

Synthesis of Cyclic Guanidines via Pd-Catalyzed Carboamination Reactions

by

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Abstract

Cyclic guanidines are an interesting class of molecules that show a wide range of interesting biological activity, including cytotoxicity, antimicrobial activity, and antibiotic activity. Unfortunately, many of these molecules are isolated from sources that are difficult to obtain, such as marine sponges, making acquiring large quantities of these compounds difficult. Existing methodology for fashioning this moiety does not allow for the facile construction of analogues. To address this limitation, the research in this thesis is dedicated to the development of creating structurally complex cyclic guanidines from easily obtainable acyclic guanidine substrates. This research also aims to create these structures in a manner that is amenable to rapid analogue generation.

In all, this dissertation focuses on Pd-catalyzed carboamination reactions that can prepare cyclic guanidines from simple precursors. Chapter 2 of this dissertation detail the development of a new approach to the synthesis of substituted 5-membered saturated cyclic guanidines. Palladium-catalyzed alkene carboamination reactions between acyclic *N*-allyl guanidines and aryl or alkenyl halides provide these products in good yield. This method allows access to a number of different cyclic guanidine derivatives in only two steps from readily available allylic amines. Chapter 3 expands upon this methodology by utilizing *N*-propargyl guanidines and aryl triflates in a carboamination reaction to afford the corresponding 2-aminoimidazole products. The utility of this reaction was demonstrated in the synthesis of the 2-aminoimidazole natural product preclathridine A.

Chapter 1

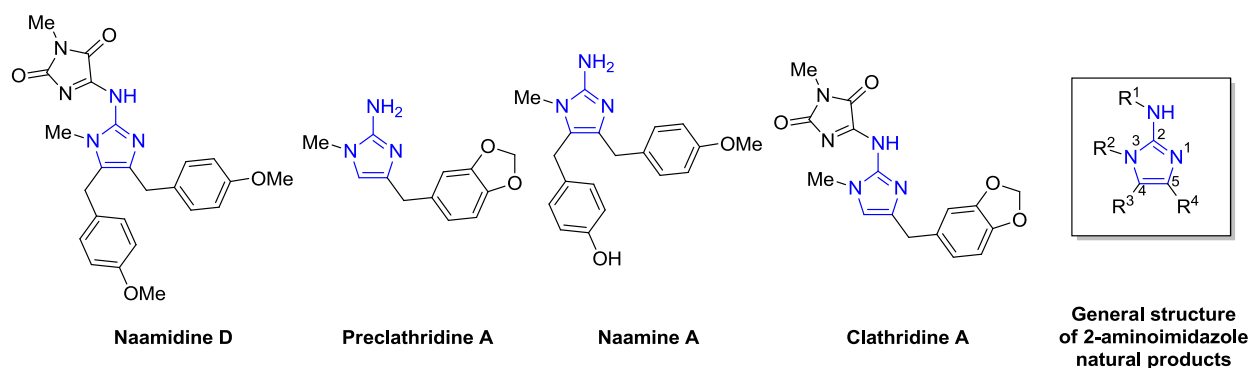
Previous Strategies for the Synthesis of Guanidines

1.1 Introduction: Biological Activity and Structural Characteristics of Mono-Cyclic Guanidines

Cyclic guanidine natural products have garnered widespread attention due to their useful biological activity. Many of these alkaloids, which are most commonly extracted from marine sponges, contain 2-aminoimidazole rings (Figure 1.1). These molecules exhibit biological activities such as cytotoxicity,^{1,2} antimicrobial activity,³⁻⁵ and antibiotic activity.⁶ Furthermore, these molecules have been shown to be human β -secretase (BACE1) inhibitors,^{7,8} tubulin-binding agents,^{9,10} nitric oxidesynthase inhibitors,⁶ and epidermal growth factor receptor inhibitors.^{2,11,12} As a result, molecules containing this structural motif have recently emerged as important pharmacophores in biomedical research.

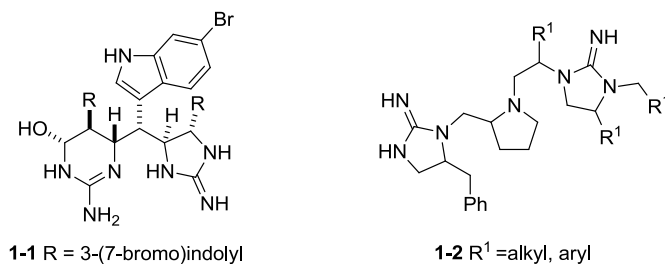
Representative examples of the different classes of 2-aminoimidazole containing natural products are shown in Figure 1.1. An identifying feature of these structures is the amino group on C-2. This amino group can be a secondary amine, as in the cases of the naamidine and clathridine family. The N-1 atom is most commonly substituted with a methyl group, while the N-3 position lacks substitution in most cases. This class of natural products gains most of its structural diversity through different substitution at the C-4 and C-5 position. In the naamidine and naamine family a substituent is linked to C-4 and C-5, while the preclathridine and clathridine family only features a substituent at C-5. Finally, the aromatic rings present in these molecules are typically oxygen rich.

Figure 1.1 2-Aminoimidazole natural products

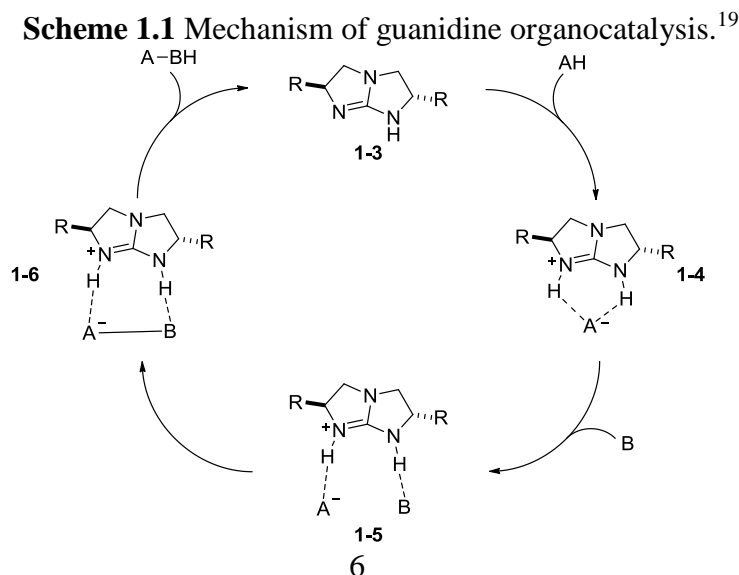


Five-membered saturated cyclic guanidine subunits are displayed in a number of natural products such as the araiosamines (e.g., araiosamine A, **1-1**)¹³ and the plumbagine alkaloids.^{12,14,15} These structures are also featured in a number of synthetic molecules with highly interesting biological activities. For example, simple monocyclic guanidine derivatives of general structure **1-2** have demonstrated potent antimicrobial activity against drug-resistant Gram-positive bacteria including MRSA (methicillin-resistant *Staphylococcus aureus*).¹⁶⁻¹⁸

Figure 1.2 Saturated 5-membered heterocyclic guanidine natural products

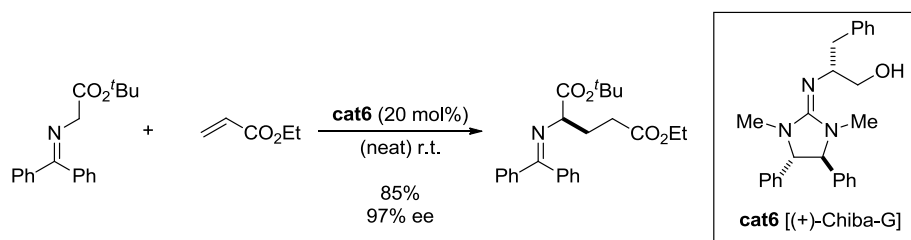


Moreover, cyclic guanidines are synthetically useful organocatalysts.¹⁹ These organocatalysts can work by acting as Brønsted bases according to the catalytic cycle depicted in Scheme 1.1.²⁰ This general catalytic cycle begins with the deprotonation of substrate AH by the guanidine base **1-3** to form the hydrogen bonding ion pair **1-4**. B is then activated via another hydrogen bond, and the adduct A-B⁻ adduct is formed. After protonation, the desired product A-BH is released, and the guanidine organocatalyst is regenerated.



Monocyclic guanidines have also been employed as chiral organocatalysts. In 2000, Ishikawa and co-workers synthesized the cyclic guanidine (+)-Chiba-G (**cat6**), which is able to catalyze the reaction between imines and Michael acceptors, inducing high levels of enantioselectivity.²⁰ The hydroxyl group in **cat6** is an important secondary hydrogen bond donor, without this functional group, no reaction is observed.

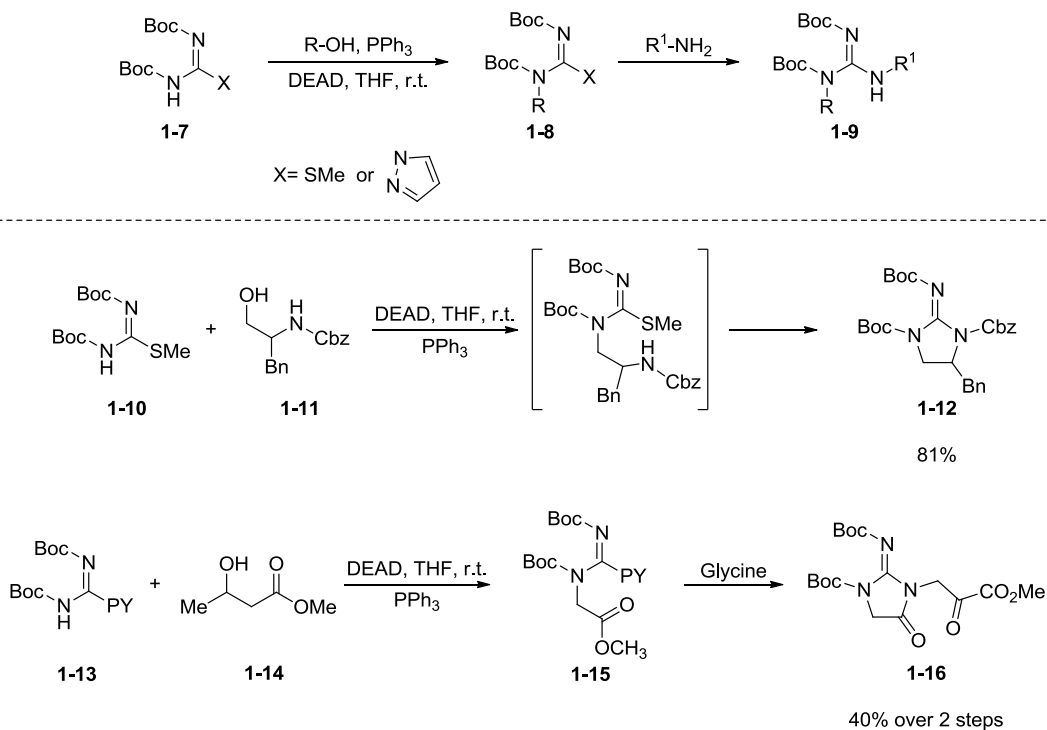
Scheme 1.2 The cyclic guanidine (+)-Chiba-G used as a chiral organocatalyst.²⁰



1.2 Previous Strategies and Limitations for the Cyclization of Guanidines

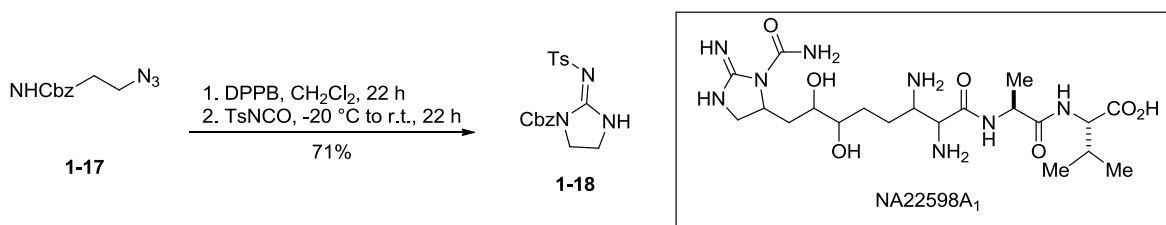
Many research groups have developed methodology for the efficient cyclization of guanidines.^{21–29} Kim and co-workers developed an approach for the synthesis of disubstituted guanidines through the use of a Mitsunobu reaction followed by the addition of a primary amine to the recently formed guanylating agent. While developing this methodology, an interesting way of constructing cyclic guanidines was discovered.²⁵ Interestingly, if an alcohol with a tethered amine (**1-11**) is coupled to the substrate, the compound can undergo cyclization *in situ* after undergoing the Mitsunobu reaction. Similarly, if a tethered ester is present in the alcohol (**1-14**), the Mitsunobu product can be sequentially treated with a primary amine to afford the cyclic guanidine product. While this reaction proceeds in good yield for primary alcohols, secondary alcohols are not well tolerated, making functionalization at C5 on the cyclic guanidine difficult to accomplish.

Scheme 1.3 Cyclization of guanidines via the addition of alcohols to guanylation agents under Mitsunobu conditions.²⁵



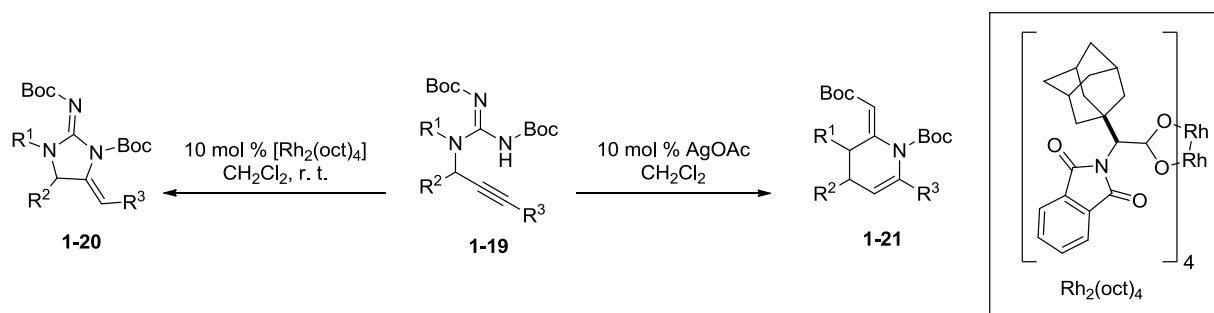
Another classical method of guanidine cyclization, discovered by Shipman and co-workers, involves the formation of an electrophilic carbodiimide *in situ*, which then undergoes an intramolecular attack by an amine. This can be accomplished by converting an azide to an iminophosphorane in a Staudinger-type reaction, which then undergoes an aza-Wittig olefination to provide the aforementioned carbodiimide. Subsequently, this carbodiimide intermediate quickly undergoes an intramolecular cyclization to afford products such as **1-18**.²⁷ The utility of this methodology was demonstrated in the total synthesis of NA22598A₁.

Scheme 1.4 Guanidine cyclization from an azide starting material.²⁷



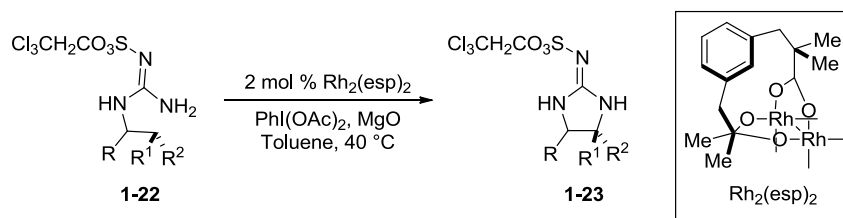
A versatile hydroamination reaction recently published by the Looer group allows for the selective synthesis of both 5 and 6-membered cyclic guanidines by controlling the mode of cyclization (5-exo vs 6-endo) via a choice of catalyst and reaction conditions.²² Formation of the 5-membered ring was highly selective in most cases, using a rhodium catalyst, while the 6-membered ring was accomplished with silver catalysis. However, these extremely powerful constructions lack the ability to form a carbon-carbon bond in the ring closing event.

Scheme 1.5 A highly versatile Rh-catalyzed hydroamination reaction.²²



In 2006, Du Bois reported a C-H functionalization reaction that was able to cyclize *N*-alkyl guanidines and ureas.²⁶ The electron withdrawing group Tces ($-\text{SO}_3\text{CH}_2\text{Cl}_3$) was proposed to deactivate the highly polar, Lewis basic nature of the guanidine nitrogen atoms, eliminating the need to protect both nitrogen atoms. Additional benefits of this protecting group include the ability to use simple, normal phase chromatography, and Tces deprotects readily when exposed to zinc. This impressive transformation was also proven to proceed stereospecifically, showing no erosion of chiral centers on substrates. The scope of the reaction tolerated a wide range of alkyl chains, however, unactivated, secondary methylene carbons failed to readily undergo the C-H activation reaction.

Scheme 1.6 Formation of cyclic guanidines via C-H activation.²⁶



While an impressive array of guanidine cyclizations exist, there are still limitations to methodologies in this field. A reaction that could induce late stage derivatization from an easily accessible substrate is highly desirable. Additionally, chiral cyclizations rely on installing stereocenters prior to cyclization, adding to the complexity of substrates, making them more difficult to prepare. If a stereoselective cyclization reaction could be developed, simple, acyclic substrates could be employed in a cyclization reaction.

1.2 Pd-catalyzed Carboamination Reactions

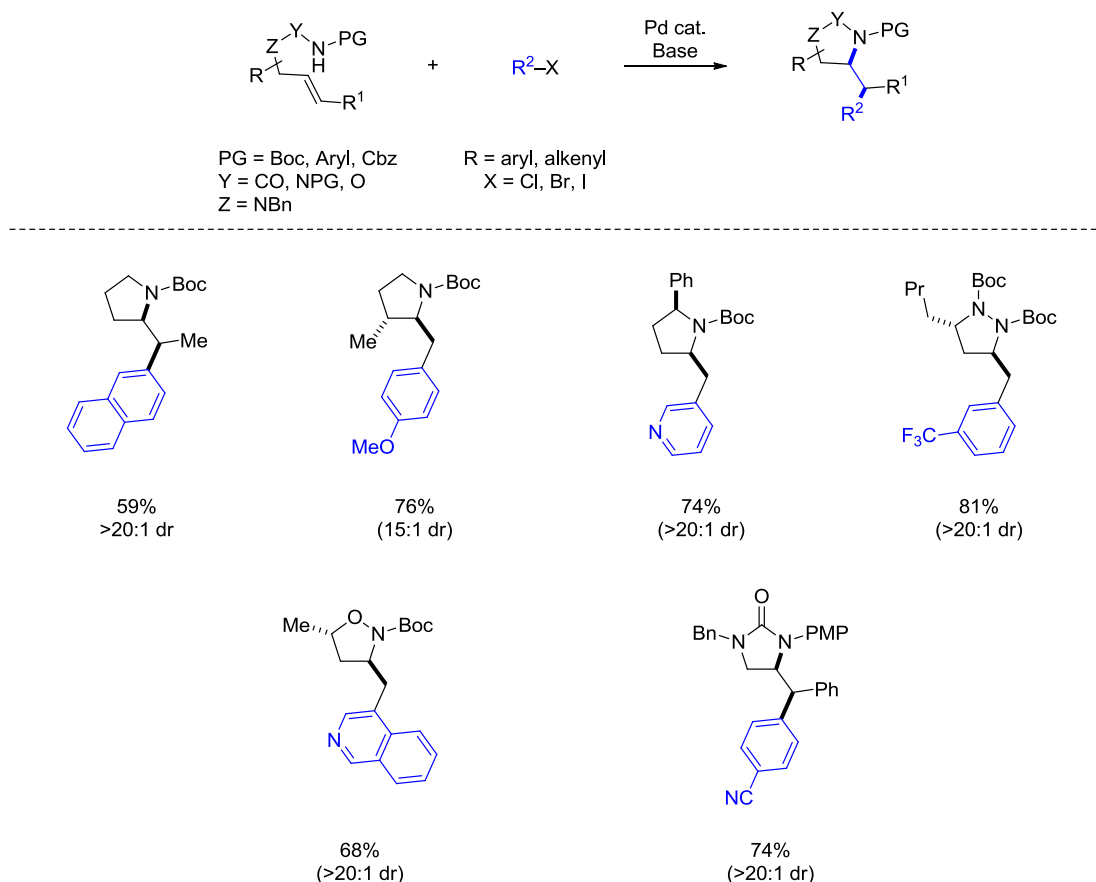
The Wolfe group has developed a series of carboamination reactions to form a number of nitrogen-containing heterocycles over the past decade (Scheme 1.7).³⁰⁻³² These reactions form a heterocycle through the formation of a carbon-nitrogen bond, which is fashioned through a proposed *syn*-aminopalladation pathway (Scheme 1.8). A carbon-carbon bond is also formed from the cross-coupling of an aryl/alkenyl halide and an olefin tethered to the cyclizing amine. These products can be made in high yield and can proceed with excellent stereocontrol. A key advantage of this method is its usefulness for the rapid generation of analogues. Consequently, a variety of readily available aryl or alkenyl halides can be coupled with a single substrate to afford products with varying steric and electronic properties.

The scope of this reaction has grown to include the cyclization of many nitrogen containing heterocycles.³⁰ This carboamination reaction first began in 2004 with seminal work on the cyclization of γ -aminoalkene derivatives by Dr. Wolfe and Dr. Ney.³³ This elegant chemistry can be used to access *cis*-2,5- and *trans*-2,3-disubstituted pyrrolidines in good yield and high diastereoselectivity. Additionally, stereocenters can be transferred from substrates without erosion of optical purity. Since this work, other 5-membered heterocycles, such as pyrazolidines,³⁴ isoxazolidines,³⁵ and N-allyl ureas^{36,37} have been efficiently prepared.

These transformations have been shown to proceed through the catalytic cycle shown in Scheme 1.8.³⁰⁻³² The cycle begins with oxidative addition of a Pd(0) complex into the bond of an aryl halide, which then coordinates to the nitrogen to form complex **1-25**. The palladium(aryl)amido complex **1-25** then undergoes the key *syn*-aminopalladation step to yield **1-26**, which generates the final cyclized product after the carbon-carbon bond forming reductive

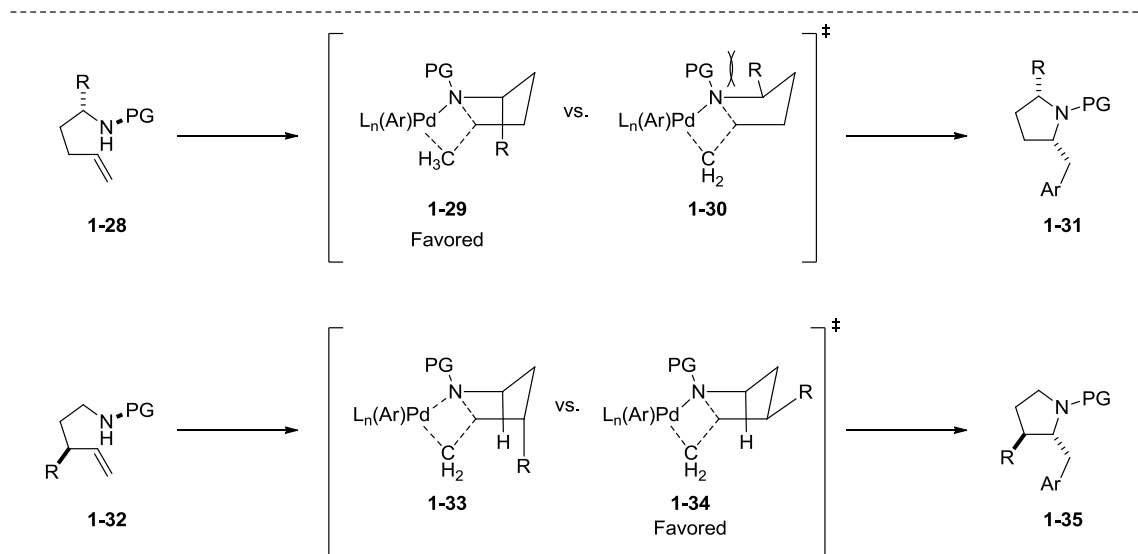
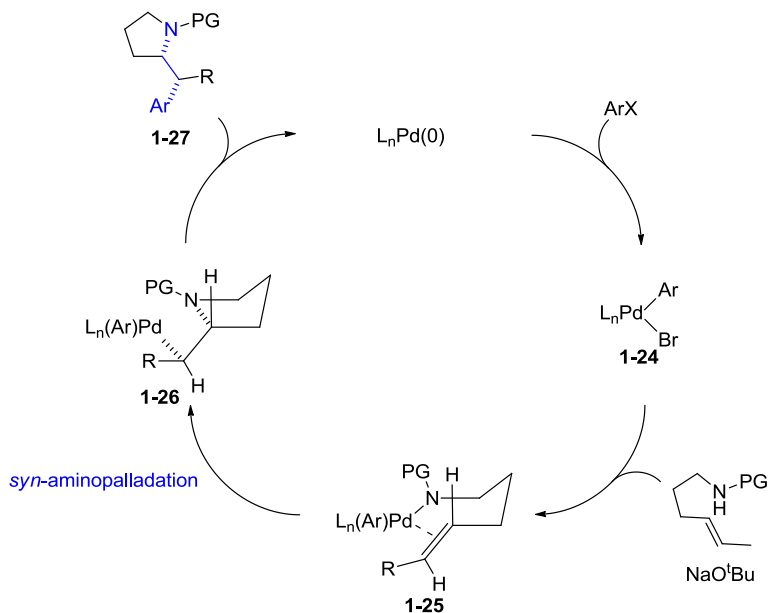
elimination step. The stereochemistry of product **1-27** is achieved from performing *syn*-aminopalladation on an (*E*)-olefin.

Scheme 1.7 Scope of carboamination reactions with nitrogen-containing heterocycles.



The substrate-controlled stereochemical outcome of these transformations found in Scheme 1.7 is determined in the *syn*-aminopalladation step.^{31,32} Substrates substituted at C-1 form *cis*-2,5-disubstituted pyrrolidines (**1-31**) due to the favored transition state **1-29**. In this transition state, the substituent is placed in an axial position in order to avoid unfavorable steric interactions with the protecting group attached to the cyclizing nitrogen. When a disubstituted pyrrolidine is substituted in the allylic position, *trans*-2,3-disubstituted pyrrolidines are formed. The transition state leading to the *trans* product (**1-34**) is favored due to the substituent being placed in an equatorial position, avoiding unfavorable 1,3-diaxial interactions.

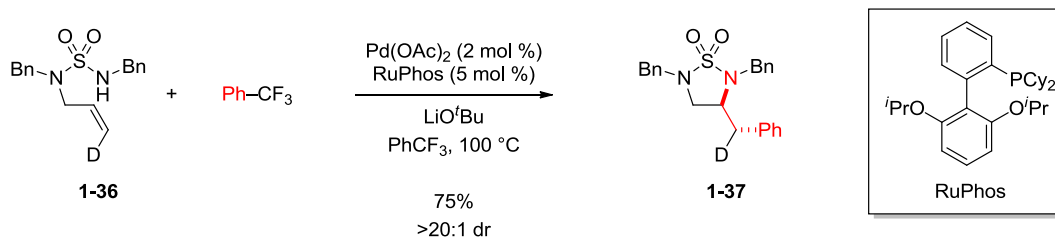
Scheme 1.8 Catalytic cycle and stereochemical rationale.



Recently in the Wolfe group, a newly developed set of conditions have been discovered that exhibits a fundamentally different mechanism for migratory insertion.³⁸ This set of conditions includes a key solvent change from the typical toluene solvent to the more polar trifluorotoluene solvent, and couples aryl triflates instead of aryl halides (Scheme 1.9). Preliminary results show

that 5-membered cyclic ureas and sulfamides can be readily prepared under these conditions. Deuterium labeling studies indicate that the migratory insertion step proceeds as *anti* addition as opposed to the aforementioned *syn* conditions. This reaction is of particular interest because it allows access to molecules with complimentary stereochemistry, and widens the stereochemical scope of molecules able to be fashioned through the use of carboamination chemistry.

Scheme 1.9 Representative example of *anti*-aminopalladation.³⁸



Scheme 1.10 outlines a reasonable catalytic cycle for this reaction. Again, the mechanism begins with the oxidative addition of a Pd(0) complex into an aryl triflate. However, the palladium in complex **1-38** has a more cationic nature due to the triflate anion's non-coordinating nature. This electrophilic palladium species coordinates to the olefin present in the substrate, which activates the olefin for an outer sphere attack from an amine nucleophile. This type of migratory insertion gives *anti* addition across the double bond. Reductive elimination then provides the desired product **1-41** and regenerates the Pd(0) catalyst.

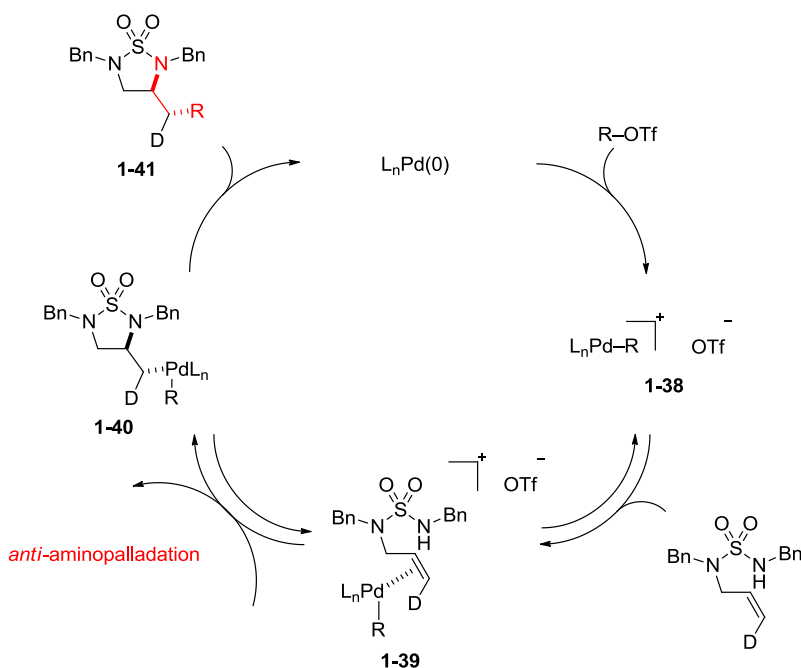
Recent work was published from our group detailing the employment of carboamination chemistry in elegant syntheses of complex cyclic guanidines, including the total synthesis of (+)-merobatzelladine B (Figure 1.3).^{39,40} While this methodology has proven to be of great utility, the key carboamination reactions in these syntheses used urea substrates. The inability to use guanidine substrates costs additional steps in the syntheses.

Figure 1.3 The tricyclic guanidine merobatzelladine B



In summary, carboamination reactions provide an efficient way to synthesize functionalized nitrogen-containing heterocycles, however, this strategy has never been successful for the construction of nitrogen-rich cyclic guanidine scaffolds. Due to the potentially useful bioactivity of these moieties, a distinct advantage of using this chemistry is the ability to rapidly generate analogues from a single substrate to create a library of drug candidates for screening. The ability to easily tune both steric and electronic parameters of pharmacophores is an invaluable asset to medicinal chemistry. Thereupon, we set out to create a carboamination reaction that would be able to cyclize an easily accessible acyclic guanidine substrate to generate functionally and stereochemically complex cyclic guanidine products. Furthermore, we anticipated the successful development of this methodology would greatly aid in the synthesis of more complex guanidine natural products, including streamlining the synthesis of merobatzelladine B.

Scheme 1.10 Catalytic cycle for *anti*-aminopalladation.³⁸



Overall, our general strategy was to construct a diverse group of cyclic guanidine products via carbomamination reactions between acyclic guanidine substrates and aryl or alkenyl halides and triflates. Chapter 2 details our development of Pd-catalyzed carboamination reactions that convert *N*-allyl guanidines and aryl or alkenyl halides to afford saturated 5-membered cyclic guanidines.

These reactions are proposed to proceed via *syn*-aminopalladation. Furthermore, chapter 3 outlines the optimization and scope of carboamination reactions between *N*-propargyl guanidines and aryl triflates, which create the corresponding 2-aminoimidazole products. In contrast to the methodology developed in chapter 2 these reactions are believed to proceed via *anti*-aminopalladation. The utility of this reaction was illustrated in the total synthesis of preclathridine A. A key feature of the synthesis is potential ability to quickly generate a library of analogues. In summary, the research described in this dissertation details our development of Pd-catalyzed carboamination reactions for the efficient synthesis of cyclic guanidines.

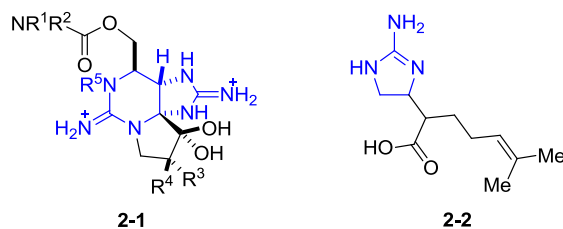
Chapter 2

Synthesis of Saturated Cyclic Guanidines via Pd-Catalyzed Alkene Carboamination Reactions

2.1 Introduction

As detailed in chapter one, saturated cyclic guanidines are molecules of significant importance.¹⁵ A well-studied example is the saxitoxin family (**2-1**). These molecules are known to inhibit voltage-gated Na⁺ ion channels, which generate the bioelectricity that is critical to many biological processes.²⁶ Moreover, simpler, monocyclic guanidine natural products have also shown interesting properties. *Plantago asiatica*, a plant in which the seeds are used as a crude drug for diuretic, antitussive, expectorant, and antiphlogistic purposes, was recently shown to contain plantagoguanidinic acid (**2-2**), a saturated cyclic guanidine, as a component.⁴¹

Figure 2.1 Saturated cyclic guanidine natural products.^{41,42}



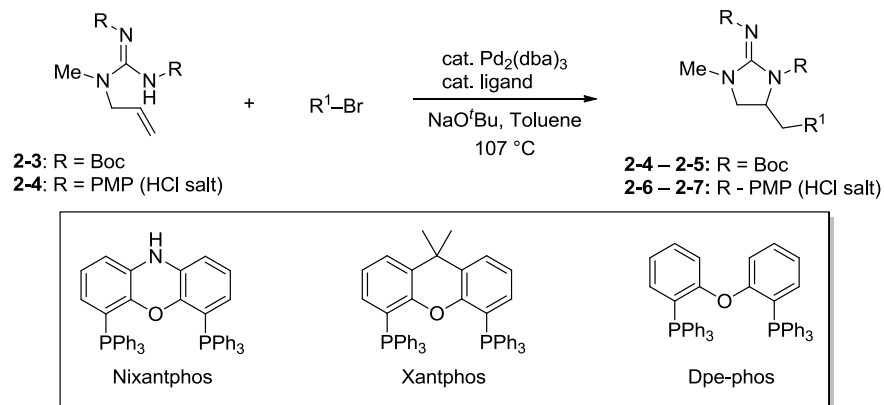
2.2 Synthetic Strategy

Our strategy for constructing cyclic guanidines began with designing a substrate that could be prepared in a high yielding, scalable fashion. As such, a protected *N*-methyl allyl guanidine would be an ideal starting point, as these molecules can be prepared from common allylic amines.^{43,44} This substrate would then be able to be coupled with an aryl bromide in a carboamination reaction to afford the desired cyclic product. We believed that a key challenge of this reaction was decreasing the basicity of the nitrogen nucleophile, as it could participate in an undesirable *N*-arylation side reaction⁴⁵ and/or bind to the catalyst⁴⁶ through covalent interactions.

2.3 Optimization of Reaction Conditions

Previous work from the Wolfe group showed that bis-Boc protected *N*-methylallyl guanidine **2-3** underwent the desired carboamination reaction with 2-bromonaphthalene. Further exploration revealed that a catalyst composed of Pd₂(dba)₃ and Xantphos provided the best results as substrate **2-3** was coupled with 2-bromonaphthalene and 4-bromotoluene to afford products **2-4** and **2-5** in moderate yield. However, these reactions were highly variable with poor reproducibility. Further experiments showed that the bis-Boc protected substrate and carboamination product were both susceptible to base mediated decomposition under the reaction conditions. Thus, employing less labile protecting groups was a logical next step in the reaction optimization.

After failed attempts with readily prepared alkyl protected guanidines, the electron-rich PMP (*p*-methoxyphenyl) protecting group was utilized. We were pleased to see that the substrate **2-4**, employed as the HCl salt, underwent the desired reaction to **2-6** and **2-7** in good yield, with excellent reproducibility. We also explored the triflate salt of the substrate, but this substrate was difficult to purify and less convenient to handle. Superior results were found when the bidentate ligand Nixantphos was used in combination with Pd₂(dba)₃, while other similar ligands gave inferior yields. Interestingly, using 8 mol % of a bidentate ligand in combination with 2 mol % of Pd₂(dba)₃ gave much better results when compared to the typically used stoichiometry of 4 mol % for a bidentate ligand.

Table 2.1 Selected results from ligand and protecting group screen.^a

Entry	Substrate	R ¹	Ligand	Product	Yield ^b (%)
1	2-3	2-naphthyl	Xantphos	2-4	20 (66)
2	2-3	4-tolyl	Xantphos	2-5	(26)
3	2-3	2-naphthyl	Nixantphos	2-4	33 (41)
4	2-3	4-tolyl	Nixantphos	2-5	26 (53)
5	2-3	2-naphthyl	Dpe-phos		0
6	2-3	4-tolyl	Dpe-phos		0
7	2-4	2-naphthyl	Xantphos	2-6	(74)
8	2-4	4-tolyl	Xantphos	2-7	(65)
9	2-4	2-naphthyl	Nixantphos	2-6	57 (81)
10	2-4	4-tolyl	Nixantphos	2-7	73 (77)

^a Conditions: 1.0 equiv of guanidine substrate, 1.5 equiv of R¹-Br, 2.4 equiv of NaO^tBu, 2 mol % Pd₂(dba)₃, 8 mol % ligand, toluene (0.1 M), 107 °C. Reactions of **2-4** were quenched with an excess of aqueous HCl (1 M) to ensure complete protonation of the guanidine. ^b Isolated yields. Numbers in parentheses are NMR yields based on phenanthrene as an internal standard.

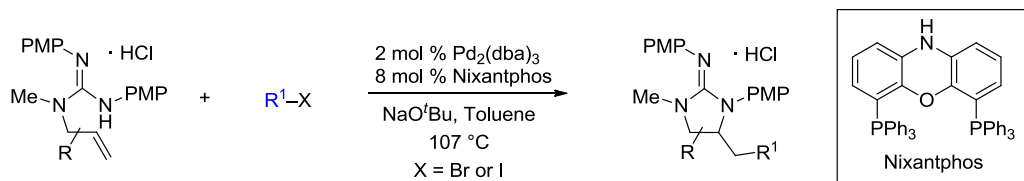
2.4 Scope of Carboamination Reaction

In order to investigate the scope of the cyclization reaction, we varied the electronic and structural properties of the aryl halide participating in the carboamination reaction (Table 2.2). We were pleased to see that electron-rich, electron-neutral, and electron-poor aryl halides were well tolerated under these reaction conditions (entries 1-6). Furthermore, an *ortho* substituted aryl halide (entry 8) also showed satisfactory results. Although these reactions were generally high-yielding, substrate **2-4** was observed to undergo an undesired deallylation side reaction. Furthermore, the carboamination products were prone to silica gel mediated oxidation during column chromatography, resulting in the formation of the corresponding 2-aminoimidazole.

Therefore, a new substrate (**2-5**) that would abate these side reactions was tested. Expectedly, this molecule, bearing an internally methyl substituted olefin, showed improved yields with previously used aryl halides (entries 9-10). Additionally, a diverse group of electrophiles were able to participate in the reaction. To our delight, an alkenyl halide was coupled to the guanidine substrate in good yield (*Z*-1-bromobutene, entry 11), as well as a 5-membered heterocyclic halide (2-bromothiophene, entry 12).

To probe the stereoselectivity of the reaction, substrates **2-6a**, **2-6b**, and **2-7** were prepared. The reaction between *E*-alkene **2-6a** and 4-bromotoluene provided product **2-22a** in excellent dr (>20:1), albeit in low yield. Unfortunately, the analogous methyl substituted *E*-alkene (**2-6b**) gave a complex mixture of products. Substrate **2-7**, substituted at the allylic position, gave good yield but poor stereoselectivity (dr = 2:1). Rationale for the stereochemical outcome of these reactions can be found in Scheme 1.8, which describes the proposed catalytic cycle for Pd-catalyzed carboamination reactions that proceed via *syn*-aminopalladation.

Table 2.2 Pd-Catalyzed Carboamination of *N*-allylguanidines^a



Entry	Substrate	Product	Yield (%) ^b
1			76 (X = I)
2			73 (X = Br)
3			62 (X = I)
4			72 (X = Br)
5			65 (X = I)
6			78 (X = Br)
7			83 (X = Br)
8			75 ^c (X = Br)

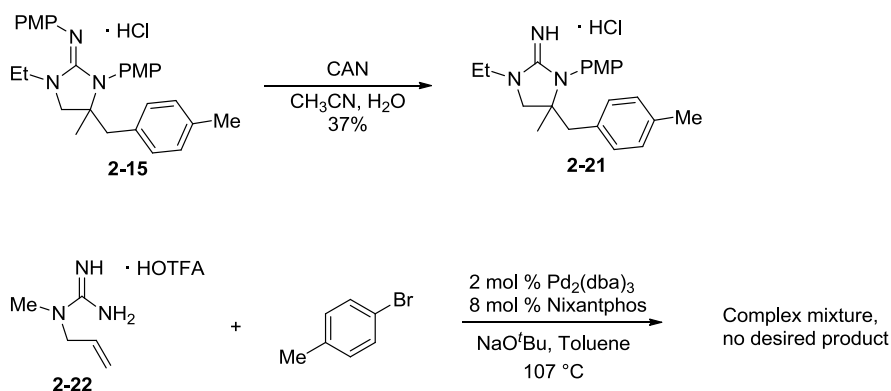
Entry	Substrate	Product	Yield (%) ^b
9	 2-5	 2-15	99 (X = Br)
10	 2-5	 2-16	99 (X = Br)
11	 2-5	 2-17	98 (X = Br)
12	 2-5	 2-18	86 ^d (X = Br)
13	 2-6a : R = Ph 2-6b : R = Me ^e	 2-19a : R = Ph	R = Ph 21 >20:1 dr (X = Br)
14	 2-6a : R = Ph 2-6b : R = Me ^e	 2-19a : R = Ph	R = Ph 21 >20:1 dr (X = Br)
15	 2-7	 2-20	62 2:1 dr (X = Br)

^a Conditions: 1.0 equiv of guanidine substrate, 1.5 equiv of R¹-X, 2.4 equiv of NaO^tBu, 2 mol % Pd₂(dba)₃, 8 mol % ligand, toluene (0.1 M), 107 °C. Reactions were quenched with an excess of aqueous HCl (1 M) to ensure complete protonation of the guanidine. ^b Isolated yields (average of two experiments). Diastereomeric ratios (dr) were determined by ¹H NMR analysis of the isolated products; diastereomeric ratios did not change significantly during purification. ^c This product contains ca. 8% of a side product tentatively assigned as the analogous 2-aminoimidazole. ^d This reaction was conducted using 4.0 equiv of the alkenyl bromide and 4.5 equiv of NaO^tBu. ^e Substrate **2-6b** was employed as a 7:1 mixture of *E*:*Z* alkene isomers.

2.5 Deprotection and Asymmetric Induction

In hopes of showcasing the synthetic utility of this reaction, removal of the PMP protecting groups was attempted. Initial attempts showed that one group can be deprotected, though in modest yield. As an attempt to avoid this issue, the free guanidine substrate **2-22** was submitted to the reaction conditions. Unfortunately, this reaction gave a complex mixture of products and did not lead to the isolation of any cyclic guanidine product.

Scheme 2.1 Attempts at synthesizing deprotected product



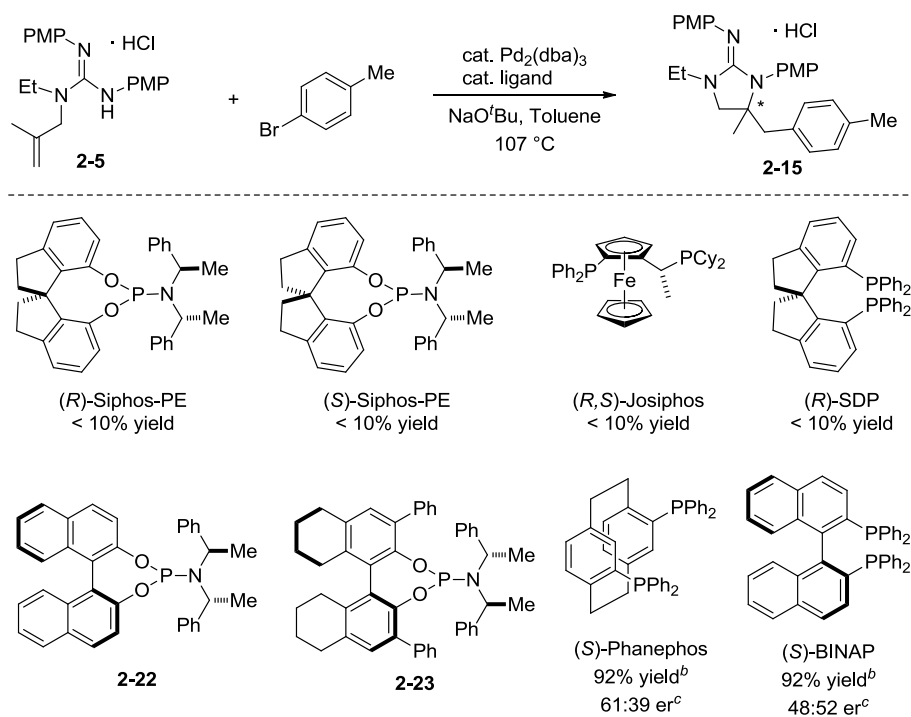
Past efforts at asymmetric induction in our group have shown success with similar molecules, cyclizing *N*-allylureas and *N*-(pent-4-enyl)carbamates in good yield and with high enantioselectivity.^{47,48} We hoped that guanidines would also be able to undergo an effective asymmetric carboamination reaction. We began these studies by examining the effects of monodentate phosphoramidite ligands (*S*)- and (*R*)-Siphos-PE, ligands that had shown success with earlier projects. A screen of other chiral ligands showed that the chelating bidentate ligands (*S*)-Phanephos and (*S*)-BINAP afforded the desired product in good yield, but with poor enantioselectivity (Table 2.3). While these results show that asymmetric induction is indeed feasible, further optimization studies will be needed to identify the correct catalytic system.

2.6 Conclusions

In summary, we have utilized Pd-catalyzed alkene carboamination reactions as a convenient route to the synthesis of substituted 5-membered cyclic guanidines. These reactions allow for the facile derivitization of these products in only two steps from the easily preparable allylic amines. This work is the first example of Pd-catalyzed alkene carboamination reactions of guanidine

nucleophiles. Future work will be dedicated to expanding the scope and improving the enantioselectivity of the asymmetric carboamination reaction.

Table 2.3 Preliminary Studies on Asymmetric Catalysis^a



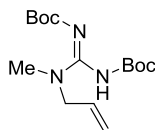
^a Conditions: 1.0 equiv of **2-5**, 1.5 equiv of 4-bromotoluene, 2.4 equiv of NaO^tBu , 2 mol % $\text{Pd}_2(\text{dba})_3$, 8 mol % ligand (for chelating ligands) or 16 mol % ligand (for monodentate ligands), toluene (0.1 M), 107°C . Reactions were quenched with an excess of aqueous HCl (1 M) to ensure complete protonation of the guanidine. ^b Isolated yields. ^c Enantiomeric ratios were determined by the cleavage of one PMP group from the product followed by conversion to the Mosher amide and analysis by ^1H NMR.

The work described in this chapter was published in Organic Letters.⁴⁹

2.7 Experimental

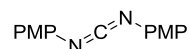
General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware unless otherwise noted. Tris(dibenzylidene)acetone dipalladium and Nixantphos were purchased from Strem Chemical Co. and used without purification. All other reagents were obtained from commercial sources and were used as obtained unless otherwise noted. (*Z*)-1-bromobutene⁵⁰ was prepared according to a slight modification of a literature procedure; the preparation was conducted at rt instead of using microwave heating. *N*-methylbut-2-en-1-ylamine was prepared as a 7:1 mixture of *E*:*Z* alkene isomers according to a published procedure.⁵¹ Sodium *tert*-butoxide was kept in a glove box and removed only prior to use. Toluene, THF, diethyl ether and dichloromethane were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be $\geq 95\%$ pure as determined by ¹H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas isolated yields reported in Tables 1–2 are averages of yields for two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Tables 1–2.

Preparation and Characterization of Guanidine Substrates



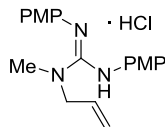
***N*¹-Allyl-*N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-methylguanidine (2-3).** The title compound was prepared using the general guanylation procedure reported by Lipton.⁴³ A flame-dried flask equipped with a stirbar was cooled under a stream of N₂, and charged with *N,N'*-bis-Boc-thiourea (1.79 g, 6.45 mmol), dichloromethane (65 mL), *N*-methylallylamine (518 μ L, 5.4 mmol), triethylamine (1.66 mL, 11.9 mmol), and *N*-methyl-2-chloropyridinium iodide (1.64 g, 6.42 mmol). The resulting solution was stirred overnight (16 h) at rt. Water was added to the reaction flask, the mixture was stirred at rt for 5 min, then was transferred to a separatory funnel. The layers were separated and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 660 mg (39%) of the title compound as a white solid: mp = 71–74 °C. This compound was found to exist as a mixture of rotamers as judged by ¹H and ¹³C NMR analysis; data are for the

mixture. ^1H NMR (700 MHz, CDCl_3) δ 10.05 (s, 1 H), 5.86–5.81 (m, 1 H), 5.26–5.21 (m, 2 H), 4.08 (s, br, 2 H), 2.96 (s, 3 H), 1.49 (s, 18 H); ^{13}C NMR (175 MHz, CDCl_3) δ 182.0, 162.6, 155.9, 151.2, 132.7, 118.5, 84.2, 81.9, 79.4, 53.4, 36.4, 28.1, 27.9; IR (film) 3286, 3175, 1748, 1612 cm^{-1} . MS (ESI) 314.2073 (314.2074 calcd for $\text{C}_{15}\text{H}_{27}\text{N}_3\text{O}_4$, $\text{M} + \text{H}^+$).

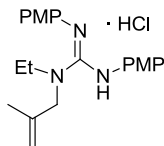


***N,N'*-Methanediylidene-bis-(4-methoxyaniline) (S1).** The title compound was prepared using a procedure published by Coppola.⁵² A flame-dried flask was cooled under a stream of N_2 , charged with 1,3-bis(4-methoxyphenyl)thiourea (5.67 g, 19.6 mmol), 4-dimethylaminopyridine (96.0 mg, 0.786 mmol), methanesulfonyl chloride (1.7 mL, 21.6 mmol), triethylamine (8.2 mL, 58.9 mmol), and dichloromethane (196 mL, 0.1 M). The resulting solution was stirred at 0°C for 5 min. The solution was then filtered through a plug of silica gel, and the silica gel was washed with 300 mL of a 1:1 mixture of ethyl acetate and hexanes. The filtrate was concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 3.98 g (80%) of the title compound as a white solid. Spectroscopic properties were identical to those previously reported:⁵⁰ mp = 48–50 $^\circ\text{C}$ (lit.⁵³ mp = 48–50 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.11 (d, $J = 8.8$ Hz, 4 H), 6.85 (d, $J = 8.8$ Hz, 4 H), 3.80 (s, 6 H).

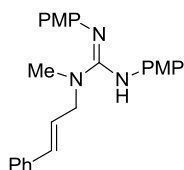
General Procedure for Synthesis of Bis(4-methoxyphenyl)guanidine Substrates. The bis(4-methoxyphenyl)guanidine derivatives were synthesized using a modification of a procedure published by Xi.⁴⁴ A flame dried round-bottom flask equipped with a stirbar was cooled under a stream of N_2 , and charged with *N,N'*-methanediylidene-bis-(4-methoxyaniline) (1.0 equiv), the appropriate amine (1.2 equiv), zinc chloride (1 equiv), dichloromethane (0.025 M), and diethyl ether (0.25 M). The resulting mixture was stirred overnight at rt, then was filtered through a plug of celite, and the celite plug was washed with dichloromethane (150 mL). The filtrate was washed with 1M aqueous HCl (5 mL/mmol) and saturated aqueous sodium chloride (5 mL/mmol). The organic layer was then concentrated *in vacuo* and the resulting crude product was purified by flash chromatography on silica gel.



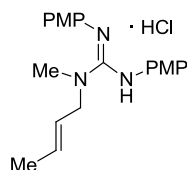
1-Allyl-2,3-bis(4-methoxyphenyl)-1-methylguanidine hydrochloride (2-4). The title compound was prepared from *N,N'*-methanediylidene-bis-(4-methoxyaniline) (1.68 g, 6.61 mmol) and *N*-methylallylamine (0.8 mL, 7.93 mmol) according to the general procedure. This procedure afforded 1.43 g (60%) of the title compound as a white foam solid: mp = 77–79 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.03 (s, 2 H), 7.00 (d, *J* = 9.0 Hz, 4 H), 6.55 (d, *J* = 8.0 Hz, 4 H), 5.88–5.78 (m, 1 H), 5.31–5.21 (m, 2 H), 4.13 (s, 2 H), 3.64 (s, 6 H), 3.08 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 157.0, 154.2, 131.4, 129.7, 123.7, 120.3, 114.1, 55.4, 55.3, 38.1; IR (film) 3203, 1625 cm⁻¹. MS (ESI) 326.1863 (326.1866 calcd for C₁₉H₂₄N₃O₂, M⁺).



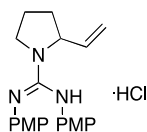
1-Ethyl-2,3-bis(4-methoxyphenyl)-1-(2-methylallyl)guanidine hydrochloride (2-5). The title compound was prepared from *N,N'*-methanediylidene-bis-(4-methoxyaniline) (2.06 g, 8.09 mmol) and *N*-ethyl-2-methylallylamine (1.28 mL, 9.7 mmol) according to the general procedure except the *N*-ethyl-2-methylallylamine was filtered through a plug of silica gel prior to addition, and the silica plug was eluted with 5 mL of dichloromethane, which was added to the reaction mixture. This procedure afforded 2.43 g (73%) of the title compound as a white foam solid: mp = 68 °C. ¹H NMR (500 MHz, CDCl₃) δ 6.92 (d, *J* = 8.0 Hz, 4 H), 6.56 (d, *J* = 8.0 Hz, 4 H), 4.99 (s, 1 H), 4.92 (s, 1 H), 4.09 (s, 2 H), 3.66 (s, 6 H), 3.63–3.58 (m, 2 H), 1.74 (s, 3 H), 1.17 (t, *J* = 7.0 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 156.8, 153.9, 139.7, 129.9, 123.6, 114.5, 114.0, 55.9, 55.3, 45.4, 20.3, 13.2; IR (film) 3040, 1619 cm⁻¹. MS (ESI) 354.2180 (354.2176 calcd for C₂₁H₂₈N₃O₂, M⁺).



1-Cinnamyl-2,3-bis(4-methoxyphenyl)-1-methylguanidine hydrochloride (2-6a). The title compound was prepared from commercially available cinnamyl bromide via a two-step procedure. A round-bottom flask equipped with a stirbar was charged with cinnamyl bromide (5.9 g, 30 mmol) and ethanol (30 mL) and cooled to 0 °C. Methylamine (37.5 mL, 300 mmol, 33% solution in ethanol) was slowly added to the reaction flask over the course of 10 min. The reaction mixture was allowed to warm to rt and was stirred overnight. The reaction mixture was concentrated, dissolved in dichloromethane (100 mL), and transferred to a separatory funnel. 1 M HCl (20 mL) was added to the separatory funnel and the layers were separated. The organic layer was washed again with 1 M HCl (20 mL). The combined aqueous layers were transferred to a round-bottom flask and dichloromethane (50 mL) was added. The biphasic mixture was basified with NH₄OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude *N*-methylcinnamylamine was then coupled with *N,N'*-methanediylidene-bis-(4-methoxyaniline) (4.3 g, 17.0 mmol) according to the general procedure described above. This procedure afforded 1.82 g (27%) of the title compound as an off-white solid: mp = 84–89 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.70 (s, br, 2 H), 7.33–7.20 (m, 5 H), 7.18 (d, *J* = 9.0 Hz, 4 H), 6.75 (d, *J* = 8.5 Hz, 4 H), 6.49 (d, *J* = 16.5 Hz, 1 H), 6.02–5.97 (m, 1 H), 4.15 (s, br, 2 H), 3.67 (s, 6 H), 2.99 (s, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 157.6, 154.8, 135.8, 135.6, 129.3, 128.6, 128.1, 126.7, 124.4, 121.6, 114.7, 55.4, 54.9, 37.7; IR (film) 3256, 3205, 1627 cm⁻¹. MS (ESI) 402.2176 (402.2176 calcd for C₂₅H₂₈N₃O₂, M⁺).

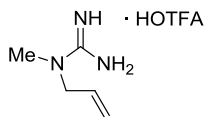


1-(But-2-en-1-yl)-2,3-bis(4-methoxyphenyl)-1-methylguanidine hydrochloride (2-6b). The title compound was prepared from *N,N'*-methanediylidene-bis-(4-methoxyaniline) (778 mg, 3.06 mmol) and *N*-methylbut-2-en-1-amine (employed as a 7:1 mixture of *E:Z* alkene isomers and as a 20% solution in EtOH) (260 mg, 3.06 mmol, 1.0 equiv,) according to the general procedure. After purification by flash column chromatography, 448 mg (39%) of the title compound was obtained as a pale brown solid (mp: 58–63 °C) and as a 7:1 mixture of *E:Z* alkene isomers as determined by ¹H NMR analysis. The ¹H data contains dichloromethane which was difficult to remove in vacuo. The data is for the mixture. ¹H NMR (500 MHz, CDCl₃) δ 8.57 (s, 2 H), 7.17–7.13 (m, 4 H), 6.81–6.78 (m, 4 H), 5.73–5.66 (m, 1 H), 5.37–5.32 (m, 1 H), 3.93 (d, *J* = 5 Hz, 2 H), 3.73 (s, 6 H), 2.92 (s, 3 H), 1.69 (d, *J* = 5.5 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 157.7, 157.4, 154.5, 133.0, 131.2, 129.3, 125.0, 124.3, 123.1, 114.7, 114.7, 55.5, 55.5, 54.7, 37.6, 17.8; IR (film) 3247, 2954, 1627 cm⁻¹. MS (ESI) 340.2019 (340.2020 calcd for C₂₀H₂₅N₃O₂, M⁺).



(±)-*N,N'*-Bis(4-methoxyphenyl)-2-vinylpyrrolidine-1-carboximidamide hydrochloride (2-7). The title compound was prepared from commercially available *N*-Boc-2-vinylpyrrolidine via a two-step procedure. A round-bottom flask equipped with a stirbar was charged with *N*-Boc-2-vinylpyrrolidine (2.5 mL, 12.5 mmol) and dichloromethane (25 mL). Trifluoroacetic acid (12.5 mL, 1.0 M) was added to the flask and the mixture was stirred at rt for 1 h until the starting material had been completely consumed as judged by TLC analysis. The solution was diluted with water, basified with NH₄OH to pH > 12, and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude amine was then coupled with *N,N'*-methanediylidene-bis-(4-methoxyaniline) (3.2 g, 12.5 mmol) according to the general procedure described above. This procedure afforded 464 mg (10%) of the

title compound as a pale yellow solid: mp = 58–62 °C. ¹H NMR (700 MHz, CD₃OD) δ 7.00 (d, *J* = 9.1 Hz, 4 H), 6.82 (d, *J* = 9.1 Hz, 4 H), 5.90–5.85 (m, 1 H), 5.27–5.22 (m, 2 H), 4.58–4.55 (m, 1 H), 3.73 (s, 6 H), 3.67–3.63 (m, 1 H), 3.58–3.54 (m, 1 H), 2.30–2.26 (m, 1 H), 2.08–2.04 (m, 1 H), 2.01–1.95 (m, 1 H), 1.87–1.82 (m, 1 H); ¹³C NMR (175 MHz, CD₃OD) δ 159.4, 153.8, 137.6, 130.7, 125.9, 118.4, 115.6, 63.5, 56.0, 51.4, 33.7, 25.0; IR (film) 3204, 1629 cm⁻¹. MS (ESI) 352.2020 (352.2020 calcd for C₂₁H₂₆N₃O₂, M⁺).

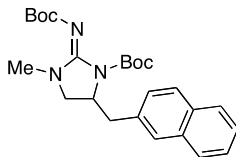


1-Allyl-1-methylguanidinium trifluoroacetate (2-22). A round-bottom flask equipped with a stirbar was charged with **2-3** (196 mg, 0.63 mmol) and dichloromethane (2.4 mL). Trifluoroacetic acid (0.9 mL) was added to the flask and the reaction mixture was stirred overnight at rt, and the solution was then concentrated *in vacuo*. Toluene (4 mL) was added and the resulting solution was concentrated *in vacuo*. The addition of toluene and subsequent concentration was repeated (3x) to remove all excess trifluoroacetic acid, at which time the compound was obtained as a crystalline white solid: mp = 159–164 °C. This procedure afforded 85 mg (60%) of the title compound. This material also contained ca. 10% of an unidentified side product. ¹H NMR (500 MHz, CD₃OD) δ 5.83–5.75 (m, 1 H), 5.26–5.17 (m, 2 H), 3.95 (d, 2 H), 2.99 (s, 3 H); ¹³C NMR (125 MHz, CD₃OD) δ 159.4, 132.8, 118.9, 45.4, 37.3; IR (film) 3312, 3150, 1663 cm⁻¹. MS (ESI) 114.1028 (114.1026 calcd for C₅H₁₁N₃, M⁺).

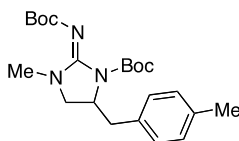
Preparation and Characterization of Cyclic Guanidine Products

General Procedure for Pd-Catalyzed Synthesis of Cyclic Guanidines. A flame-dried Schlenk tube was cooled under vacuum and charged with the appropriate guanidine substrate (1.0 equiv), Pd₂(dba)₃ (0.02 equiv), Nixantphos (0.08 equiv), and NaOtBu (1.5 equiv). The flask was evacuated and purged with N₂. Toluene (0.1 M) was added via syringe and the resulting mixture was stirred at rt for 2 min. The appropriate aryl or alkenyl bromide (1.5 equiv) was added and the tube was heated to 107 °C and stirred overnight (~16 h). The mixture was cooled to room temperature and 1 M HCl (10 mL/mmol substrate) and dichloromethane (25 mL/mmol substrate) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (10 mL/mmol).

The organic layers were combined and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

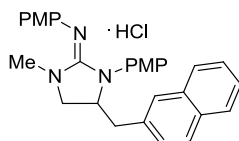


***tert*-Butyl 2-[(*tert*-butoxycarbonyl)imino]-3-methyl-5-(naphthalen-2-ylmethyl)imidazolidine-1-carboxylate (2-4).** The general procedure was employed for the coupling of **2-3** (94 mg, 0.3 mmol) and 2-bromonaphthalene (93 mg, 0.45 mmol) using a catalyst composed of Pd₂(dba)₃ (5.5 mg, 0.006 mmol) and Nixantphos (13 mg, 0.024 mmol). Saturated aqueous NH₄Cl was used during the workup instead of 1 M HCl. This procedure afforded 43 mg (33%) of the title compound as an off-white solid: mp = 56–58 °C. This compound was found to exist as a mixture of rotamers as judged by ¹H and ¹³C NMR analysis; data are for the mixture. ¹H NMR (700 MHz, CDCl₃) δ 7.81–7.79 (m, 3 H), 7.70 (s, 1 H), 7.48–7.43 (m, 2 H), 7.36 (dd, *J* = 1.4, 8.4 Hz, 1 H), 4.47–4.44 (m, 1 H), 3.44–3.40 (m, 1 H), 3.35 (dd, *J* = 4.9, 14.0 Hz, 1 H), 3.07 (dd, *J* = 2.1, 9.8 Hz, 1 H), 2.93 (dd, *J* = 9.1, 14.0 Hz, 1 H), 2.83 (s, 3 H), 1.54 (s, 9 H), 1.45 (s, 9 H); ¹³C NMR (175 MHz, CDCl₃) δ 159.6, 151.5, 149.8, 133.9, 133.5, 132.4, 128.4, 128.2, 127.6, 127.6, 127.5, 126.2, 125.8, 82.5, 78.7, 56.7, 49.9, 40.2, 32.1, 28.3, 28.1; IR (film) 1748, 1629 cm⁻¹. MS (ESI) 440.2538 (440.2544 calcd for C₂₅H₃₃N₃O₄, M + H⁺).



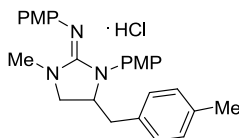
***tert*-Butyl 2-[(*tert*-butoxycarbonyl)imino]-3-methyl-5-(4-methylbenzyl)imidazolidine-1-carboxylate (2-5).** The general procedure was employed for the coupling of **2-3** (63 mg, 0.2 mmol) and 4-bromotoluene (51 mg, 0.3 mmol) using a catalyst composed of Pd₂(dba)₃ (3.7 mg, 0.004 mmol) and Nixantphos (8.8 mg, 0.016 mmol). Saturated aqueous NH₄Cl was used during the workup instead of 1 M HCl. This procedure afforded 21 mg (26%) of the title compound as a pale yellow oil. This compound was found to exist as a mixture of rotamers as judged by ¹H and ¹³C

NMR analysis; data are for the mixture. ^1H NMR (700 MHz, CDCl_3) δ 7.12 (d, $J = 7.7$ Hz, 2 H), 7.09 (d, $J = 7.7$ Hz, 2 H), 4.29–4.26 (m, 1 H), 3.25–3.21 (m, 2 H), 3.04 (dd, $J = 2.8, 9.1$ Hz, 1 H), 2.76 (s, 3 H), 2.65 (dd, $J = 9.8, 13.3$ Hz, 1 H), 2.32 (s, 3 H), 1.57 (s, 9 H), 1.45 (s, 9 H); ^{13}C NMR (175 MHz, CDCl_3) δ 165.5, 154.1, 150.6, 136.5, 133.3, 129.4, 129.2, 82.3, 53.2, 47.7, 39.0, 30.5, 28.2, 21.0; IR (film) 1750, 1627 cm^{-1} . MS (ESI) 404.2545 (404.2544 calcd for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_4$, $\text{M} + \text{H}^+$).



***N*,3-Bis(4-methoxyphenyl)-1-methyl-4-(naphthalen-2-ylmethyl)imidazolidin-2-imine**

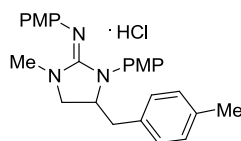
hydrochloride (2-6): The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 2-bromonaphthalene (47 mg, 0.23 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 42 mg (57%) of the title compound as a pale yellow-brown foam solid: mp = 67–68 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 7.80–7.77 (m, 3 H), 7.60 (s, 1 H), 7.50–7.46 (m, 2 H), 7.21 (d, $J = 8.0$ Hz, 1 H), 7.04–7.02 (m, 2 H), 6.97–6.94 (m, 2 H), 6.63–6.60 (m, 2 H), 6.52–6.49 (m, 2 H), 4.50–4.44 (m, 1 H), 3.83–3.79 (m, 1 H), 3.70–3.68 (m, 3 H), 3.39–3.36 (m, 3 H), 3.61–3.59 (m, 1 H), 3.39–3.62 (m, 3 H), 3.23–3.19 (m, 1 H), 3.04 (dd, $J = 10.0, 13.0$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.2, 157.7, 156.5, 133.4, 132.5, 132.4, 132.4, 132.3, 129.5, 128.8, 128.0, 127.7, 127.5, 126.9, 126.6, 126.6, 126.1, 114.6, 113.8, 63.8, 55.5, 55.4, 54.0, 39.5, 35.7; IR (film) 3050, 1632 cm^{-1} . MS (ESI) 452.2328 (452.2333 calcd for $\text{C}_{29}\text{H}_{30}\text{N}_3\text{O}_2$, M^+).



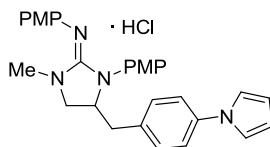
***N*,3-Bis(4-methoxyphenyl)-1-methyl-4-(4-methylbenzyl)imidazolidin-2-imine**

hydrochloride (2-7): The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 4-iodotoluene (49 mg, 0.23 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 42 mg (62%) of the title compound as a pale yellow-brown foam solid: mp = 73–75 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 7.14 (d, $J = 8.5$

Hz, 2 H), 7.11–7.06 (m, 4 H), 7.02 (d, $J = 8.0$ Hz, 2 H), 6.67 (d, $J = 9.0$ Hz, 2 H), 6.56 (d, $J = 9.0$ Hz, 2 H), 4.49–4.42 (m, 1 H), 3.90–3.86 (m, 1 H), 3.72 (s, 3 H), 3.66 (s, 3 H), 3.60 (dd, $J = 7.5$, 10.0 Hz, 1 H), 3.23 (s, 3 H), 2.96 (dd, $J = 4.5$, 13.5 Hz, 1 H), 2.91 (dd, $J = 10.0$, 13.5 Hz, 1 H), 2.30 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.4, 158.2, 156.1, 137.0, 131.8, 129.6, 129.2, 129.0, 128.7, 127.7, 126.9, 114.8, 113.9, 63.6, 55.6, 55.5, 54.2, 38.4, 36.2, 21.0; IR (film) 3133, 1631 cm^{-1} . MS (ESI) 416.2340 (416.2333 calcd for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_2$, M^+).

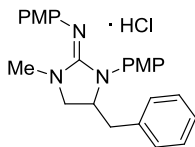


***N*,3-Bis(4-methoxyphenyl)-1-methyl-4-(4-methylbenzyl)imidazolidin-2-imine hydrochloride (2-8):** The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 4-bromotoluene (39 mg, 0.225 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 50 mg (73%) of the title compound as a pale yellow-brown foam solid. Spectroscopic data were identical to those provided above.



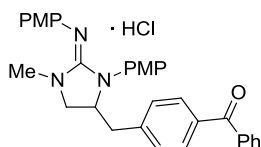
4-[4-(1*H*-Pyrrol-1-yl)benzyl]-*N*,3-bis(4-methoxyphenyl)-1-methylimidazolidin-2-imine hydrochloride (2-9): The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 1-(4-iodophenyl)pyrrole (61 mg, 0.23 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 48 mg (63%) of the title compound as a pale yellow-brown foam solid: mp = 70–71 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.30 (d, $J = 8.0$ Hz, 2 H), 7.21–7.17 (m, 4 H), 7.14 (d, $J = 8.5$ Hz, 2 H), 7.04 (t, $J = 2.5$ Hz, 2 H), 6.69 (d, $J = 9.0$ Hz, 2 H), 6.58 (d, $J = 9.0$ Hz, 2 H), 6.33 (t, $J = 3.0$ Hz, 2 H), 4.58–4.51 (m, 1 H), 3.95–3.91 (m, 1 H), 3.72 (s, 3 H), 3.70–3.68 (m, 1 H), 3.67 (s, 3 H), 3.22 (s, 3 H), 3.06–3.04 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.4, 158.2, 156.2, 139.8, 132.4, 130.3, 129.3,

128.6, 127.7, 127.0, 120.7, 119.2, 114.8, 113.9, 110.6, 63.5, 55.6, 55.5, 54.3, 38.2, 36.0; IR (film) 3058, 1635 cm^{-1} . MS (ESI) 467.2450 (467.2442 calcd for $\text{C}_{29}\text{H}_{31}\text{N}_4\text{O}_2$, M^+).



4-Benzyl-N,3-bis(4-methoxyphenyl)-1-methylimidazolidin-2-imine hydrochloride (2-10):

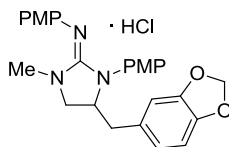
The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and bromobenzene (24 μL , 0.23 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 48 mg (73%) of the title compound as a pale yellow-brown foam solid: mp = 58–59 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 7.31 (t, $J = 7.0$ Hz, 2 H), 7.27–7.26 (m, 1 H), 7.13 (d, $J = 8.0$ Hz, 2 H), 6.98 (d, $J = 9.0$ Hz, 2 H), 6.92 (d, $J = 9.0$ Hz, 2 H), 6.61 (d, $J = 8.5$ Hz, 2 H), 6.50 (d, $J = 9.0$ Hz, 2 H), 4.34–4.27 (m, 1 H), 3.83–3.78 (m, 1 H), 3.69 (s, 3 H), 3.65 (s, 3 H), 3.51 (dd, $J = 3.5, 13.5$ Hz, 1 H), 3.40 (s, 3 H), 3.06 (dd, $J = 3.5, 13.5$ Hz, 1 H), 2.85 (dd, $J = 10.0, 14.0$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0, 157.5, 156.5, 135.0, 129.9, 129.1, 129.0, 128.6, 128.3, 127.5, 126.5, 114.5, 113.8, 63.9, 55.5, 55.5, 53.8, 39.5, 35.4; IR (film) 3003, 1640 cm^{-1} . MS (ESI) 402.2177 (402.2176 calcd for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_2$, M^+).



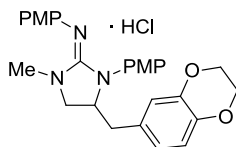
[4-{3-(4-Methoxyphenyl)-2-[(4-methoxyphenyl)imino]-1-methylimidazolidin-4-ylmethyl}phenyl](phenyl)methanone hydrochloride (2-11):

The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 4-iodobenzophenone (69 mg, 0.23 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 56 mg (69%) of the title compound as a pale yellow-brown foam solid: mp = 70–71 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 8.75 (s, 1 H), 7.73 (d, $J = 8.0$ Hz, 2 H), 7.67 (d, $J = 7.0$ Hz, 2 H), 7.59 (t, $J = 8.0$ Hz, 1 H), 7.48 (t, $J = 7.5$ Hz, 2 H), 7.30 (d, $J = 8.5$ Hz, 2 H), 7.20 (d, 7.5 Hz, 2 H), 7.15 (d, $J = 8.0$ Hz, 2 H), 6.67 (d, $J = 7.5$ Hz, 2 H), 6.57 (d, $J = 7.5$ Hz,

2 H), 4.72–4.65 (m, 1 H), 4.02–3.98 (m, 1 H), 3.76–3.73 (m, 1 H), 3.70 (s, 3 H), 3.65 (s, 3 H), 3.23 (s, 3 H), 3.21–3.17 (m, 1 H), 3.10 (dd, $J = 4.5, 13.5$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.2, 159.5, 158.3, 156.1, 140.2, 137.3, 136.3, 132.6, 130.5, 129.9, 129.5, 129.2, 128.3, 128.2, 128.0, 126.6, 114.8, 113.9, 63.1, 55.6, 55.5, 54.4, 38.8, 36.1; IR (film) 3135, 1655, 1630 cm^{-1} . MS (ESI) 506.2437 (506.2438 calcd for $\text{C}_{32}\text{H}_{32}\text{N}_3\text{O}_3$, M^+).

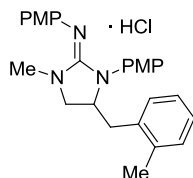


4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*,3-bis(4-methoxyphenyl)-1-methylimidazolidin-2-imine hydrochloride (2-12): The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 4-bromo-1,2-(methylenedioxy)benzene (27 μL , 0.23 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 59 mg (81%) of the title compound as a pale yellow-brown foam solid: mp = 66–68 $^\circ\text{C}$. ^1H NMR (700 MHz, CDCl_3) δ 7.01 (d, $J = 9.1$ Hz, 2 H), 6.92 (d, $J = 9.1$ Hz, 2 H), 6.73 (d, $J = 7.7$ Hz, 1 H), 6.61–6.58 (m, 4 H), 6.51 (d, $J = 9.1$ Hz, 2 H), 5.93 (s, 2 H), 4.31–4.26 (m, 1 H), 3.84–3.81 (m, 1 H), 3.70 (s, 3 H), 3.65 (s, 3 H), 3.53 (dd, $J = 7.0, 9.8$ Hz, 1 H), 3.39 (s, 3 H), 2.95 (dd, $J = 4.2, 13.3$ Hz, 1 H), 3.78 (dd, $J = 9.8, 14.0$ Hz, 1 H); ^{13}C NMR (175 MHz, CDCl_3) δ 159.1, 157.7, 156.4, 148.1, 146.8, 129.6, 128.7, 128.4, 127.8, 126.8, 122.2, 114.5, 113.7, 109.2, 108.6, 101.1, 63.9, 55.5, 55.4, 53.8, 38.9, 35.6; IR (film) 3005, 1640 cm^{-1} . MS (ESI) 446.2077 (446.2074 calcd for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_4$, M^+).



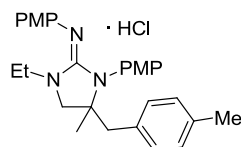
4-[(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl]-*N*,3-bis(4-methoxyphenyl)-1-methylimidazolidin-2-imine hydrochloride (2-13): The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 6-bromo-1,4-benzodioxane (30 μL , 0.225 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 67 mg (90%) of the title compound as a pale yellow-brown foam solid: mp = 76–77 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 6.95 (d, $J = 9.0$ Hz, 2 H), 6.88 (d, $J = 9.0$ Hz, 2 H), 6.78

(d, $J = 8.0$ Hz, 1 H), 6.61–6.57 (m, 4 H), 6.49 (d, $J = 8.5$ Hz, 2 H), 4.29–4.24 (m, 1 H), 4.23 (s, 4 H), 3.84–3.80 (m, 1 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.49 (dd, $J = 7.0, 10.5$ Hz, 1 H), 3.39 (s, 3 H), 2.92 (dd, $J = 4.5, 13.5$ Hz, 1 H), 2.72 (dd, $J = 9.5, 14.0$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0, 157.5, 156.4, 143.7, 142.9, 129.9, 128.5, 128.3, 127.9, 126.5, 122.0, 117.7, 117.7, 114.5, 113.7, 64.4, 64.3, 63.9, 55.5, 55.4, 53.7, 38.5, 35.3; IR (film) 3000, 1639 cm^{-1} . MS (ESI) 460.2226 (460.2231 calcd for $\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_4$, M^+).



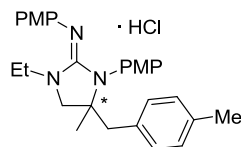
***N*,3-Bis(4-methoxyphenyl)-1-methyl-4-(2-methylbenzyl)imidazolidin-2-imine hydrochloride**

(2-14): The general procedure was employed for the coupling of **2-4** (54 mg, 0.15 mmol) and 2-bromotoluene (27 μL , 0.23 mmol) using a catalyst composed of $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 52 mg (76%) of the title compound as a pale yellow-brown foam solid. The material contained ca. 8% of an unsaturated cyclic guanidine resulting from oxidation of the title compound (tentatively assigned as the 2-aminoimidazole derivative (*E*)-*N*,3-bis(4-methoxyphenyl)-1-methyl-4-(2-methylbenzyl)-1,3-dihydro-2*H*-imidazol-2-imine hydrochloride). mp = 78–79 $^\circ\text{C}$. ^1H NMR (700 MHz, CDCl_3) δ 7.15–7.11 (m, 3 H), 7.08–7.07 (m, 1 H), 7.00 (d, $J = 9.1$ Hz, 2 H), 6.90 (d, $J = 8.4$ Hz, 2 H), 6.60 (d, $J = 9.1$ Hz, 2 H), 6.49 (d, $J = 9.1$ Hz, 2 H), 4.33–4.29 (m, 1 H), 3.81–3.78 (m, 1 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.54 (dd, $J = 7.7, 10.5$ Hz, 1 H), 3.42 (s, 3 H), 3.06 (dd, $J = 4.2, 14.0$ Hz, 1 H), 2.81 (dd, $J = 10.5, 14.0$ Hz, 1 H), 2.10 (s, 3 H); ^{13}C NMR (175 MHz, CDCl_3) δ 159.0, 157.5, 156.4, 136.3, 133.4, 130.8, 129.6, 129.6, 128.6, 128.2, 127.5, 126.6, 126.4, 114.5, 113.7, 62.6, 55.5, 55.4, 54.1, 36.8, 35.5, 19.3; IR (film) 3002, 1630 cm^{-1} . MS (ESI) 416.2328 (416.2333 calcd for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_2$, M^+).



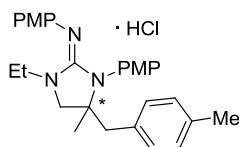
1-Ethyl-*N*,3-bis(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-imine

hydrochloride (2-15): The general procedure was employed for the coupling of **2-5** (59 mg, 0.15 mmol) and 4-bromotoluene (35 mg, 0.23 mmol) using a catalyst composed of Pd₂(dba)₃ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 71 mg (99%) of the title compound as a pale yellow-brown foam solid: mp = 61–62 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.18 (d, *J* = 8.0 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 6.90–6.87 (m, 4 H), 6.61 (d, *J* = 8.5 Hz, 2 H), 6.50 (d, *J* = 8.5 Hz, 2 H), 4.02–3.95 (m, 1 H), 3.87–3.80 (m, 2 H), 3.70 (s, 3 H), 3.65 (s, 3 H), 3.35 (d, *J* = 10.5 Hz, 1 H), 2.98 (d, *J* = 13.5 Hz, 1 H), 2.75 (d, *J* = 13.5 Hz, 1 H), 2.36 (s, 3 H), 1.26–1.20 (m, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 159.2, 157.3, 155.2, 137.6, 131.5, 130.2, 130.0, 129.5, 128.7, 127.0, 126.2, 114.3, 113.7, 65.7, 55.9, 55.5, 55.5, 45.1, 42.0, 25.3, 21.1, 12.3; IR (film) 2971, 1630 cm⁻¹. MS (ESI) 444.2645 (444.2646 calcd for C₂₈H₃₄N₃O₂, M⁺).

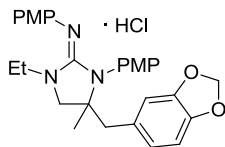


(+)-1-Ethyl-*N*,3-bis(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-imine

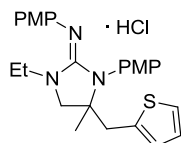
hydrochloride (2-15; prepared using (*S*)-Phanephos as ligand): The general procedure for the asymmetric synthesis of cyclic guanidine products was employed for the coupling of **2-5** (58.5 mg, 0.15 mmol) and 4-bromotoluene (39 mg, 0.225 mmol) using a catalyst composed of Pd₂(dba)₃ (2.7 mg, 0.003 mmol), and (*S*)-Phanephos (6.9 mg, 0.012 mmol) except the reaction was run for 36 hrs in order to ensure complete conversion. This procedure afforded 65.0 mg (84%) of the title compound as a pale yellow-brown foam solid: [α]²³_D +18.0 (c 1.3, CH₂Cl₂). Spectroscopic data were identical to those provided above. The enantiomeric purity was determined to be 61:39 er as assessed by converting this compound to the corresponding Mosher amide (see below for details).



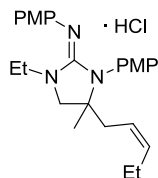
(+)-1-Ethyl-*N*,3-bis(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-imine hydrochloride (2-15; prepared using (*S*)-BINAP as ligand): The general procedure for the asymmetric synthesis of cyclic guanidine products was employed for the coupling of **2-5** (39 mg, 0.1 mmol) and 4-bromotoluene (26 mg, 0.15 mmol) using a catalyst composed of Pd₂(dba)₃ (1.8 mg, 0.002 mmol), and (*S*)-BINAP (5.0 mg, 0.008 mmol). This procedure afforded 48 mg (99%) of the title compound as a pale yellow-brown foam solid: $[\alpha]_D^{23} -5.9$ (c 0.9, CH₂Cl₂). Spectroscopic data were identical to those provided above. The enantiomeric purity was determined to be 48:52 er as assessed by converting this compound to the corresponding Mosher amide (see below for details).



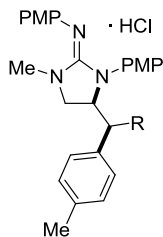
4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-ethyl-*N*,3-bis(4-methoxyphenyl)-4-methylimidazolidin-2-imine hydrochloride (2-16): The general procedure was employed for the coupling of **2-5** (59 mg, 0.15 mmol) and 4-bromo-1,2-(methylenedioxy)benzene (27 μL, 0.225 mmol), using a catalyst composed of Pd₂(dba)₃ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 76 mg (99%) of the title compound as a pale yellow-brown foam solid: mp = 66–67 °C. ¹H NMR (500 MHz, CDCl₃) δ 6.93–6.83 (m, 4 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 6.71–6.68 (m, 2 H), 6.62 (s, br, 2 H), 6.51 (d, *J* = 8.5 Hz, 2 H), 5.98 (s, 2 H), 4.01–3.94 (m, 1 H), 3.88 (d, *J* = 10.0 Hz, 1 H), 3.84–3.77 (m, 1 H), 3.71 (s, 3 H), 3.66 (s, 3 H), 3.42 (d, *J* = 10.5 Hz, 1 H), 2.96 (d, *J* = 13.5 Hz, 1 H), 2.69 (d, *J* = 13.5 Hz, 1 H), 1.26–1.19 (m, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 159.3, 157.6, 155.3, 148.0, 147.2, 129.8, 128.1, 128.0, 126.7, 126.7, 123.6, 114.4, 113.7, 110.4, 108.5, 101.3, 65.8, 55.9, 55.5, 55.5, 45.0, 42.1, 25.3, 12.3; IR (film) 2972, 1627 cm⁻¹. MS (ESI) 474.2379 (474.2387 calcd for C₂₈H₃₂N₃O₄, M⁺).



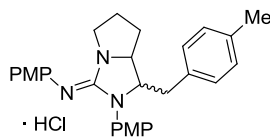
1-Ethyl-*N*,3-bis(4-methoxyphenyl)-4-methyl-4-(thiophen-2-ylmethyl)imidazolidin-2-imine hydrochloride (2-17): The general procedure was employed for the coupling of **2-5** (59 mg, 0.15 mmol) and 2-bromothiophene (22 μ L, 0.225 mmol), using a catalyst composed of Pd₂(dba)₃ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol). This procedure afforded 70 mg (99%) of the title compound as a pale yellow-brown foam solid: mp = 63–65 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.31–7.30 (m, 1 H), 7.06–6.97 (m, 6 H), 6.62 (d, J = 8.5 Hz, 2 H), 6.49 (d, J = 9.5 Hz, 2 H), 3.98–3.87 (m, 2 H), 3.69–3.60 (m, 8 H), 3.24 (d, J = 15.5 Hz, 1 H), 3.05 (d, J = 15.0 Hz, 1 H), 1.27 (s, 3 H), 1.10 (t, J = 7.5 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 159.3, 157.4, 155.2, 136.3, 130.3, 128.4, 128.1, 127.2, 126.7, 126.4, 125.5, 114.4, 113.7, 65.3, 55.9, 55.5, 55.4, 41.9, 39.9, 26.0, 11.9; IR (film) 3041, 1630 cm⁻¹. MS (ESI) 436.2057 (436.2053 calcd for C₂₅H₂₉N₃O₂S, M⁺).



(*Z*)-1-Ethyl-*N*,3-bis(4-methoxyphenyl)-4-methyl-4-(pent-2-en-1-yl)imidazolidin-2-imine hydrochloride (2-18): The general procedure (using modified stoichiometries of reactants) was used for the coupling of **2-5** (59 mg, 0.15 mmol) and 1-bromobutene (300 μ L, 0.60 mmol, 4.0 equiv, 2 M solution in toluene) using a catalyst composed of Pd₂(dba)₃ (2.7 mg, 0.003 mmol), and Nixantphos (6.6 mg, 0.012 mmol) in the presence of NaOtBu (64.9 mg, 0.60 mmol, 4.5 equiv). This procedure afforded 57 mg (86%) of the title compound as a pale yellow-brown foam. ¹H NMR (700 MHz, CDCl₃) δ 6.99 (s, br, 1 H), 6.92 (d, J = 8.4 Hz, 2 H), 6.76 (s, br, 1 H), 6.65–6.53 (m, br, 2 H), 6.49 (d, J = 9.1 Hz, 2 H), 5.74–5.70 (m, 1 H), 5.39–5.35 (m, 1 H), 4.10–4.05 (m, 1 H), 3.92–3.86 (m, 1 H), 3.71–3.67 (m, 1 H), 3.68 (s, 3 H), 3.64 (s, 3 H), 3.59 (d, J = 9.8 Hz, 1 H), 2.42 (dd, J = 6.3, 14.7 Hz, 1 H), 2.28 (dd, J = 7.7, 15.4 Hz, 1 H), 2.10–2.06 (m, 2 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.25 (s, 3 H), 1.01 (t, J = 7.7 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 159.2, 157.3, 155.0, 137.3, 130.5, 129.7, 128.1, 126.3, 120.7, 114.2, 113.7, 65.3, 56.2, 55.4, 55.4, 42.2, 37.1, 25.6, 21.0, 13.9, 12.3; IR (film) 3006, 1627 cm⁻¹. MS (ESI) 408.2643 (408.2646 calcd for C₂₅H₃₄N₃O₂, M⁺).



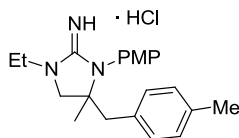
(±)-(*S**,*S**)-*N*,3-Bis(4-methoxyphenyl)-1-methyl-4-(phenyl(*p*-tolyl)methyl)imidazolidin-2-imine hydrochloride (**2-19a**). The general procedure was employed for the coupling of **2-6a** (132 mg, 0.3 mmol) and 4-bromotoluene (76 mg, 0.45 mmol), using a catalyst composed of Pd₂(dba)₃ (5.5 mg, 0.006 mmol), and Nixantphos (13.2 mg, 0.024 mmol). This procedure afforded 35 mg (22%) of the title compound as a pale yellow-brown solid: mp = 91–93 °C. This compound was judged to be a single diastereomer (> 20:1 dr) by ¹H NMR analysis. ¹H NMR (700 MHz, CDCl₃) δ 11.33 (s, br, 1 H), 7.38–7.36 (m, 2 H), 7.31–7.29 (m, 1 H), 7.25–7.24 (m, 2 H), 7.04 (d, *J* = 7.7 Hz, 2 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 6.76 (d, *J* = 9.1 Hz, 2 H), 6.46 (d, *J* = 9.1 Hz, 2 H), 6.40 (s, 4 H), 4.65–4.62 (m, 1 H), 4.35 (d, *J* = 8.4 Hz, 1 H), 4.15–4.12 (m, 1 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 3.51 (dd, *J* = 4.9, 11.2 Hz, 1 H), 3.27 (s, 3 H), 2.28 (s, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 158.9, 158.1, 157.7, 139.3, 137.3, 136.6, 132.0, 129.6, 129.2, 128.6, 128.5, 128.2, 128.2, 127.9, 126.3, 114.1, 113.7, 66.7, 55.4, 54.8, 53.3, 35.2, 21.0 (one carbon signal is absent due to incidental equivalence); IR (film) 3105, 1641 cm⁻¹. MS (ESI) 492.2652 (492.2646 calcd for C₃₂H₃₄N₃O₂, M⁺).



(±)-*N*,2-Bis-(4-methoxyphenyl)-1-(4-methylbenzyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-imine hydrochloride (**2-20**). The general procedure was employed for the coupling of **2-7** (77.6 mg, 0.2 mmol) and 4-bromotoluene (52 mg, 0.3 mmol), using a catalyst composed of Pd₂(dba)₃ (3.6 mg, 0.004 mmol), and Nixantphos (8.8 mg, 0.016 mmol). This procedure afforded 53 mg (60%) of the title compound as a pale brown solid and as a 1.5:1 mixture of diastereomers as determined by ¹H NMR analysis. The data is for the mixture except the ¹H NMR data, which is

only for the major isomer. Mp = 58–61 °C. ¹H NMR (700 MHz, CDCl₃) δ 10.94, (s, br, 1 H), 7.21–7.14 (m, 4 H), 7.12–7.08 (m, 2 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 6.84–6.80 (m, 2 H), 6.68–6.67 (m, 2 H), 4.50–4.47 (m, 1 H), 3.95–3.92 (m, 1 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 3.45–3.44 (m, 1 H), 3.35–3.32 (m, br, 1 H), 2.98 (dd, *J* = 3.5, 13.3 Hz, 1 H), 2.53 (dd, *J* = 11.2, 14.0 Hz, 1 H), 2.31 (s, 3 H), 2.07–2.03 (m, 1 H), 1.87–1.79 (m, 1 H), 1.62–1.58 (m, 2 H); ¹³C NMR (175 MHz, CDCl₃) δ 159.6, 159.5, 157.8, 157.7, 137.0, 136.8, 132.4, 131.7, 129.7, 129.5, 129.4, 128.8, 128.4, 128.0, 126.6, 126.0, 125.4, 115.1, 115.1, 114.1, 68.4, 66.2, 64.9, 64.6, 55.5, 55.4, 49.3, 48.7, 38.2, 35.2, 31.2, 26.7, 26.2, 25.8, 21.0, 20.0; IR (film) 1625 cm⁻¹. MS (ESI) 442.2484 (442.2489 calcd for C₂₈H₃₂N₃O₂, M⁺).

Deprotection of Cyclic Guanidine Product 18

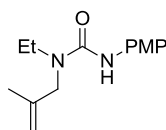
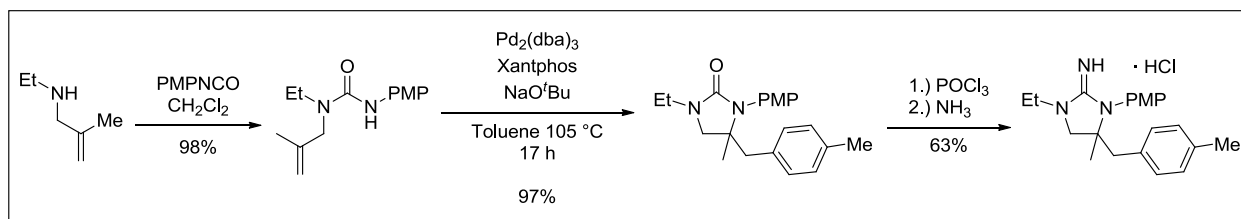


1-Ethyl-3-(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-imine

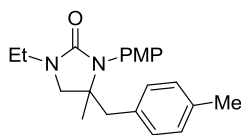
hydrochloride (2-21). A Schlenk tube was charged with a stirbar, **2-15** (48 mg, 0.1 mmol) and CH₃CN (1 mL). A solution of ceric ammonium nitrate (329 mg, 0.6 mmol) in H₂O (6 mL) was added to the reaction flask and the mixture was stirred at rt for 5 min. The mixture was then heated at 50 °C for 12 h before being cooled to rt, at which time dichloromethane (15 mL) was added. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 14.6 mg (39%) of the title compound as white solid: mp = 223–226 °C. ¹H NMR (700 MHz, CDCl₃) δ 7.19 (s, br 2 H), 7.13 (d, *J* = 7.7 Hz, 2 H), 7.03 (d, *J* = 9.1 Hz, 2 H), 6.98 (d, *J* = 7.7 Hz, 2 H), 3.91–3.88 (m, 1 H), 3.88 (s, 3 H), 3.84–3.81 (m, 1 H), 3.77 (d, *J* = 9.8 Hz, 1 H), 3.18 (d, *J* = 9.8 Hz, 1 H), 2.94 (d, *J* = 13.3 Hz, 1 H), 2.70 (d, *J* = 13.3 Hz, 1 H), 2.33 (s, 3 H), 1.31 (s, 3 H) 1.25 (t, *J* = 7.0

Hz, 3 H); ^{13}C NMR (175 MHz, CDCl_3) δ 161.1, 155.9, 137.5, 131.4 (br, 1 C), 131.3, 129.9, 129.6, 123.5, 115.8, 65.8, 55.7, 55.6, 43.7, 41.3, 23.9, 21.0, 12.2; IR (film) 3250, 1658 cm^{-1} . MS (ESI) 338.2228 (338.2227 calcd for $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}$, M^+).

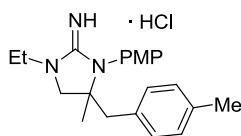
Structural Assignment of Deprotected Cyclic Guanidine Product 2-21.



1-Ethyl-3-(4-methoxyphenyl)-1-(2-methylallyl)urea (S2). A flame-dried flask equipped with a stirbar was charged with *N*-ethyl-2-methylallylamine (1.3 mL, 10 mmol) and dichloromethane (100 mL). 4-methoxyphenyl isocyanate (1.55 mL, 12 mmol) was added to the flask and the mixture was stirred at rt for 1 h. The crude reaction mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel to afford 2.43 mg (98%) of the title compound as a pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.23 (d, $J = 8.5$ Hz, 2 H), 6.82 (d, $J = 8.5$ Hz, 2 H), 6.30 (s, 1 H), 5.02 (s, br, 2 H), 3.83 (s, br, 2 H), 3.77 (s, 3 H), 3.42 (q, $J = 7.0$ Hz, 2 H), 1.79 (s, 3 H), 1.20 (t, $J = 7.0$ Hz, 3 H).



1-Ethyl-3-(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-one (S3): A flame-dried Schlenk tube was cooled under vacuum and charged with Pd₂(dba)₃ (110 mg, 0.12 mmol), xantphos (139 mg, 0.24 mmol), NaO^tBu (865 mg, 9.0 mmol), and 4-bromotoluene (1.5 g, 9.0 mmol). A solution of **S2** (1.5 g, 6.0 mmol) in toluene (30 mL) was added via syringe and the tube was heated to 105 °C for 3 h. The mixture was cooled to rt and saturated aqueous NH₄Cl (15 mL) and ethyl acetate (25 mL) were added. The layers were separated and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 1.96 mg (97%) of the title compound as an orange yellow oil. ¹H NMR (700 MHz, CDCl₃) δ 7.18 (d, *J* = 9.1 Hz, 2 H), 7.08 (d, *J* = 7.7 Hz, 2 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 6.92 (d, *J* = 9.1 Hz, 2 H), 3.82 (s, 3 H), 3.46 (d, *J* = 8.4 Hz, 1 H), 3.37–3.32 (m, 1 H), 3.27–3.22 (m, 1 H), 2.92 (d, *J* = 13.3 Hz, 1 H), 2.84 (d, *J* = 9.1 Hz, 1 H), 2.65 (d, *J* = 13.3 Hz, 1 H), 2.31 (s, 3 H), 1.22 (s, 3 H), 1.11 (t, *J* = 7.0 Hz, 3 H).

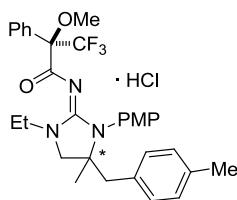
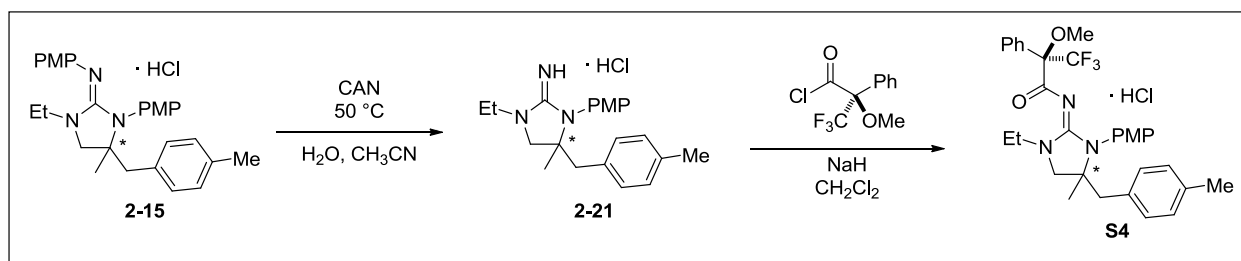


1-Ethyl-3-(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-imine hydrochloride (2-21). A flame-dried flask was cooled under a stream of N₂ and charged with **S3** (100 mg, 0.3 mmol) and toluene (2 mL). POCl₃ (0.6 mL) was added and the mixture was stirred at 100 °C until the starting material had been consumed as judged by ESI⁺ MS analysis (ca. 2 hr). The reaction mixture was cooled to rt and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (10 mL) and a solution of ammonia in ethanol (15 mL, 2 M in ethanol) was added. The mixture was stirred at rt until the starting material had been consumed as judged by ESI⁺ MS analysis (ca. 1 hr). The reaction mixture was concentrated and dissolved in dichloromethane (5 mL). Water (5 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer was washed with 1 M HCl (10 mL) and saturated aqueous sodium chloride (2 x 10 mL). The combined aqueous layers were extracted with dichloromethane (3 x 10 mL). The combined organics layers were dried over anhydrous sodium sulfate, filtered,

and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 70 mg (63%) of the title compound as a white solid. The spectroscopic properties of this compound were identical to that of compound **2-21** described above that was prepared by deprotection of **2-15**.

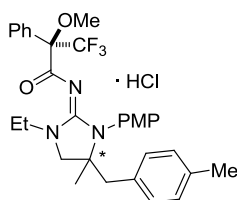
Stereochemical Analysis of Enantioenriched Cyclic Guanidine Product **2-15**.

In order to assess the enantiomeric purity of cyclic guanidine products **2-15** prepared from (*S*)-Phanephos and (*S*)-BINAP, the carboamination products were converted to the corresponding Mosher amides **S4** via the two-step procedure illustrated below. The enantiomeric ratio of **2-15** was assigned based on the diastereomeric ratio of crude **S4** as determined by ¹H NMR analysis.



(2*R*)-*N*-(1-Ethyl-3-(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-ylidene)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide hydrochloride (S4** prepared from (+)-**2-15** that was generated using (*S*)-Phanephos as ligand).** The chiral guanidine (+)-**18** prepared using (*S*)-Phanephos as the ligand (51.5 mg, 0.11 mmol) was deprotected with ceric ammonium nitrate (361 mg, 0.66 mmol) according to the procedure detailed above. After flash chromatography, this procedure afforded 8.0 mg (20%) of enantioenriched **2-21** as a brown solid. The spectroscopic properties of this compound were identical to that of racemic **2-21** described above. The purified nonracemic material **27** (8.0 mg, 0.02 mmol) was dissolved in dichloromethane (1 mL) and stirred

at rt. NaH (2.5 mg, 0.06 mmol, 60% dispersion in mineral oil) was added and the mixture was allowed to stir at rt for 10 min. Neat (*S*)-(+)- α -Methoxy- α -trifluoromethylphenylacetyl chloride (6 μ L, 0.03 mmol) was added via syringe and the mixture was stirred at rt until the starting material had been consumed as judged by ESI⁺MS analysis of an aliquot removed from the reaction mixture (ca. 1 hr). Brine (2 mL) was added and the biphasic mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 4 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. This procedure afforded a crude mixture that was determined to be a 61:39 mixture of diastereomers by ¹H NMR analysis. The crude material was purified by flash chromatography on silica gel to afford 8.9 mg (77%) of the title compound as a pale brown foamy-oil and as a 57:43 mixture of diastereomers (note that product er was assigned based on dr of the crude product, as some separation of diastereomers likely occurred during purification). Data are for the mixture of isomers. ¹H NMR (500 MHz, CDCl₃) δ 7.44–7.40 (m, 3.5 H), 7.29–7.24 (m, 3.75 H), 7.23–7.16 (m, 5 H), 7.12–7.10 (m, 3.5 H), 7.05–7.02 (m, 3.5 H), 6.89–6.87 (m, 3.5 H), 3.83 (s, 5.25 H), 3.77 (d, *J* = 10.0 Hz, 0.75 H), 3.73 (d, *J* = 10.0 Hz, 1 H), 3.35–3.25 (m, 2.75 H), 3.24 (s, 3 H), 3.22 (s, 2.25 H), 3.20–3.18 (m, 0.75 H), 3.16 (d, *J* = 10.0 Hz, 1 H), 3.10 (d, *J* = 10.5 Hz, 0.75 H), 3.07–3.03 (m, 1.75 H), 2.75 (d, *J* = 13.5 Hz, 1 H), 2.69 (d, *J* = 13.5 Hz, 0.75 H), 2.32 (s, 5.25 H), 1.31 (s, 2.25 H), 1.28 (s, 3 H), 1.12–1.08 (m, 5.25 H); ¹³C NMR (125 MHz, CDCl₃) δ 167.9, 167.8, 164.4, 164.3, 159.7, 159.6, 136.9, 136.9, 135.8, 135.7, 132.2, 132.2, 131.6, 131.6, 130.2, 130.1, 129.3, 129.3, 127.9, 127.6, 127.5, 127.5, 127.4, 125.7, 123.4, 114.1, 64.5, 64.5, 55.5, 55.0, 54.7, 54.3, 44.3, 43.9, 40.2, 40.1, 24.5, 24.4, 21.0, 12.4, 12.3; ¹⁹F NMR (376 MHz, CDCl₃) δ –69.56, –69.58; IR (film) 2925, 1653, 1559 cm⁻¹. MS (ESI) 554.2625 (554.2625 calcd for C₃₁H₃₄F₃N₃O₃, M⁺).



(2R)-N-(1-Ethyl-3-(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-ylidene)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide hydrochloride (S4 prepared from (–)-2-15 that was generated using (S)-BINAP as ligand). The chiral guanidine (–)-2-15 prepared using (S)-BINAP as the ligand (48 mg, 0.1 mmol) was deprotected with ceric ammonium nitrate (329 mg, 0.6 mmol) according to the procedure detailed above. After flash chromatography, this procedure afforded 14.4 mg (39%) of enantioenriched **2-21** as a brown solid. The spectroscopic properties of this compound were identical to that of compound racemic **2-21** described above. The purified nonracemic material **27** (14.4 mg, 0.04 mmol) was dissolved in dichloromethane (1 mL) and stirred at rt. NaH (4.8 mg, 0.12 mmol, 60% dispersion in mineral oil) was added and the mixture was allowed to stir at rt for 10 min. Neat (S)-(+)- α -Methoxy- α -trifluoromethylphenylacetyl chloride (11 μ L, 0.06 mmol) was added via syringe and the mixture was stirred at rt until the starting material had been consumed as judged by ESI⁺MS analysis of an aliquot removed from the reaction mixture (ca. 1 hr). Brine (2 mL) was added and the biphasic mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 4 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. This procedure afforded a crude mixture that was determined to be a 48:52 mixture of diastereomers by ¹H NMR analysis. The crude material was purified by flash chromatography on silica gel to afford 10.8 mg (48%) of the title compound as a pale brown foamy-oil and as a 51:49 mixture of diastereomers. Spectroscopic data were identical to those described above (although integration ratios differed due to the differences in product distribution).

Chapter 3

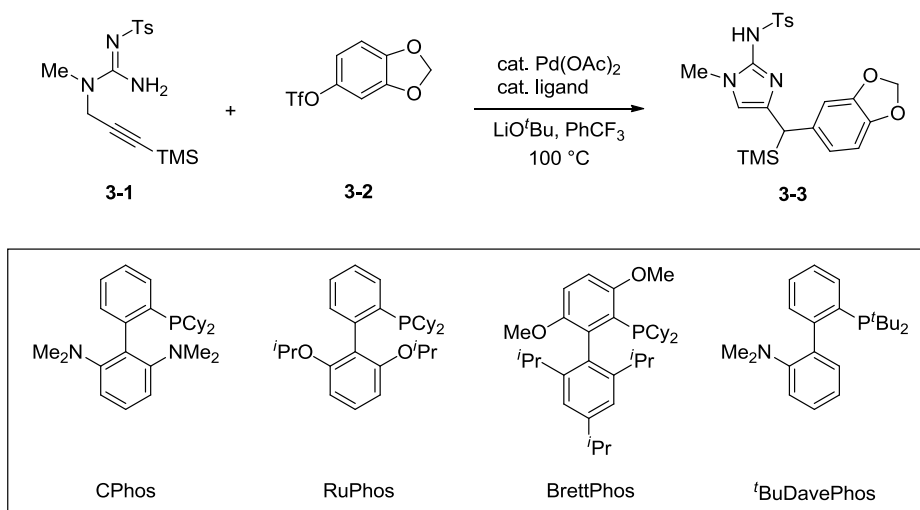
Synthesis of 2-Aminoimidazoles via Pd-Catalyzed Alkyne Carboamination Reactions and Applications to Natural Product Synthesis

3.1 Introduction

As detailed in Chapter 1, the unsaturated cyclic guanidine structural motif is ubiquitous in many biologically active natural products (see Figure 1.1).^{1-7,9,11-15,54,55} As such, many research groups have developed elegant syntheses that can rapidly and efficiently fashion these products from commercially available sources.^{9,10,12,14,15,42} However, none of these routes accommodate late stage derivatization of the targeted product. For this reason, we set out to develop a methodology that has the ability to create libraries of analogues from a simple, easily accessible substrate.

3.2 Optimization of Reaction Conditions

In light of the deprotection issues of bis-PMP protected substrates found in chapter 2, along with the lack of stability of bis-Boc protected substrate **2-3**, we targeted a new series of substrates. As such, the mono-protected *N*-tosyl guanidine **3-1** was constructed. To our delight, **3-1** was smoothly converted to the unsaturated carboamination product **3-3** by using a variety of different Buchwald ligands (Table 3.1, entries 1-4). The monodentate ligand RuPhos (entry 2) afforded the desired product in the highest yield.

Table 3.1 Optimization of Ligand Choice^a

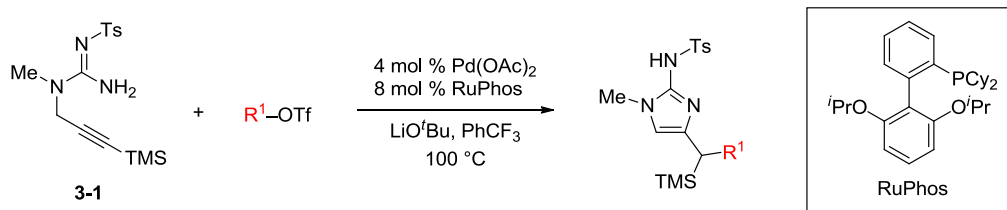
Entry	Ligand	Yield (%) ^b
1	CPhos	(80)
2	RuPhos	(81) 80
3	BrettPhos	(45)
4	^t BuDavePhos	(41)

^a Conditions: 1.0 equiv of guanidine substrate, 1.2 equiv of **3-2**, 2.4 equiv of LiO^tBu, 4 mol % Pd(OAc)₂, 8 mol % ligand, trifluorotoluene (0.1 M), 100 °C, reactions run for 3 h. ^b Isolated yields. Numbers in parentheses are NMR yields based on phenanthrene as an internal standard.

3.3 Examination of Scope

With optimized conditions in hand, the scope of these Pd-catalyzed carboamination transformations was analyzed by coupling **3-1** with a variety of aryl triflates (Table 3.2). Gratifyingly, aryl triflates bearing electron-donating, electron-neutral, and electron-withdrawing groups (entries 1-5) afforded the corresponding unsaturated cyclic guanidine in good yields. However, coupling substrate **3-1** with 4-benzoylphenyl trifluoromethanesulfonate required a shorter reaction time in order to prevent conversion to the desilylated product (entry 5). Another issue regarding electron poor aryl triflates is decomposition of the triflate to the corresponding alcohol, which was solved by using 2 equivalents of the aryl triflate. Additionally, the use of an *ortho* substituted aryl triflate underwent smooth conversion to the desired carboamination product (entry 4).

Table 3.2 Scope of Carboamination Reaction^a



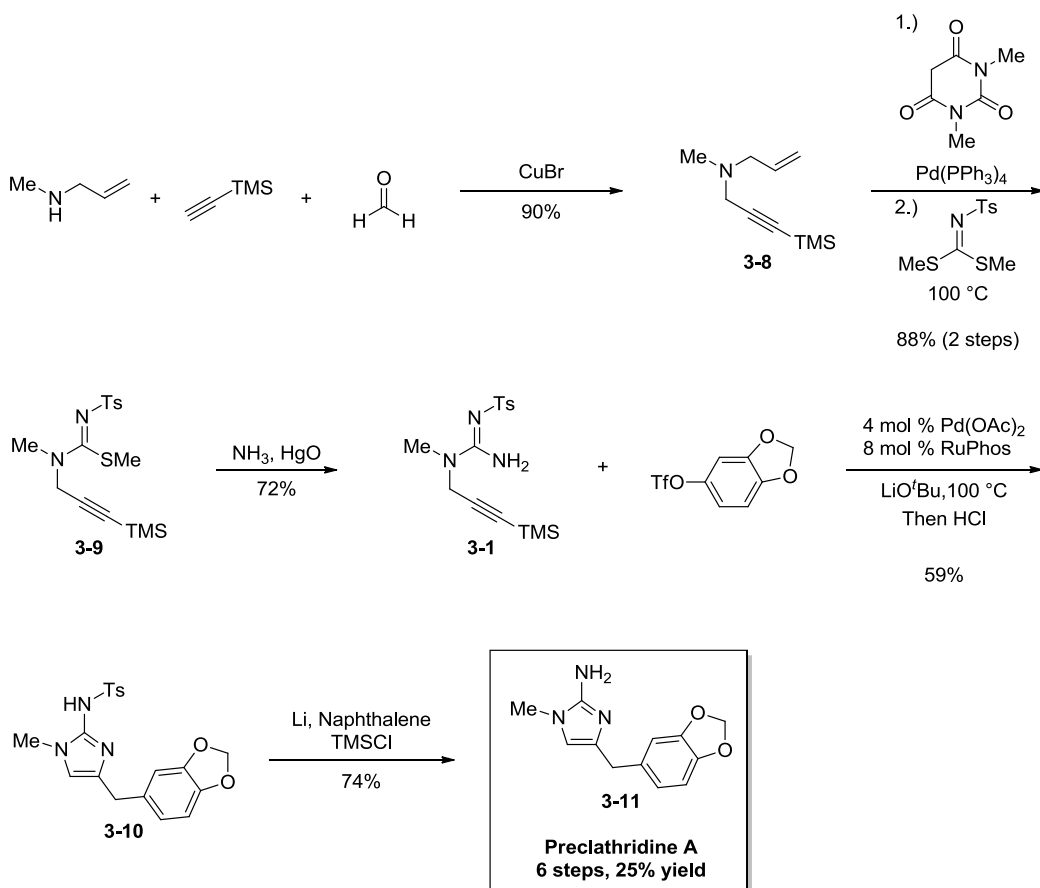
Entry	Product	Yield (%) ^b
1 ^c	 3-3	81
2 ^c	 3-4	85
3	 3-5	82
4	 3-6	78
5 ^d	 3-7	95

^a Conditions: 1.0 equiv of guanidine substrate, 2.0 equiv R^1-OTf , 2.4 equiv of $LiOtBu$, 4 mol % $Pd(OAc)_2$, 8 mol % RuPhos, trifluorotoluene (0.1 M), reactions run overnight. ^b Isolated yields. ^c This reaction ran for 3 h and was conducted using 1.2 equiv of R^1-OTf . ^d Reaction was run for 30 min.

3.4 Application to Total Synthesis

To showcase the utility of this carboamination reaction, it was employed as a key step in the synthesis of preclathridine A. The tertiary amine **3-8** was efficiently prepared from commercially available reagents, following a procedure from Looper and coworkers.²² This molecule was then deprotected and coupled to afford the pseudothiourea **3-9** in good yield. Careful selection of metal and reaction temperature were necessary to produce guanidine **3-1** without generation of the undesirable 2-aminoimidazole side product, formed via hydroamination. The carboamination reaction of **3-1** proceeded smoothly, followed by an acidic workup to afford the desilylated cyclic guanidine **3-10**. Deprotection of *N*-tosyl resulted in the synthesis of preclathridine A, in 6 steps and 25% overall yield. This strategy allows for the rapid functionalization of a late stage intermediate, an approach that can readily access analogues of the biologically active natural product from an easily accessible substrate that has been made on gram scale.

Scheme 3.1 Total synthesis of preclathridine A



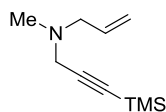
3.5 Conclusion

In conclusion, we have developed a new method for the construction of unsaturated 5-membered cyclic guanidines. The carboamination reactions proceed in good yields (78-95%) and tolerates a wide variety of aryl triflates. Additionally, this reaction was employed in the highly flexible synthesis of preclathridine A. Further studies are aimed at examining the substrate scope, as well as the synthesis of more 2-aminoimidazole containing natural products.

3.6 Experimental

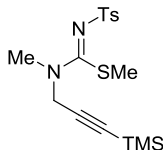
General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware unless otherwise noted. Palladium acetate and ligands used in this section were purchased from Strem Chemical Co. and used without purification. Aryl triflates were prepared according to a procedure published by Frantz and coworkers,⁵⁶ followed by additional purification by column chromatography. All other reagents were obtained from commercial sources and were used as obtained unless otherwise noted. Lithium *tert*-butoxide was kept in a glove box and removed only prior to use. Toluene, THF, diethyl ether and dichloromethane were purified using a GlassContour solvent purification system. Trifluorotoluene was purified by distillation under N₂ prior to use. Yields refer to isolated yields of compounds estimated to be $\geq 95\%$ pure as determined by ¹H NMR analysis unless otherwise noted.

Preparation and Characterization of Guanidine Substrate 3-2



***N*-methyl-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl)prop-2-en-1-amine (3-8).** The title compound was prepared using the general procedure reported by Looper.²² A flame-dried flask equipped with a stirbar was cooled under a stream of N₂, and charged with acetonitrile (78 mL), *N*-methylallylamine (1.5 mL, 15.6 mmol), formaldehyde (3 mL, 69 mmol, 37% solution in water), ethynyltrimethylsilane (1.67 mL, 11.7 mmol), and copper (I) bromide (224 mg, 1.56 mmol). The resulting reaction mixture was stirred overnight (16 h) at rt, and had turned to a pale green solution. The solution was then concentrated *in vacuo* to afford the crude product, which was then dissolved in diethyl ether (15 mL). The mixture was filtered through a plug of celite, and the celite was washed with 200 mL of dichloromethane. The filtrate was transferred to a separatory funnel, and 1 M NaOH (60 mL) was added to the separatory funnel. The layers were separated, and the organic layer was extracted. The organic layer was washed with 1 M NaOH (2 x 60 mL), then dried over anhydrous sodium sulfate. The crude product concentrated *in vacuo*, and was purified by flash chromatography on silica gel to afford 1.91 g (90%) of the title compound as a clear and colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 5.87–5.79 (m, 1 H), 5.21 (d, *J* = 17 Hz, 1 H), 5.15 (d, *J* = 10

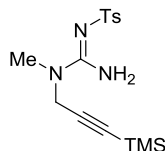
Hz, 1 H), 3.31 (s, 2 H), 3.04 (d, $J = 7$ Hz, 2 H), 2.29 (s, 3 H), 0.17 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.6, 118.3, 101.2, 90.1, 59.3, 46.4, 41.8, 0.3; IR (film) 2218 cm^{-1} . MS (ESI) 182.1365 (182.1360 calcd for $\text{C}_{10}\text{H}_{19}\text{NSi}$, $\text{M} + \text{H}^+$).



(Z)-methyl N-methyl-N'-tosyl-N-(3-(trimethylsilyl)prop-2-yn-1-yl)carbamimidothioate (3-9). The intermediate compound was prepared using the general procedure reported by Looper.²² A Schlenk flask equipped with a stirbar was flame-dried under vacuum, and was evacuated and backfilled with nitrogen. The flask was charged with tetrakis(triphenylphosphine)palladium(0) and 1,3-dimethylbarbituric acid (2.96 g, 19 mmol), and was then evacuated and backfilled with nitrogen. A solution of **3-8** (2.29 g, 12.7 mmol) and dichloromethane (63 mL) was added through a rubber septum. The resulting solution was stirred overnight (16 h) at rt, and had turned to a golden yellow color. The crude material was dissolved in ether (70 mL) and transferred to a separatory funnel. A solution of saturated bicarbonate (25 mL) was added to the separatory funnel. The layers were separated, and the organic layer was extracted. The organic layer was washed with a solution of saturated bicarbonate (2 x 25 mL), then washed with 1 M HCl (3 x 25 mL). The combined acidic aqueous layers were basified with potassium carbonate, then transferred to a separatory funnel. Dichloromethane (25 mL) was added to the separatory funnel. The layers were separated, and the organic layer was extracted. The aqueous layer was washed with dichloromethane (2 x 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and gently concentrated *in vacuo*. The obtained product *N*-methyl-3-(trimethylsilyl)prop-2-yn-1-amine was directly carried on to the next step of the reaction.

A flame-dried bomb flask equipped with a stirbar was cooled under a stream of N_2 , and charged with dimethyl tosylcarbonimidodithioate (2.89 g, 10.5 mmol), *N*-methyl-3-(trimethylsilyl)prop-2-yn-1-amine (1.78 g, 12.6 mmol), and toluene (12 mL). The resulting solution was stirred for 2.5 h at $100\text{ }^\circ\text{C}$, then dissolved in diethyl ether (50 mL) and transferred to a separatory funnel. 1 M HCl (5 mL) was added to the separatory funnel. The layers were separated, and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 3.41 g (88% over both steps) of the title

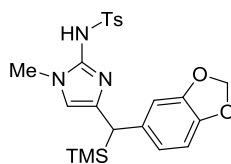
compound as a white solid. The material contained ca. 6% of substrate tosylcarbonimidodithioate. mp = 66–70 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.83 (d, *J* = 8 Hz, 2 H), 7.25 (d, *J* = 8 Hz, 2 H), 4.36 (s, 2 H), 3.25 (s, 3 H), 2.58 (s, 3 H), 2.40 (s, 3 H), 0.17 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 167.3, 142.0, 141.7, 129.3, 126.3, 98.1, 91.4, 43.5, 38.6, 21.6, 18.1, -0.1; IR (film) 2178, 1527 cm⁻¹. MS (ESI) 369.1123 (369.1121 calcd for C₁₆H₂₄N₂O₂S₂Si, M + H⁺).



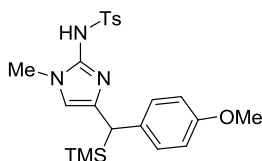
(E)-N-(amino(methyl(3-(trimethylsilyl)prop-2-yn-1-yl)amino)methylene)-4-

methylbenzenesulfonamide (3-1). A flame-dried bomb flask equipped with a stirbar was cooled under a stream of N₂, and charged with **3-9** (1.38 g, 3.7 mmol), mercury (II) oxide (1.22 g, 5.6 mmol), ammonia (37 mL, 2 M solution in ethanol), and triethylamine (2.35 mL, 16.8 mmol). The resulting reaction mixture was stirred at rt overnight (15 h), during which the mixture changed from bright orange to gray with hints of orange. The reaction mixture was filtered through a plug of celite, and the celite was washed with dichloromethane (200 mL). The filtrate was concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography on silica gel to afford 907 mg (72%) of the title compound as an off white powder solid: mp = 136–137 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* = 8 Hz, 2 H), 7.23 (d, *J* = 8 Hz, 2 H), 6.35 (s, br, 2 H), 4.22 (s, 2 H), 3.00 (s, 3 H), 2.39 (s, 3 H), 0.15 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 156.0, 142.1, 141.2, 129.3, 126.2, 99.1, 90.8, 40.0, 34.7, 21.6, -0.1; IR (film) 3415, 3330, 2178, 1629, 1544, 1495 cm⁻¹. MS (ESI) 338.1354 (338.1353 calcd for C₁₅H₂₃N₃O₂SSi, M + H⁺).

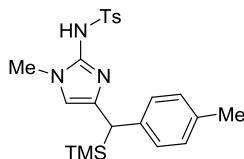
General Procedure for the Pd-Catalyzed Synthesis of 2-Aminoimidazoles. A flame-dried Schlenk tube equipped with a stir bar was cooled under vacuum and charged with **3-1** (1.0 equiv), RuPhos (0.08 equiv), and lithium *tert*-butoxide (2.4 equiv). The appropriate aryl triflate (2.0 equiv) was added. The flask was evacuated and purged with N₂. A pre-stirred solution of palladium (II) acetate (0.04 equiv) in trifluorotoluene (0.9 mg/mL) was added via syringe and the tube was heated to 100 °C and stirred overnight (~16 h). The mixture was cooled to rt and H₂O (10 mL/mmol substrate) and ethyl acetate (25 mL/mmol substrate) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (25 mL/mmol substrate). The organic layers were combined and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.



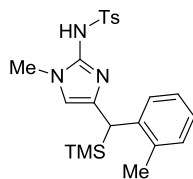
***N*-(4-(benzo[*d*][1,3]dioxol-5-yl(trimethylsilyl)methyl)-1-methyl-1*H*-imidazol-2-yl)-4-methylbenzenesulfonamide (3-3).** The general procedure was employed for the coupling of **3-1** (51 mg, 0.15 mmol) and benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate (31 μL, 0.18 mmol), using a catalyst composed of Pd(OAc)₂ (1.3 mg, 0.006 mmol) and RuPhos (5.6 mg, 0.012 mmol). This procedure afforded 55 mg (80%) of the title compound as a light orange powder solid: mp = 90–93 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.70 (s, br, 1 H), 7.75 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8 Hz, 2 H), 6.73–6.71 (m, 1 H), 6.50–6.48 (m, 2 H), 6.13 (s, 1 H), 5.94 (s, 2 H), 3.32 (s, 3 H), 3.22 (s, 1 H), 2.37 (s, 3 H), 0.05 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 148.0, 146.8, 145.9, 141.7, 132.9, 129.3, 126.3, 126.0, 121.0, 111.3, 108.6, 108.4, 101.2, 34.6, 31.7, 21.6, -2.0 (one carbon signal is missing due to incidental equivalence); IR (film) 3293, 1619, 1585, 1485 cm⁻¹. MS (ESI) 458.1569 (458.1564 calcd for C₂₂H₂₇N₃O₄SSi, M + H⁺).



***N*-(4-((4-methoxyphenyl)(trimethylsilyl)methyl)-1-methyl-1*H*-imidazol-2-yl)-4-methylbenzenesulfonamide (3-4).** The general procedure was employed for the coupling of **3-1** (51 mg, 0.15 mmol) and 4-methoxyphenyl trifluoromethanesulfonate (33 μ L, 0.18 mmol), using a catalyst composed of Pd(OAc)₂ (1.3 mg, 0.006 mmol) and RuPhos (5.6 mg, 0.012 mmol). This procedure afforded 57 mg (85%) of the title compound as a pale yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 9.76 (s, br, 1 H), 7.75 (d, *J* = 8.5, 2 H), 7.17 (d, *J* = 8 Hz, 2 H), 6.95 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 6.13 (s, 1 H), 3.78 (s, 3 H), 3.31 (s, 3 H), 3.28 (s, 1 H), 2.36 (s, 3 H), 0.03 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 157.9, 146.7, 141.8, 141.6, 131.1, 129.2, 129.0, 126.7, 126.0, 114.2, 111.1, 55.4, 33.9, 31.7, 21.5, 2.1; IR (film) 3289, 1616, 1581, 1508 cm⁻¹. MS (ESI) 444.1784 (444.1772 calcd for C₂₂H₂₉N₃O₃SSi, M + H⁺).

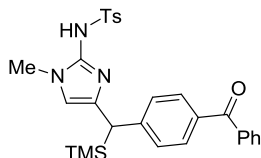


4-methyl-*N*-(1-methyl-4-(*p*-tolyl(trimethylsilyl)methyl)-1*H*-imidazol-2-yl)benzenesulfonamide (3-5). The general procedure was employed for the coupling of **3-1** (51 mg, 0.15 mmol) and *p*-tolyl trifluoromethanesulfonate (54 μ L, 0.30 mmol), using a catalyst composed of Pd(OAc)₂ (1.3 mg, 0.006 mmol) and RuPhos (5.6 mg, 0.012 mmol). This procedure afforded 53 mg (82%) of the title compound as an off-white powder solid: mp = 172–173 °C ¹H NMR (500 MHz, CDCl₃) δ 9.73 (s, br, 1 H), 7.74 (d, *J* = 8 Hz, 2 H), 7.16 (d, *J* = 8 Hz, 2 H), 7.06 (d, *J* = 7.5 Hz, 2 H), 6.91 (d, *J* = 8 Hz, 2 H), 6.13 (s, 1 H), 3.30 (s, 3 H), 3.27 (s, 1 H), 2.36 (s, 3 H), 2.30 (s, 3 H), 0.03 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 146.9, 141.9, 141.8, 136.1, 135.7, 129.6, 129.4, 128.0, 126.6, 126.1, 111.3, 34.7, 31.8, 21.7, 21.2, -2.0; IR (film) 3288, 1618, 1581 cm⁻¹. MS (ESI) 428.1825 (428.1823 calcd for C₂₂H₂₉N₃O₂SSi, M + H⁺).



4-methyl-N-(1-methyl-4-(*o*-tolyl(trimethylsilyl)methyl)-1*H*-imidazol-2-

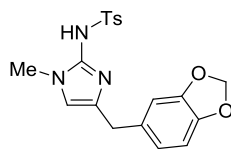
yl)benzenesulfonamide (3-6): The general procedure was employed for the coupling of **3-1** (51 mg, 0.15 mmol) and *o*-tolyl trifluoromethanesulfonate (53 μ L, 0.30 mmol), using a catalyst composed of Pd(OAc)₂ (1.3 mg, 0.006 mmol) and RuPhos (5.6 mg, 0.012 mmol). This procedure afforded 50 mg (78%) of the title compound as an off-white powder solid: mp = 188–190 °C ¹H NMR (500 MHz, CDCl₃) δ 9.65 (s, br, 1 H), 9.74 (d, *J* = 8.5, 2 H), 7.19–7.09 (m, 5 H), 7.01 (d, *J* = 8 Hz, 1 H), 6.08 (s, 1 H), 3.54 (s, 1 H), 3.29 (s, 3 H), 2.36 (s, 3 H), 2.27 (s, 3 H), 0.06 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 146.6, 141.9, 141.5, 137.5, 135.7, 131.3, 129.4, 127.9, 126.6, 126.5, 126.3, 126.1, 111.1, 31.8, 30.1, 21.8, 20.9, -1.7; IR (film) 3292, 1616, 1580, 1483 cm⁻¹. MS (ESI) 428.1824 (428.1823 calcd for C₂₂H₂₉N₃O₂SSi, M + H⁺).



N-(4-((4-benzoylphenyl)(trimethylsilyl)methyl)-1-methyl-1*H*-imidazol-2-yl)-4-

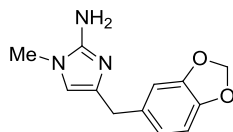
methylbenzenesulfonamide (3-7). The general procedure was employed for the coupling of **3-1** (51 mg, 0.15 mmol) and 4-benzoylphenyl trifluoromethanesulfonate (99.1 mg, 0.30 mmol), using a catalyst composed of Pd(OAc)₂ (1.3 mg, 0.006 mmol) and RuPhos (5.6 mg, 0.012 mmol). This procedure afforded 74 mg (95%) of the title compound as an off-white powder solid: mp = 206–208 °C ¹H NMR (700 MHz, CDCl₃) δ 9.98 (s, br, 1 H), 7.77 (t, *J* = 8.4 Hz, 4 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.58 (t, *J* = 7.7 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 2 H), 7.16 (d, *J* = 7.7 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H) 6.24 (s, 1 H), 3.58 (s, 3 H), 2.34 (s, 3 H), 0.04 (s, 9 H); ¹³C NMR (175 MHz, CDCl₃) δ 196.4, 146.7, 144.8, 141.9, 141.7, 137.9, 135.2, 132.5, 130.7, 130.1, 129.3, 128.5, 127.8, 126.0, 125.5, 111.8, 35.3, 31.8, 21.6, -2.2; IR (film) 3290, 1619, 1581 cm⁻¹. MS (ESI) 518.1938 (518.1928 calcd for C₂₈H₃₁N₃O₃SSi, M + H⁺).

Conversion of 3-1 to Preclathridine A



***N*-(4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-1-methyl-1*H*-imidazol-2-yl)-4-**

methylbenzenesulfonamide (3-10). A flame-dried Schlenk tube equipped with a stir bar was cooled under vacuum and charged with **3-1** (51 mg, 0.15 mmol), RuPhos (5.6 mg, 0.012 mmol), and lithium *tert*-butoxide (29 mg, 0.36 mmol). Benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate (64 μ L, 0.30 mmol) was added. The flask was evacuated and purged with N₂. A pre-stirred solution of palladium (II) acetate (1.3 mg, 0.006 mmol) in trifluorotoluene (1.5 mL) was added via syringe and the tube was heated to 100 °C and stirred overnight (~16 h). 4 M HCl in dioxane (2 mL) was added, and reaction continued stirring at 100 °C for 25 min. The mixture was cooled to rt and saturated sodium bicarbonate was added to the reaction mixture (4 mL). The mixture was transferred to a separatory funnel, and ethyl acetate was added (30 mL). The layers were separated, and the organic layer was extracted. The aqueous layer was washed with ethyl acetate (2 x 30 mL). The organic layers were combined and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 34 mg (59%) of the title compound as an off-white solid: mp = 193–194 °C ¹H NMR (500 MHz, CDCl₃) δ 9.95 (s, br, 1 H), 7.78 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8 Hz, 2 H), 6.72 (d, *J* = 8.5 Hz, 1 H), 6.61 (d, *J* = 6.5 Hz, 2 H), 5.97 (s, 1 H), 5.94 (s, 2 H), 3.66 (s, 2 H), 3.27 (s, 3 H), 2.37 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 148.2, 147.3, 146.9, 141.8, 141.7, 130.0, 129.3, 126.0, 125.0, 121.9, 112.1, 109.2, 108.6, 101.3, 31.7, 31.2, 21.6; IR (film) 3287, 1581, 1488 cm⁻¹. MS (ESI) 386.1172 (386.1169 calcd for C₁₉H₁₉N₃O₄S, M + H⁺).



Preclathridine A (3-11): A Schlenk tube equipped with a stir bar was flame-dried under vacuum. The flask was then evacuated and backfilled with nitrogen. The vessel was charged with an excess of lithium wire (100 mg), naphthalene (55.5 mg, 0.43 mmol), and THF (1 mL). The reaction mixture was allowed to stir at rt for 30 minutes, during which the mixture turned from clear, to dark green, to a deep red. The flask was then purged with nitrogen and cooled to $-78\text{ }^{\circ}\text{C}$. Compound **3-10** (33 mg, 0.072 mmol) was allowed to stir in THF (2 mL) at $60\text{ }^{\circ}\text{C}$ for 30 min. The solution of compound **3-10** in THF was quickly transferred to the cooled vessel containing the mixture of lithium, naphthalene, and THF. No color change was observed. The reaction mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1.5 h. The flask was then allowed to warm to rt. During this period, the reaction was slowly quenched with a solution of saturated sodium bicarbonate (10 mL). The mixture was transferred to a separatory funnel. Dichloromethane (30 mL) and a solution of saturated sodium bicarbonate (15 mL) were added to the separatory funnel. The layers were separated, and the organic layer was extracted. The aqueous layer was washed with dichloromethane (3 x 30 mL). The organic layers were combined, dried, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 12 mg (74%) of the title compound as a light brown solid. The compound matches characterization data found in the literature.⁵⁷ ^1H NMR (500 MHz, CDCl_3) δ 7.27 (s, br, 2 H), 6.73 (d, $J = 8.5\text{ Hz}$, 1 H), 6.68 (d, $J = 6\text{ Hz}$, 2 H), 6.00 (s, 1 H), 5.92 (s, 2 H), 3.68 (s, 2 H), 3.53 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 147.9, 147.2, 146.7, 129.6, 127.0, 121.9, 112.7, 109.1, 108.5, 101.0, 32.8, 30.9; IR (film) 3104, 1669, 1489 cm^{-1} . MS (ESI) 232.1089 (232.1081 calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$, $\text{M} + \text{H}^+$).

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