was followed for the coupling of 1-allyl-1-benzyl-3-(4-nitrophenyl)urea (31.1 mg, 0.1 mmol) with tert-butyl 4-(benzoyloxy)piperazine-1-carboxylate **(4-S7)** (91.9 mg, 0.3 mmol). This procedure afforded 21 mg (42%) of the title compound as a yellow solid, m.p. 65–68 °C. ^{1}H NMR (500 MHz, C_6H_6) δ 8.04 (d, *J* = 9.1 Hz, 2 H), 7.57 (d, *J* = 9.0 Hz, 2 H), 7.14–7.03 (m, 5 H), 4.28–4.18(m, 2 H), 3.41–3.35 (m, 1 H), 3.22 (br s, 4 H), 2.79 (dd, *J* = 8.9, 2.7 Hz, 1 H), 2.71 (t, *J* = 8.7 Hz, 1 H), 1.91–1.83 (m, 3 H), 1.81–1.72 (m, 2 H), 1.67 (dd, *J* = 13.1, 9.2 Hz, 1 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, C_6H_6) δ 155.8, 154.0, 145.0, 142.0, 136.6, 128.6, 128.2, 127.9, 124.6, 116.7, 79.1, 58.2, 53.1, 50.2, 47.5, 45.2, 28.1, 28.0; IR (film) 2927, 1693 cm^{-1}; MS (ESI+) 496.2548 (496.2554 calcd for $C_{26}H_{33}N_5O_5$, M + H+).



1-Benzyl-5-methyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (4-12): The general procedure was followed for the coupling of 1-benzyl-1-(but-3-en-2-yl)-3-(4-nitrophenyl)urea (32.5 mg, 0.1 mmol) with tert-butyl 4-(benzoyloxy)piperazine-1-carboxylate **(4-S7)** (91.9 mg, 0.3 mmol). This procedure afforded 13 mg (34%) of the title compound as a viscous yellow oil. This compound was obtained as a 2:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the major diastereomer. ^{1}H

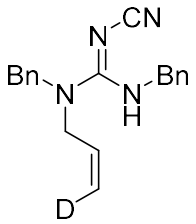
NMR (400 MHz, CDCl3) δ 8.20 (m, 2 H), 7.12 (m, 2 H), 7.37–7.24 (m, 5 H), 4.93 (d, *J* = 15.2 Hz, 1 H), 4.06 (d, *J* = 15.2 Hz, 1 H), 3.89–3.86 (m, 1 H), 3.57–3.51 (m, 5 H), 2.55–2.36 (m, 4 H), 2.29–2.23 (m, 2 H), 1.25 (d, *J* = 6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 155.6, 1445.5, 145.3, 142.3, 141.9, 136.7, 136.4, 128.8, 128.7, 128.2, 128.1, 127.8, 127.7, 125.0, 124.7, 118.9, 117.3, 66.9, 66.7, 58.8, 58.7, 55.5, 54.2, 54.0, 53.7, 51.9, 51.1, 45.1, 45.0, 18.9, 13.0; IR (film) 2923, 1708; MS (ESI+) 411.2027 (411.2027 calcd for $C_{22}H_{26}N_4O_4$, M + H+).

Synthesis of deuterated substrates and products

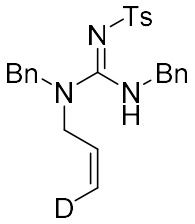


(Z)-*N*-benzylprop-2-en-3-d-1-amine (4-S8). A flame dried flask was cooled under a stream of nitrogen and charged with *N*-benzylprop-2-en-1-ylamine (1.00 g, 6.84 mmol) and diethyl ether (12 mL). The solution was cooled to -42 °C, and then n-butyl lithium (8.2 mmol, 2.5 M) was added slowly. After 30 minutes tert-butyl lithium (15 mmol, 1.7 M) was added slowly. After stirring at -42 °C for 30 minutes the reaction was transferred to an ice-water bath and allowed to stir for 1 hour. The reaction was then cooled to -78 °C, and deuterium oxide was added (2.5 mL, 136.8 mmol). After stirring overnight the reaction was cooled on an ice-water bath, and then quenched with water (15 mL). The mixture was extracted with diethyl ether (2 x 20 mL) and separated. The combined organic layers were then dried, filtered, and evaporated. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes) to afford 0.568 g (56%) of the title compound as a pale yellow oil, with 84% deuterium incorporation as determined by ^{1}H

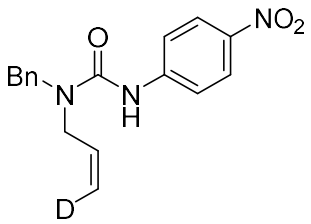
NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 4.5 Hz, 4 H), 7.2–7.18 (m, 1 H), 6.03–5.79 (m, 1 H), 5.22–5.15 (m, 1 H), 5.12–5.06 (m, 1 H), 3.78 (s, 3 H), 3.27 (d, 6 Hz, 2 H).



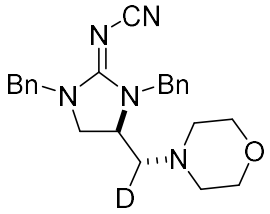
1-[(*Z*)-allyl-3-d]-1,3-dibenzyl-2-cyanoguanidine (4-13).[73] A round bottom flask was charged with methyl *N*-benzyl-*N*'-cyanocarbamimidothioate **(4-S1)** (0.196 g, 0.96 mmol), ethanol (10 mL), and mercuric oxide (0.312 g, 1.44 mmol), then purged with nitrogen. Triethylamine (0.5 mL, 3.84 mmol) was added followed by (Z)-*N*-benzylprop-2-en-3-d-1-amine **(4-S8)** (0.170 g, 1.15 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes to yield 0.153 g (52%) of the title compound as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 6 H), 7.24-7.18 (m, 4 H), 5.80–5.72 (m, 1 H), 5.23 (d, *J* = 10.4 Hz, 1 H), 5.15 (d, *J* = 17.2 Hz, 1 H), 4.98 (br, 1 H), 4.74 (d, *J* = 5.2 Hz, 2 H), 4.58 (s, 2 H), 3.95 (d, *J* = 5.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.1, 135.8, 129.0, 128.9, 128.0, 127.9, 127.7, 127.3, 118.2 (t, *J* = 23.5 Hz, 117.2, 52.2, 51.4, 47.5; IR (film) 3249, 2162, 1536 cm^{-1}; MS (ESI+) 306.1827 (306.1823 calcd for $C_{19}H_{19}DN_4$, M + H^+).



***N*-{[(*Z*)-allyl-3-d](benzyl)amino}-benzylaminomethylene-4-methylbenzenesulfonamide (4-15).**[73] A round bottom flask was charged with dimethyl tosylcarbonimidodithioate **(4-S3)** (0.569 g, 1.70 mmol), ethanol (17 mL), and mercuric oxide (0.548 g, 2.53 mmol), then purged with nitrogen. Triethylamine (0.95 mL, 6.75 mmol) was added followed by (Z)-*N*-benzylprop-2-en-3-d-1-amine **(4-S8)** (0.300 g, 2.0 mmol). The reaction mixture was then stirred at rt for 72 h. The mixture was filtered through celite. The celite was rinsed with acetone, and the solution was concentrated *in vacuo*. The crude product was purified via flash column chromatography on silica gel (ethyl acetate/hexanes) to yield 0.363 g (49%) of the title compound as a white solid, m.p. 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2 H), 7.33–7.20 (m, 6 H), 7.18–7.06 (m, 6 H), 6.96 (br, 1 H), 5.75–5.67 (m, 1 H), 5.16 (d, J = 10.4 Hz, 1 H), 5.08 (d, J = 17.3 Hz, 1 H), 4.47 (s, 2 H), 4.37 (d, J = 5.9 Hz, 2 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 141.7, 141.0, 136.9, 136.4, 132.3, 129.1, 128.9, 128.7, 128.0, 127.61, 127.6, 127.58, 127.4, 126.0, 118.6 (t, J = 25 Hz), 51.8, 51.75, 49.7; IR (film) 3322, 1564 cm^{-1}; MS (ESI+) 435.1965 (435.1960 calcd for $C_{25}H_{26}DN_3O_2S$, M + H$^+$).

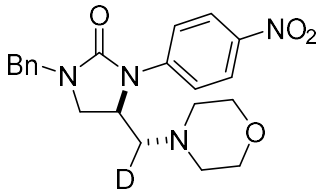


(Z)-1-(allyl-3-d)-1-benzyl-3-(4-nitrophenyl)urea (4-14). A flame dried flask was cooled under a stream of nitrogen and charged with *p*-nitrophenyl isocyanate (0.244 g, 1.48 mmol) in DCM (1.5 mL). (Z)-*N*-benzylprop-2-en-3-d-1-amine **(4-S8)** (0.220 mg, 1.48 mmol) was then added, and the reaction stirred at rt overnight. The reaction mixture was then concentrated *en vacuo*, and the crude product was purified via flash column chromatography on silica gel to afford 0.245 g (53%) of the title compound as a yellow solid, m.p. 108–110 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.89 (d, *J* = 9.2 Hz, 2 H), 7.12–7.04 (m, 7 H), 6.17 (s, 1 H), 5.37–5.30 (m, 1 H), 4.83–4.76 (m, 2 H), 4.17 (s, 2 H), 3.34 (d, *J* = 4.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 145.3, 142.5, 136.9, 133.3, 129.1, 128.0, 127.5, 125.0, 118.3, 117.8 (t, *J* = 23.6 Hz), 50.9, 50.2; IR (film) 3346, 1652 cm^{-1}; MS (ESI+) 313.1405 (313.1405 calcd for $C_{17}H_{16}N_3O_3$, M + H+).

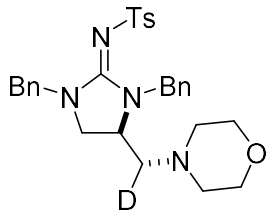


***N*-((S)-1,3-dibenzyl-4-((R)-morpholinomethyl-d)imidazolidin-2-ylidene)cyanamide (4-16)**. The general procedure was followed for the coupling of 1-[(*Z*)-allyl-3-d]-1,3-dibenzyl-2-cyanoguanidine **(4-13)** (30.5 mg, 0.1 mmol) with morpholino benzoate **(4-S5)** (62.2 mg, 0.3 mmol). This procedure afforded 26 mg (67%) of the title compound as a tan, viscous oil. This compound was obtained as a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, C_6H_6) δ 7.17–7.12 (m, 4 H), 7.11–6.98 (m, 6 H), 5.25 (d, *J* = 15.5 Hz, 1 H), 4.52 (q, *J* = 15.1 Hz, 2 H), 4.08–4.02 (m, 1 H), 3.29 (br s, 4 H), 3.01 (q, *J* = 7.4 Hz, 1 H), 2.65 (dd, *J* = 11.5, 7.3 Hz, 1 H), 2.54

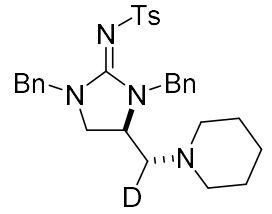
(q, *J* = 8.2 Hz, 1 H), 1.89–1.84 (m, 1 H), 1.78–1.68 (m, 4 H), 1.58–1.51 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 135.9, 135.4, 128.9, 128.8, 128.2, 128.1, 128.0, 127.9, 66.7, 60.5 (t, *J* = 21.9 Hz), 54.0, 51.8, 49.5, 49.3, 47.8; IR (film) 2924, 2169, 1583 cm^{-1}; MS (ESI+) 391.2355 (391.2351 calcd for $C_{23}H_{26}DN_5O$, M + H+).



(S)-1-benzyl-4-((R)-morpholinomethyl-d)-3-(4-nitrophenyl)imidazolidin-2-one (4-17). The general procedure was followed for the coupling of (*Z*)-1-(allyl-3-d)-1-benzyl-3-phenylurea **(4-14)** (31.2 mg, 0.1 mmol) with with morpholino benzoate **(4-S5)** (62.2 mg, 0.3 mmol). This procedure afforded 28 mg (70%) of the title compound as a yellow . This compound was obtained as a 5.7:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, C_6H_6) δ 8.04 (d, *J* = 9.3 Hz, 2 H), 7.61 (d, *J* = 9.3 2 H), 7.14–7.02 (m, 5 H), 4.31–4.19 (m, 2 H), 3.52–3.24 (m, 5 H), 2.85 (dd, *J* = 8.9, 2.8 Hz, 1 H), 2.75 (t, *J* = 8.7 Hz, 1 H), 1.95–1.88 (m, 3 H), 1.83–1.79 (m, 2 H), 1.72 (dd, *J* = 13.7, 9.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 145.2, 142.0, 136.1, 128.8, 128.3, 127.9, 124.9, 117.4, 66.7, 58.9 (t, *J* = 19.0 Hz), 54.2, 50.8, 47.8, 45.9; IR (film) 2922, 1710 cm^{-1}; MS (ESI+) 398.1929 (398.1933 calcd for $C_{21}H_{23}DN_4O_4$, M + H+).



***N*-((S)-1,3-dibenzyl-4-((R)-morpholinomethyl-d)imidazolidin-2-ylidene)-4-methylbenzenesulfonamide (4-18)**. The general procedure was followed for the coupling of *N*-{[(Z)-allyl-3-d](benzyl)amino}-benzylaminomethylene-4-methylbenzenesulfonamide **(4-15)** (43.5 mg, 0.1 mmol) with morpholino benzoate **(4-S5)** (62.2 mg, 0.3 mmol). This procedure afforded 39 mg (75%) of the title compound as a tan, viscous oil. This compound was obtained as a 6:1 mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (400 MHz, C_6H_6) δ 8.26 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 6.8 Hz, 4 H), 7.20–6.98 (m, 6 H), 6.81 (d, *J* = 8.1 Hz, 2 H), 5.47 (d, *J* = 15.4 Hz, 1 H), 4.83 (d, *J* = 15.0 Hz, 1 H), 4.66 (d, *J* = 14.9 Hz, 1 H), 4.12 (d, *J* = 15.3 Hz, 1 H), 3.33 (br s, 4 H), 3.15–3.05 (m, 1 H), 2.75 (t, *J* = 9.7 Hz, 1 H), 2.66 (d, *J* = 7.3 Hz, 1 H), 1.92–1.87 (m, 4 H), 1.84–1.70 (m, 4 H), 1.77–1.72 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 142.9, 141.2, 136.1, 135.7, 129.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 125.8, 66.7, 60.2 (t, *J* = 19 Hz), 54.1, 51.6, 50.8, 49.0, 48.7, 21.4; IR (film) 2922, 1559 cm^{-1}; MS (ESI+) 520.2482 (520.2487 cacld for $C_{29}H_{33}DN_4O_3S$, M + H+).



***N*-((S)-1,3-dibenzyl-4-((R)-piperidin-1-ylmethyl-d)imidazolidin-2-ylidene)-4-methylbenzenesulfonamide (4-19)**.The general procedure was followed for the

coupling of *N*-{[(Z)-allyl-3-d](benzyl)amino}-benzylaminomethylene-4-methylbenzenesulfonamide **(4-15)** (43.5 mg, 0.1 mmol) with piperidin-1-yl benzoate **(4-S6)** (61.5 mg, 0.3 mmol). This procedure afforded 40 mg (77%) of the title compound as a tan, viscous oil. This compound was obtained as a mixture of diastereomers as judged by ^{1}H NMR analysis; data are for the mixture. ^{1}H NMR (500 MHz, C_6H_6) δ 8.26 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 7.5 Hz, 2 H), 7.15–7.07 (m, 4 H), 7.05–7.00 (m, 2 H), 6.82 (d, *J* = 8 Hz, 2 H), 5.46 (d, *J* = 15 Hz, 1 H), 4.82 (d, *J* = 14.5 Hz, 1 H), 4.65 (d, *J* = 15.5 Hz, 1 H), 4.22 (d, *J* = 15 Hz, 1 H), 3.19 (q, *J* = 9.5 Hz, 1 H), 2.80 (t, *J* = 9.5 Hz, 1 H), 2.72 (dd, *J* = 16.5 Hz, 6.5 Hz, 1 H), 2.05–2.00 (m, 1 H), 1.89 (s, 3 H), 1.86 (br s, 4 H), 1.76–1.71 (m, 1 H); ^{13}C NMR (125 MHz, C_6H_6) δ 156.2, 144.3, 140.4, 137.1, 136.5, 128.8, 128.6, 128.7, 128.6, 128.5, 128.4, 127.5, 126.2, 60.7 (t, *J* = 22 Hz), 54.8, 51.7, 50.8, 48.8, 48.7, 25.8, 24.1, 20.7; IR (film) 2931, 1559 cm^{-1}; MS (ESI+) 518.2692 (518.2695 calcd for $C_{30}H_{35}DN_4O_2S$, M + H+).

References

1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

2) a)Schwartz, R. E.; et al. *J. Antibiot.* **1988**, *41*, 1774–1779. b) Sobin, B. A.; Tanner Jr., F. W. *J. Am. Chem. Soc.* **1954**, *76*, 4053. c) Shibano, M.; Kitagawa, S.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 505–508.

3) Shi, M.: Liu, L.P.; Tang, J. *Org Lett.*, **2006**, *8*, 4043-4046.

4) Cardillo, G.; Orena, M. *Tetrahedron,* **1990**, 46, 3321–3408.

5) Hegedus, L. S. *J. Mol. Catal*. **1983**, *19*, 201-211.

6) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328-6335.

7) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.*, **2008**, *73*, 8851-8860.

8) Betrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447-66459.

9) Duy N. Mai, Brandon R. Rosen, and John P. Wolfe, *Org. Lett.* **2011**, *13*, 2932-2935.

10)Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. Eur. J.* **2014**, *20*, 8782–8790.

11)a) Berlinck, R. G. S.; Romminger, S. *Nat. Prod. Rep*. **2016**, *33*, 456. b) Berlinck, R. G. S.; Trindade-Silva, A. E.; Santos, M. F. C. *Nat. Prod. Rep*. **2012**, *29*, 1382−1406. c) Berlinck, R. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. *Nat. Prod. Rep*. **2010**, *27*, 1871−1907.

12)For reviews, see: a) Wolfe, J. P. *Eur. J. Org. Chem*. **2007**, 517–582; b) Wolfe, J. P. *Synlett*, **2008**, 2913–2937; c) Schultz, D. M.; Wolfe, J. P. *Synthesis*, **2012**, *44*, 351–361; d) Wolfe, J. P. *Top. Heterocycl. Chem*. **2013**, *32*, 1–38.

13)a) Ney, J. E.; Wolfe, J. P. *Angew. Chem*. **2004**, *116*, 3689–3692; *Angew. Chem. Int. Ed*. **2004**, *43*, 3605–3608; b) Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal*. **2005**, *347*, 1614–1620; c) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447–6459; d) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem*. **2009**, *74*, 2533–2540.

14)For examples of Cu-catalyzed intramolecular carboamination reactions of *N*-tosyl aminoalkene derivatives, see: a) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc*. **2007**, *129*, 12948–12949; b) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem*. **2007**, *72*, 3896–3905; c) Miao, L.; Haque, I.; Manzoni, M. R.;

Tham, W. S.; Chemler, S. R. *Org. Lett*. **2010**, *12*, 4739–4741; d) Casavant, B. J.; Hosseini, A. S.; Chemler, S. R. *Adv. Synth. Catal*. **2014**, *356*, 2697–2702.

15) For examples of Cu-catalyzed intermolecular carboamination reactions between alkenes and *N*-tosyl aminoalkene derivatives, see: Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc*. **2012**, *134*, 2020–2023.

16) For examples of Au-catalyzed carboamination reactions between boronic acids and N-tosyl aminoalkene derivatives, see: a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc*. **2010**, *132*, 1474–1475; b) Brenzovich Jr, W. E.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard III, W. A.; Toste, F. D. *Angew. Chem*. **2010**, *122*, 5651–5654; *Angew. Chem. Int. Ed*. **2010**, *49*, 5519–5522; c) Tkatchouk, E.; Mankad, N. P.; Benitez, D.; Goddard III, W. A.; Toste, F. D. *J. Am. Chem. Soc*. **2011**, *133*, 14293–14300; d) Zhu, S.; Ye, L.; Wu, W.; Jiang, H. *Tetrahedron*, **2013**, *69*, 10375–10383.

17) For an example of a dual photoredox/gold-catalyzed carboamination reaction between aryl diazonium salts and aminoalkene derivatives, see: a) Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Adv. Synth. Catal*. **2014**, *356*, 2794–2800; b) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc*. **2013**, *135*, 5505–5508.

18) a) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 6276–6277; b) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *Organometallics* **2011**, *30*, 1269–1277.

19) Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. Eur. J*. **2014**, *20*, 8782–8790.

20) a) Surry, D. S.; Buchwald, S. L. *Chem. Sci*. **2011**, *2*, 27–50; b) Surry, D. S.; Buchwald, S. L. *Angew. Chem*. **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed*. **2008**, *47*, 6338–6361.

21) Amatore, C.; Jutand, A.; *J. Organomet. Chem*. **1999**, *576*, 254–278.

22) Our prior studies have shown factors that facilitate generation of cationic palladium intermediates (such as polar solvents, non-coordinating triflate ligands, and electron-rich phosphine ligands) promote the anti-aminopalladation pathway. See ref.[19]

23) Mai, D. N.; Rosen, B. R.; Wolfe, J. P. *Org. Lett*. **2011**, *13*, 2932–2935.

24) We have previously described the conversion of nonracemic 12 to (+)-aphanorphine via cleavage of the *N*-tosyl group, *N*-methylation, and *O*-demethylation. See ref.[23]

25) Stahl has previously illustrated that bases, ligands, and oxidants influence syn- vs. anti-aminopalladation pathways in Wacker-type oxidative cyclizations of aminoalkenes. See: a) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc*. **2007**, *129*, 6328–6335; b) Weinstein, A. B.; Stahl, S. S. *Angew. Chem*. **2012**, *124*, 11673–11677; *Angew. Chem. Int. Ed*. **2012**, *51*, 11505–11509; c) Ye, X.; White, P. B.; Stahl, S. S. *J. Org. Chem*. **2013**, *78*, 2083–2090; d) Martinez, C.; Wu, Y.; Weinstein, A. B.; Stahl, S. S.; Liu, G.; Muniz, K. *J. Org. Chem*. **2013**, *78*, 6309–6315.

26)For reviews on stereochemical pathways in alkene aminopalladation reactions, see: a) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev*. **2011**, *111*, 2981–3019; b) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem*. **2008**, *6*, 4083–4088.

27)For examples of Pd-catalyzed carboamination reactions that proceed via C-H functionalization of solvent followed by anti-aminopalladation of the alkene, see: a) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc*. **2009**, *131*, 9488–9489; b) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc*. **2009**, *131*, 15945–15951.

28)It is also possible the diminished selectivity derives from a diminished preference for axial vs. equatorial orientation of the substituent at the 2-position in tosyl protected substrates. However, studies on addition of nucleophiles to N-tosyliminium ions suggest the tosyl group enforces axial orientation of 2-substituents to minimize A1,3-strain in a manner comparable to acyl or boc groups. See: Silveira, C. C.; Felix, L. A.; Braga, A. L.; Kaufman, T. S. *Org. Lett*. **2005**, *7*, 3701–3704.

29)Zavesky, B. P.; Babij, N. R.; Wolfe, J. P. *Org. Lett*. **2014**, *16*, 4952–4955.

30)White, P. B.; Stahl, S. S. *J. Am. Chem. Soc*. **2011**, *133*, 18594–18597.

31)Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett*. **2002**, *4*, 4717– 4718.

32)Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 12157–12159.

33)Pinkho, P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett*. **2003**, *5*, 239.

34)Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc*. **2010**, *132*, 1474–1475.

35)Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc*. **2009**, *131*, 16354–16355.

36)Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett*. **2005**, *7*, 2575–2578.

37)Thai, K.; Wang, L.; Dudding, T.; Bilodeau, F.; Gravel, M. *Org. Lett*. **2010**, *12*, 5708–5711.

38)Dang, L.; Liang, L.; Qian, C.; Fu, M.; Ma, T.; Xu, D.; Jiang, H.; Zeng, W. *J. Org. Chem*. **2014**, *79*, 769–776.

39)W. K. Anderson, G. Lai, Synthesis 1995, 1287–1290.

40)Pan, Z.; Pound, S. M.; Rondla, N. R.; Douglas, C. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 5170– 5174.

41)Teichert, J. F.; Fananas-Mastral, M.; Feringa, B. L. *Angew. Chem. Int. Ed*. **2011**, 50, 688– 691.

42) Zhu, S.; Ye, L.; Wu, W.; Jiang, H. *Tetrahedron*. **2013**, *69*, 10375–10383.

43)Massah, A. R.; Ross, A. J.; Jackson, R. F. W. *J. Org. Chem*. **2010**, *75*, 8275–8278.

44)Mai, D. N.; Rosen, B. R.; Wolfe, J. P. *Org. Lett*. **2011**, *13*, 2932–2935.

45)Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem*. **2008**, *73*, 8851–8860.

46)For recent reviews on guanidine-containing natural products, see: a) Berlinck, R. G. S.; Romminger, S. *Nat. Prod. Rep*. **2016**, *33*, 456. b) Berlinck, R. G. S.; Trindade-Silva, A. E.; Santos, M. F. C. *Nat. Prod. Rep*. **2012**, *29*, 1382−1406. c) Berlinck, R. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. *Nat. Prod. Rep*. **2010**, *27*, 1871−1907.

47)For reviews on the synthesis of natural products that contain cyclic guanidines, see: a) Ma, Y.; De, S.; Chen, C. *Tetrahedron* **2015**, *71*, 1145. b) Aron, Z. D.; Overman, L. E. *Chem. Commun*. **2004**, 253. c) Heys, L.; Moore, C. G.; Murphy, P. *J. Chem. Soc. Rev*. **2000**, *29*, 57.

48)Alkene diamination: a) Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun*. **2008**, 2334−2336. b) Zhao, B.; Du, H.; Shi, Y. *Org. Lett*. **2008**, *10*, 1087−1090. C−H functionalization: c) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, *J. Org. Lett*. **2006**, *8,* 1073−1076. Oxidative amination: d) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc*. **2008**, *130*, 12630−12631. Hydroamination: e) Bhonde, V. R.; Looper, R. E. *J. Am. Chem. Soc*. **2011**, *133*, 20172−20174. f) Gibbons, J. B.; Gligorich, K. M.; Welm, B. E.; Looper, R. E. *Org. Lett*. **2012**, *14*, 4734−4737. g) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem., Int. Ed*. **2009**, *48*, 3116−3120. h) Kwon, K.-H.; Serrano, C. M.; Koch, M.; Barrows, L. R.; Looper, R. E. *Org. Lett*. **2014**, *16*, 6048. i) Garlets, Z. J.; Silvi, M.; Wolfe, J. P. *Org. Lett*. **2016**, *18*, 2331−2334. Ring expansion of aziridines: j) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem*. **2000**, *65*, 5887−5890. Allylic alkylation: k) Büchi, G.; Rodriguez, A. D.; Yakushijin, K. *J. Org. Chem*. **1989**, *54*, 4494−4496. Carbenylative amination: l) Kitamura, M.; Yuasa, R.; Van Vranken, D. L. *Tetrahedron Lett*. **2015**, *56*, 3027.

49)For other recent approaches to the synthesis of saturated cyclic guanidines that do not utilize metal catalysts, see: a) Mailyan, A. K.; Young, K.; Chen, J. L.; Reid, B. T.; Zakarian, A. *Org. Lett*. **2016**, *18*, 5532. b) Fedoseev, P.; Sharma, N.; Khunt, R.; Ermolat'ev, D. S.; Van der Eycken, E. V. *RSC Adv*. **2016**, *6*, 75202. c) Daniel, M.; Blanchard, F.; Nocquet-Thibault, S.; Cariou, K.; Dodd, R. H. *J. Org. Chem*. **2015**, *80*, 10624.

50)Zavesky, B. P.; Babij, N. R.; Fritz, J. A.; Wolfe, J. P. *Org. Lett*. **2013**, *15*, 5420.

51)Zavesky, B. P.; Babij, N. R.; Wolfe, J. P. *Org. Lett*. **2014**, *16*, 4952.

52)a) Wenzel, M.; Light, M. E.; Davis, A. P.; Gale, P. A. *Chem. Commun*. **2011**, *47*, 7641. b) Perez-Medrano, A.; Brune, M. E.; Buckner, S. A.; Coghlan, J. J.; Fey, T. A.; Gopalakrishnan, M.; Gregg, R. J.; Kort, M. E.; Scott, V. E.; Sullivan, J. P.; Whiteaker, K. L.; Carroll, W. A. *J. Med. Chem*. **2007**, *50*, 6265. c) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem*. **1977**, *20*, 901.

53) For reviews, see: a) Garlets, Z. J.; White, D. R.; Wolfe, J. P. Asian. *J. Org. Chem*. **2017**, in press, doi: 10.1002/ajoc.201600577. b) Wolfe, J. P. *Top. Heterocycl. Chem*. **2013**, *32*, 1. c) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351.

54) The relative stereochemistry of products illustrated in Scheme 3-1 and eqs 3-4−3-6 was assigned by ^{1}H NMR NOE experiments. See the Supporting Information for complete details.

55) a) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838. b) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett*. **2006**, *8*, 2531.

56) a) Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem. - Eur. J*. **2014**, *20*, 8782. (b) Babij, N. R.; McKenna, G. M.; Fornwald, R. M.; Wolfe, J. P. *Org. Lett*. **2014**, *16*, 3412.

57) The low yield of **3-8n** is due to competing base-mediated hydroamination of the starting material. This hydroamination side reaction was not observed with the less nucleophilic *N*-tosyl guanidine substrates.

58) In our prior studies on Pd-catalyzed carboamination reactions of PMP-protected guanidines with aryl bromides (ref 1) we observed the stereochemistry of a product closely related to 8n resulted from *syn*-addition to a *Z*-alkene. This assignment was originally based on analogy to the outcome of reactions of related ureas, and has since been confirmed via NOE studies.

59) For a detailed discussion of epimerization via β-hydride elimination pathways that occur after alkene heteropalladation in the conversion of 4-penten-1-ol derivatives to substituted tetrahydrofurans, see: Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc*. **2005**, *127*, 16468.

60) *Syn*-heteropalladation reactions are believed to proceed via organized chair-like transition states that result from a need for an eclipsed orientation between the Pd−N bond and the alkene. In general, reactions that proceed via syn-heteropalladation provide products similar to 8k and 9h with much higher selectivities than in analogous transformations that involve anti-heteropalladation. For further discussion, see: Peterson, L. J.; Wolfe, J. P. *Adv. Synth. Catal*. **2015**, *357*, 2339.

61) a) Fujino, M.; Wakimasu, M.; Kitada, C*. Chem. Pharm. Bull*. **1981**, *29*, 2825. b) Wakimasu, M.; Kitada, C.; Fujino, M. *Chem. Pharm. Bull*. **1982**, *30*, 2766.

62) Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett*. **2002**, *4*, 4717–4718.

63) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838–6852.

64) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076–3086.

65) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997–1000.

66)a) Becke, A. D. *J.Chem.Phys*. **1993**, *98*, 5648–5652. b) Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev*. **1988**, *37*, 785–789. c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys*. **1980**, *58*, 1200–1211. d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J.Phys.Chem*. **1994**, *98*, 11623–11627.

67)Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio Jr., R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C-P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W. Z.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock III, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. *Phys. Chem. Chem. Phys*. **2006**, *8*, 3172. Spartan'14; Wavefunction, Inc.: Irvine, CA, 2014.

68)For general reviews on 1,2-diamines, see: a) Bennani, Y. L.; Hanessian, S. *Chem. Rev*. **1997**, *97*, 3161. b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed*. **1998**, *37*, 2580. c) Viso, A.; de la Pradilla, R. F.; García, A.; Flores, A. *Chem. Rev*. **2005**, *105*, 3167. d) Bogatcheva, E.; Hanrahan, C.; Nikonenko, B.; Samala, R.; Chen, P.; Gearhart, J.; Barbosa, F.; Einck, L.; Nacy, C. A.; Protopova, M. *J. Med. Chem*. **2006**, *49*, 3045. e) Kizirian, J.-C. *Chem. Rev*. **2008**, *108*, 140. f) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des*. **2006**, *67*, 101. g) Grygorenko, O. O.; Radchenko, D. S.; Volochnyuk, D. M.; Tomalchev, A. A.; Komarov, I. V. *Chem. Rev*. **2011**, *111*, 5506.

69)Wei, X.; Henriksen, N. M.; Skalicky, J. J.; Harper, M. K.; Cheatham, T. E., III; Ireland, C. M.; Van Wagoner, R. M. *J. Org. Chem*. **2011**, *76*, 5515–5523., For recent reviews on guandine-containing natural products, see: a) Berlinck, R. G. S.; Trindade-Silva, A. E.; Santos, M. F. C. *Nat. Prod. Rep*. **2012**, *29*, 1382–1406. b) Berlinck, R. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. *Nat Prod. Rep*. **2010**, *27*, 1871–1907. c) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep*. **2008,** *25*, 919–954.

70)Peterson, L. J.; Luo, J.; Wolfe, J. P. *Organic Letters* **2017,** *19,* 2817-2820.
71)He, J.; Shigenari, T.; Yu, J.-Q. *Angew. Chem. Int. Ed*, **2015**, *54*, 6545.
72)Shen, K.; Wang, Q. *Chem. Sci*., **2015**, *6*, 4279.
73)Ward, A. F.; Wolfe, J. P.*Chem. Commun.* **2012,** *48*, 609-611.

74)Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998,** *37*, 2387.

75)Biloski, A. J.; Ganem, B. *Synthesis* **1983,** *7*, 537–538.