A New Guanidinylation Procedure for the Preparation of Functionalized Guanidines and Investigations Towards the Synthesis of Cyclic Guanidine Compounds

by

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A thesis submitted in conformity with the requirements
for the degree of Master's of Science
Graduate Department of Chemistry
University of Toronto
Toronto, Ontario Canada

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Master of Science, 2003

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Abstract

This thesis is a summary of research conducted since October 2000 at the University of Toronto in the laboratory of Dr. Robert A. Batey. This manuscript is divided into three chapters. Chapter one provides a brief introduction to the guanidine functional group and guanidine-containing compounds, both natural and synthetic.

Chapter two describes a new method for alkylation of guanidine-containing compounds using a convenient and mild biphasic protocol. This approach requires limited purification of the obtained products, yielding highly functionalized guanidines in good to excellent yields. This protocol has been used with a variety of alkyl halides and mesylates and provides an alternate approach to methods currently utilized in the literature.

Chapter three describes investigations towards the synthesis of cyclic guanidine compounds. Initially, iodocyclization reactions were attempted; however, limited success was encountered with this approach. Palladium-catalyzed π-allyl chemistry was then investigated to synthesize the cyclic guanidine compounds. Thus far, investigations with this approach have been successful and a general approach for the synthesis of cyclic guanidine compounds using palladium π-allyl chemistry is described for the first time within our labs.

Table of Contents

Abstract ii

Table of Figures and Tables vii

Abbreviations viii

Acknowledgements x

Chapter 1: A General Introduction to the Guanidine Functional Group

1.1 Introduction 2

1.1.1 Naturally-Occurring Guanidines 3

1.1.2 Synthetic Guanidines 9

1.2 References 10

Chapter 2: Phase-Transfer Catalyzed Alkylation of Guanidine by Alkyl Halides Under Biphasic Conditions: A Convenient Protocol for the Synthesis of Highly Functionalized Guanidines

2.1 Introduction 15

2.1.1 General Introduction 15

2.1.2 Guanylation Reactions 17

2.1.2.1 N^1,N^2-Disubstituted Thiourea as a Guanylating Reagent 17

2.1.2.1.1 *The $HgCl_2$-Promoted Guanylation Reaction* 17

2.1.2.1.2 *The EDCI-Promoted Guanylation Reaction* 20

2.1.2.1.3 *The Mukaiyama-Promoted Guanylation Reaction* 23

2.1.2.1.4 *The DMC-Promoted Guanylation Reaction* 24

2.1.2.2 N^1,N^2-Bis-Carbamate Protected *S*-Methylisothiourea as Guanylating Reagent 26

2.1.2.2.1 *The Guanylation Reaction in the Absence of an Activating*

Metal Salt 26

2.1.2.2.2 The Heavy Metal-Promoted Guanylation with S-Methylisothiourea 29

2.1.2.3 Pyrazole Carboxamidines as Guanylating Reagents 31

2.1.2.4 Diprotected Triflylguanidines 32

2.1.2.5 Aminoimino-Methanesulfonic Acids 33

2.1.2.6 Guanidines Synthesized from Cyanamides 35

2.1.2.7 Miscellaneous Guanylation Reactions 36

2.1.3 Guanidinylation Reactions 37

2.1.3.1 The Sodium Hydride Method 38

2.1.3.2 The Mitsunobu Method 39

2.2 Results and Discussion 41

2.2.1 Guanidinylation Reactions with Allyl Bromide Using a Variety of Guanidine Nucleophiles 42

2.2.2 Guanidinylation Reactions of a Variety of Electrophiles with Pyrrolidine-Derived Guanidines 46

2.2.3 Conclusions 50

2.3 Experimental Section 51

2.3.1 Chemical Characterization 51

2.3.2 General Procedures 51

2.3.3 Experimental Procedures 53

2.4 References 59

Chapter 3: Intramolecular Reactions to Generate Cyclic Guanidine-Containing Compounds: Applications Towards Cyclic Guanidine Natural Product

3.1 Introduction 64

3.1.1 Cyclic Guanidine Natural Products 64

3.1.2 Literature Methods Available for the Synthesis of Cyclic Guanidine Natural Products 66

3.1.3 Cyclization Reactions Initiated by Iodine: Iodocyclization Reactions 69

3.1.4 Transition-Metal Catalyzed Allylic Cyclization Reactions 72

3.1.4.1 Enantioselective π-Allyl Reactions Catalyzed by Palladium 74

3.1.4.2 Enantiofacial Exchange in the η^3-Allyl Complex 77

3.1.4.3 Pioneering Aminopalladation Reactions` 83

3.2 Results and Discussion 87

3.2.1 Introduction 87

3.2.2 Cyclization Reactions Initiated by Iodine: Iodocyclization Reactions 87

3.2.2.1 Iodocyclization Reactions: Cyclization Precursors Derived from Guanylation of Amino-alkene Reagents 89

3.2.2.1.1 *Preparation of Cyclization Precursors* 89

3.2.2.1.2 *Iodocyclization Reactions Using the Allylamine-Derived Guanidine* 90

3.2.2.1.3 *Analysis of the Iodocyclization Method Using Allylamine-Derived Guanidine* 91

3.2.2.2 Iodocyclization Reactions: Cyclization Precursors Derived from the Mitsunobu Protocol 92

3.2.2.2.1 *Preparation of Cyclization Precursors* 92

3.2.2.2.2 *Iodocyclization Reactions Using Guanidines Derived from the Mitsunobu Protocol* 94

3.2.2.2.3 *Possible Steric Factors Inhibiting Iodocyclization* 95

3.2.2.2.4 *Ananylsis of the Iodocyclization Reactions on Guanidines Derived from the Mitsunobu Protocol* 97

3.2.2.2.5 *Iodocyclization Conclusions* 97

3.2.3 Palladium-Catalyzed Allylic Cyclization Reactions 98

3.2.3.1 Introduction 98

3.2.3.2 Intramolecular Palladium-Catalyzed π-Allyl Cyclization Methods 100

3.2.3.2.1 *Preparation of the Cyclization Precursors* 100

3.2.3.2.2 Palladium-Catalyzed Cyclization Attempts with Achiral Ligands 101

3.2.3.2.2.1 Cyclization Reactions Forming the N-Benzyl Cyclized Regioisomer (64) 103

3.2.3.2.2 Cyclization Reactions Forming the N-Boc Cyclized Regioisomer (66) 105

3.2.3.2.3 Analysis of the Cyclization Reactions with Achiral Ligands 108

3.2.3.2.3.1 The Observed Affect of the Acetate Counterions 108

3.2.3.2.4 Cyclization Attempts with Chiral Ligands 109

3.2.3.2.5 Analysis of the Cyclization Reactions with Chiral Ligands 111

3.2.3.3 Conclusions 112

3.2.3.4 Future Work 113

3.2.3.4.1 Intramolecular Cyclization Reactions 113

3.2.3.4.2 Intermolecular Cyclization Reactions 113

3.3 Experimental Section 115

3.3.1 Chemical Characterization 115

3.3.2 General Procedures 115

3.3.3 Experimental Procedures 116

3.3.3.1 Iodocyclization General Procedures 116

3.3.3.2 Iodocyclization Experimental Procedures 117

3.3.3.3 Palladium-Catalyzed π-Allyl General Procedures 124

3.3.3.4 Palladium-Catalyzed π-Allyl Experimental Procedures 124

3.4 References 132

Table of Figures and Tables

Figure 1.1	Tautomerization Between the Imino and Amino Guanidine	3
Figure 2.1	Representative Unsuccessful Thioureas	19
Table 2.1	Phase-Transfer Catalyzed Coupling of Guanidines with Allylbromide	43
Table 2.2	Phase-Transfer Catalyzed Alkylation of N^1,N^2-Di-Boc-N^3-pyrrolidine-1-carboxamidine **3a** with Various Electrophiles	47
Figure 3.1	Possible Substitution Patterns on Guanidine Functional Groups	64
Figure 3.2	Select Examples of Cyclic Guanidine Natural Products	65
Figure 3.3	Sources of Enantiodiscrimination in Transition-Metal Catalyzed Allylic Alkylations	74
Figure 3.4	Enantiotopic Allylic Complexes Formed from Enantiofacial Ionization	75
Figure 3.5	Substrates Capable of Racemization Via the η^3-η^1-η^3 Mechanism	78
Figure 3.6	Substrates that Racemize Via Enantiofacial Exchange	78
Figure 3.7	Syn and Anti Substituents for Allylic Compounds	79
Figure 3.8	Structure of Anatoxin-a(s) (**1**)	87
Table 3.1	Iodocyclization Precursors Synthesized Via the Mitsunobu Protocol	93
Table 3.2	Preparation of the Cyclization Precursors	100
Table 3.3	Cyclization Reactions Forming the *N*-Benzyl Cyclized Regioisomer (**64**)	104
Table 3.4	Cyclization Reactions Forming the *N*-Boc Cyclized Regioisomer (**66**)	105
Figure 3.10	Chiral Ligands Used for Intramolecular Cyclization Reactions	110
Table 3.5	Intramolecular Cyclization Reactions with Chiral Ligands	110

Abbreviations

Ac	acetyl
Ar	aryl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
bp	boiling point
cat.	catalytic
Cbz	carbobenzyloxy
d	doublet
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMF	dimethylformamide
e.e.	enantiomeric excess
EI	electron impact
EtOAc	ethyl acetate
equiv	equivalent
h	hours
IR	infra-red
m	multiplet
M	molarity
M^+	molecular ion
MeCN	acetonitrile
min	minutes
mmol	millimole
mp	melting point
MS	molecular sieves
MS	mass spectrometry
NMR	nuclear magnetic resonance
Ph	phenyl
q	quartet

R	alkyl group
rt	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran

Acknowledgements

I would like to thank my supervisor, Dr. Robert A. Batey, for his advice and insight throughout the course of this research project. Additionally, I would like to thank Dr. Mark Lautens for taking the time to read this thesis.

I would also like to thank my co-workers in the lab for creating a pleasant working environment. Both past and current group members are acknowledged: Tan Quach, Julia Gavrilyuk, Dave Powell, Sze Wan Li, Ernest Lee, Craig Miller, Chris Tan, Ghotas Evindar, Justyna Grzyb, Dr. Heather Twin, Ryan Jaecques, Dave Smil, Avinash Thadani, Jinyu Shen.

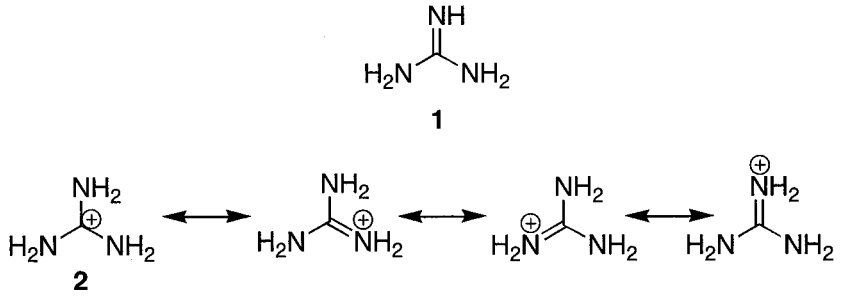
I would like to thank my family for their love and support over all of these tedious years. Finally, I would like to thank Joanne for putting up with me and for your support.

Chapter 1:

A General Introduction to the Guanidine Functional Group

1.1 Introduction

Synthetic and naturally occurring guanidine-containing compounds are an important class of molecules having a wide range of biological activities, due to their capacity to form hydrogen-bond mediated interactions through guanidinium ions.[1] Guanidine **1** is one of the strongest organic bases (pK_a 13.6)[2] due to resonance stabilization of the guanidinium ion **2** by the well known Y-delocalization effect.[3-8] Until the synthesis of the proton sponges, guanidine **1** was considered the strongest organic base.[9,10] As a result of their strong basicity, guanidine **1** derivatives are very polar compounds, therefore, requiring non-standard techniques for their isolation and purification.[11] The standard explanation for the unusually high basicity of guanidine **1** is given in terms of resonance theory,[12] where protonation of **1** yields the symmetrical guanidinium cation **2**, which can be written as three equivalent resonance structures (Scheme 1.1). Pauling related the high basicity of **1** to the resonance stabilization of the guanidinium ion **2** by about 8 kcal/mole compared to guanidine **1**. Pauling also proposed that *N*,*N*,*N*',*N*'-tetraalkylguanidines ought to be less strongly basic; however, mono- or polysubstituted guanidines were found to be as basic as the corresponding unsubstituted guanidine **1**.[2,12]



Scheme 1.1

The hydrogen-bonding donor and acceptor abilities of the guanidine functionality play a crucial role in bioactivity of many highly potent guanidine-containing compounds.[13] In addition, the hydrogen-bonding abilities of guanidines have had implications in supramolecular formation,[14-18] as well as in the binding sites of many proteins.[19,20]

Over the past 40 years, many studies have been undertaken in order to clarify the bonding and electronic properties of many guanidine-containing compounds. For example, empirical studies obtained through X-ray analyses, as well as IR and Raman spectroscopy,[21-24] revealed the guanidinium ion **2** was a highly symmetrical, planar structure, which allowed for a high degree of electron delocalization. However, mono- and disubstituted guanidines can exist as two

tautomers: the imino **3** and amino **4** form (Figure 1.1). Spectroscopic studies undertaken on monosubstituted guanidines have shown that the imino form **3** is favoured when R^1 is an alkyl substituent (R^2 = H),[25] while the amino form **4** is favoured when R^1 is an aryl or an electron-withdrawing group, such as cyano or nitro.[26]

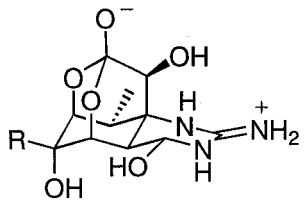
imino form **3** amino form **4**

Figure I.1. Tautomerisation Between the Imino and Amino Guanidine

Due to the strong basicity of guanidine functional group, it exists in the fully protonated form under physiological conditions.[27] The imposed positive charge aids in specific interactions between the guanidinium ligand and the receptor site of the enzyme and these interactions are made possible through hydrogen bonds and/or electrostatic interactions.[27] Guanidine-containing compounds are prevalent in nature and due to their potent bioactivity have attracted interest from the field of medicinal chemistry.[28]

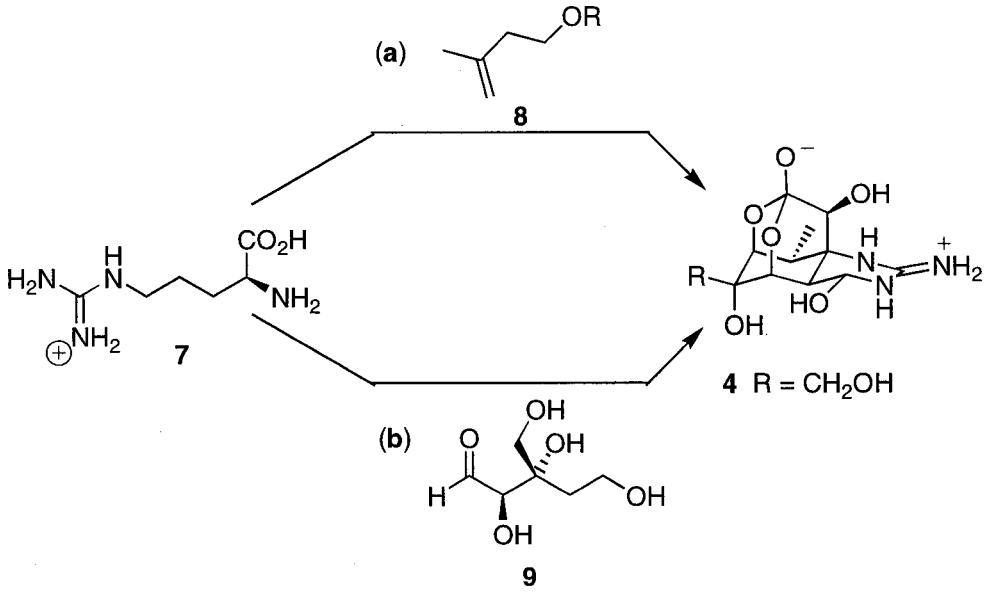
1.1.1 Naturally-Occurring Guanidines

Since compounds containing the guanidine moiety are abundant in nature, they have been the focus of several reviews.[28] Many guanidine-containing compounds have been isolated from a variety of living organisms and these compounds are diverse in their structure as well as their biological activity. Perhaps the most well-known naturally-occurring guanidine is tetrodotoxin **5**, a sexual pheromone from the puffer fish *Fugu niphobles*.[29] Tetrodotoxin **5** is a sodium-channel blocker and has implications in public health due to the consumption of the puffer fish. Studies indicate that tetrodotoxin **5** is released from the female puffer fish *F. niphobles* and acts as a chemical attractant, which can be detected by the males of *F. niphobles* on a 1.5-15 pM level.[29] In addition, 11-oxotetrodotoxin **6**, isolated from the puffer fish *Arothron nigropunctatus*, has been found to be a more potent sodium-channel blocker compared to tetrodotoxin **5**. It was hypothesized the hydroxyl group at C-11 on 11-oxotetrodotoxin **6** enabled a greater amount of hydrogen bonding with the tetrodotoxin receptor in the sodium-channel protein, which would allow for faster association and slower dissociation compared to tetrodotoxin **5**.



5 R = CH_2OH
6 R = $CH(OH)_2$

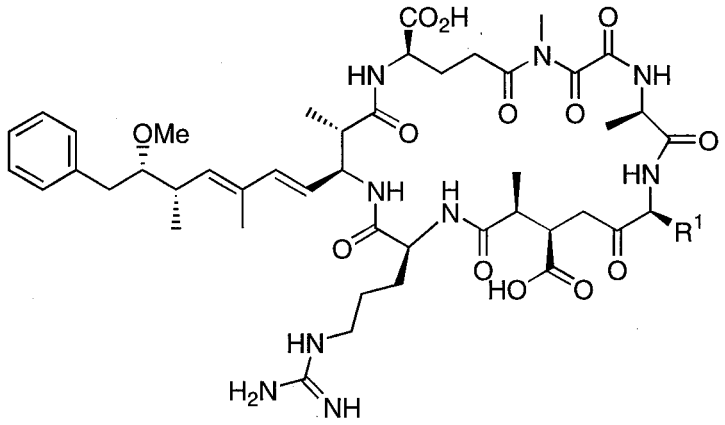
In addition to 11-oxotetrodotoxin **6**, there are many derivatives of tetrodotoxin and it has been established that these compounds are prevalent in nature.[28,30] There has been some debate as to the origin of tetrodotoxin **5** and its derivatives; however, it has been suggested by Yasumoto and co-workers[31] that tetrodotoxin **5** is formed biogenetically from arginine **7** and an isoprene unit **8** (Scheme 1.2, route **a**). Previously, the condensation of arginine **7** and a branched apiose-type C5 sugar **9** was proposed as the biosynthetic pathway to tetrodotoxin **5** (Scheme 1.2, route **b**).



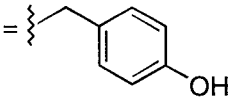
Scheme 1.2

In addition to tetrodotoxin **5** and its derivatives, many other guanidine-containing natural products have been isolated from marine or freshwater microorganisms. Microalgae toxins have been responsible for one of the most serious cases of human mortality. In 1996 during the fall season in Brazil, water containing a variety of toxins, produced by cyanobacetria *Microcystis aeruginosa*, was ingested and over 80 people died as a result of the potent activity of the consumed toxins. HPLC analysis of the liver-tissue extracts indicated microcystin-YR **10**, LR

11, and AR **12** were present and it was proposed that these toxins, containing guanidine functionalites, played a major role in these mortalities.[32]

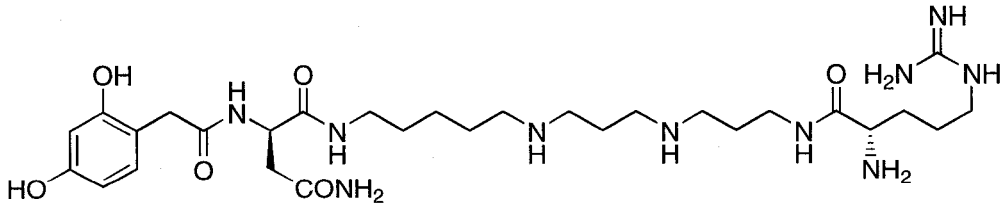


10 R^1 =

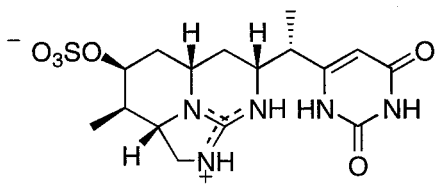


11 $R^1 = CH_2CH(Me)_2$
12 $R^1 = Me$

Guanidine toxins can also be found in terrestrial invertebrates. The isolation of these toxins from a variety of species of spiders have been the focus of several reviews.[33,34] Argiotoxin$_{636}$ **13** has been isolated from the venom a spider, *Argiope lobata*, and this toxin has been the focus of several studies in order to understand its potency.[35] Results from these studies indicate that Argiotoxin$_{636}$ **13** binds to the *N*-methyl-D-aspartate receptors and prevents Mg^{2+} cations from passing through this channel. Cylindrospermopsin **14** is also a potent toxin isolated from two cyanobacteria, *Cylindrospermopsis raciborskii* and *Umezakia natans*,[36,37] present in marine and freshwater organisms. Upon ingestion of this potent toxin, liver tissue is affected as well as the thymus, kidneys, and heart.

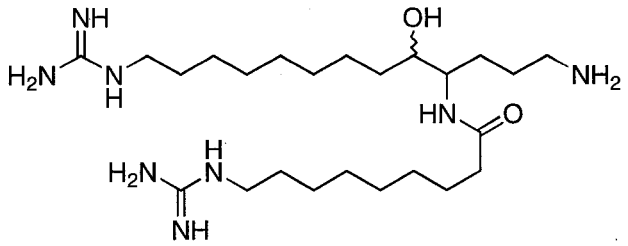


13



14

Despite the adverse impact that certain guanidine-containing natural products have had on public health, there are many examples of beneficial compounds. As an example, Eulicin **15** is a potent antibiotic isolated from a bacterial strain of *Streptomyces*.[38] Eulicin **15** is highly active against both Gram-positive and Gram-negative bacteria. Aside from its beneficial antibiotic activity, Eulicin **15** has also been found to be highly active in a dose-dependent manner against HIV infection and replication.[39] GE202372 factor A **16** is another guanidine-containing natural product isolated from a *Streptomyces* strain and has been shown to be a potent HIV-1 protease inhibitor.



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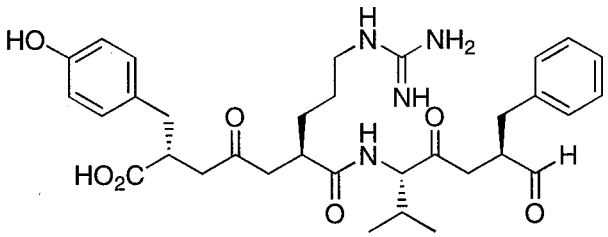
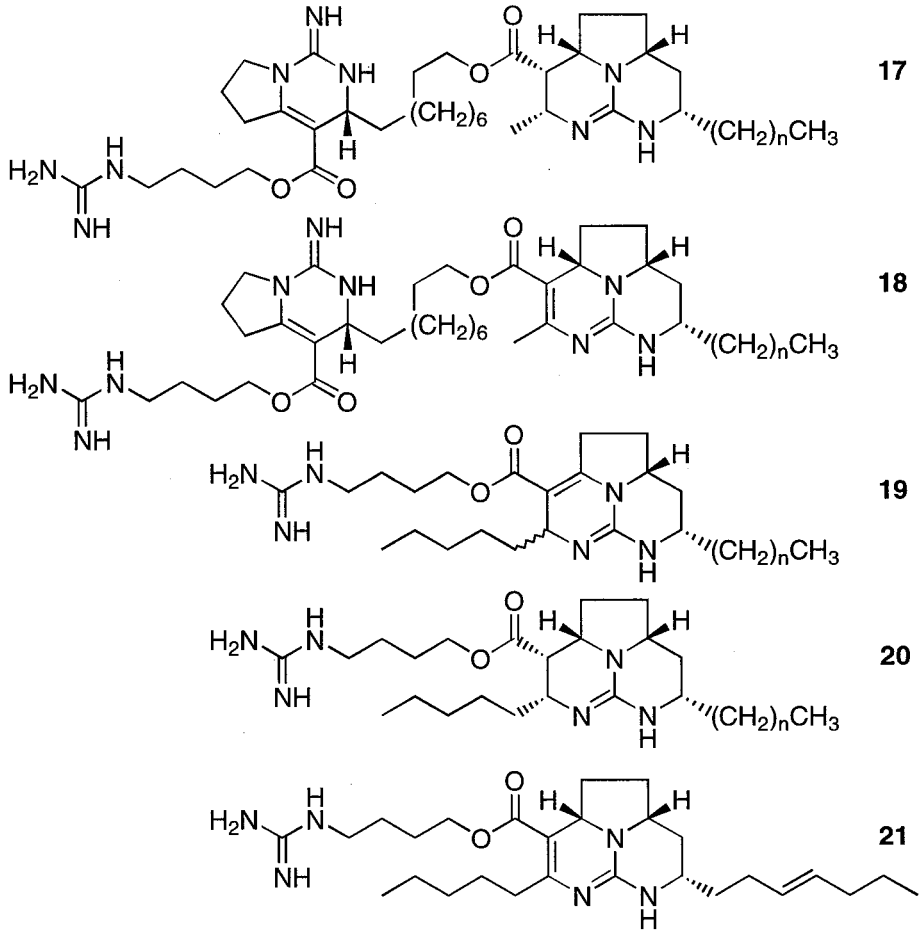


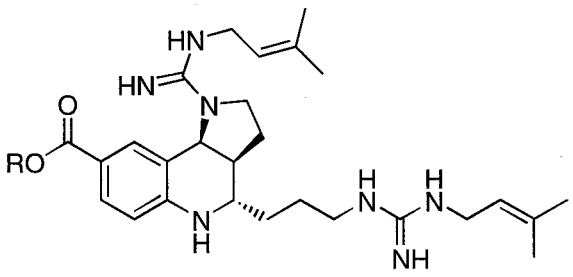
16

The acquired immunodeficiency virus (AIDS) is characterized by causing a decline in the number of $CD4^+$ cells in the infected host. This decline leads to an immune system that is more susceptible to infections and these subsequent infections are the primary cause of death in infected patients. The HIV-1 virus is the primary reason for the development of AIDS[40] and this virus has been shown to be highly selective for $CD4^+$ cells. However, the exact manner in which the decline occurs has not been established. As a result, a large number of potential anti-HIV drugs have been synthesized and utilized. The search for new drugs for the treatment of HIV has resulted in marine-derived natural products being examined as potential therapeutic agents. A large number of terrestrial and marine plants and organisms were screened and several inhibitors were initially found; however, the majority of these inhibitory compounds were only active in the presence of ambient light.[41] It was later discovered this effect was due to the presence of

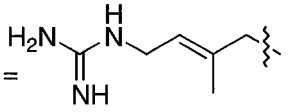
photoactive compounds, such as porphyrins, in the extracts of the inhibitory compounds.[41] However, the extracts of the Carribean sponge *Batzella sp.*, were found to inhibit HIV in the absence of ambient light. Purification of the extracts led to the isolation of 21 compounds that included several known compounds, as well as five new compounds known as batzelladine A-E (**17**-**20**). After the isolation of batzelladine A-E (**17**-**20**), many other batzelladines have been isolated and many of the products display strong anti-HIV potency.[42]



Another guanidine-containing natural product possessing interesting medicinal properties is martinelline **22**. For many years, the extracted roots of the *Martinella iquitosenis* vine were utilized by indigenous people of the Amazonian-lowland rainforests to treat various eye ailments.[43] The medicinal benefits of these extracts have been attributed to martinellic acid **23** and martinelline **22**, with the later being identified as the first naturally occurring nonpeptidic bradykinin B2 receptor antagonist. Recently, the first racemic synthesis of martinelline **22** was completed by Powell and Batey using a multi-component Povarov reaction to synthesize the hexahydropyrrolo[3,2-*c*]quinoline core structure.[44]

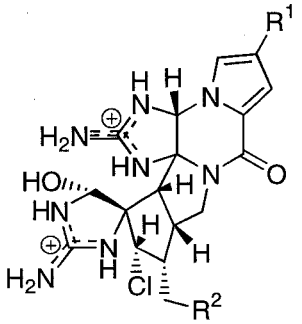


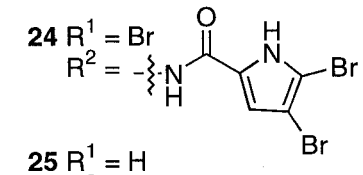
22 R =



23 R = H

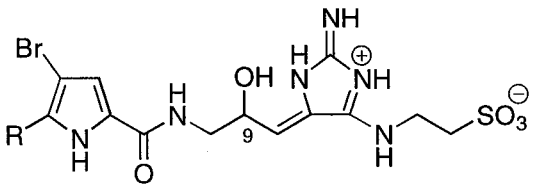
Guanidine-containing natural products have also been isolated from marine invertebrates. Konbu'acidin **24** is a structurally complex molecule consisting of a polycyclic bis-guanidine core; isolated from the marine sponge *Hymeniacidon sp.* Konbu'acidin **24** did not display any significant cytotoxic activity and represents a challenge for the synthetic organic chemist. Structurally related to Konbu'acidin **24** is Palau'amine **25**, which has also not been synthesized although Overman has developed a route towards its total synthesis, in addition to the enantioselective strategy employed by Romo and co-workers.[45,46] Tauroacidins A **26** and B **27** have been isolated from the marine sponge *Hymeniacidon*, whose structures have been determined from spectroscopic studies.[47] High performance liquid chromatography analysis of the derivatized Tauroacidins indicate a mixture of epimers at C9. Both Tauroacidin A **26** and B **27** displayed activity against the EGF receptor kinase and c-erbB-2 kinase at IC_{50} 20 μg/mL.





24 R^1 = Br
R^2 =

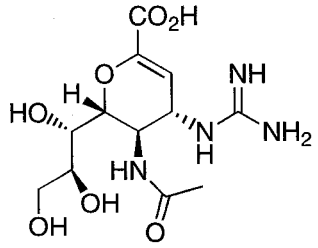
25 R^1 = H
R^2 = NH_2



26 R = Br (9*S*:9*R* = 6:4)
27 R = H (9*S*:9*R* = 1:1)

1.1.2 Synthetic Guanidines

To date, influenza remains the major cause of death among those affected with respiratory diseases.[48,49] Until recent years, only two general methods were available to inhibit the impact of the influenza virus.[50] The first method was the use of vaccines, although they were not utilized extensively due to the ability of the influenza virus to change the surface of its viral protein. The second method was the use of antiviral drugs, such as amantadine and rimantadine. These drugs were soon deemed ineffective due to the emergence of resistant viral strains as well as their limited activity against the influenza B virus.[51] Due to a lack of effective treatment for both stains of the influenza virus, a need for new antiviral drugs arose. Neuraminidase is one of the glycoproteins present on the surface of the influenza virus that has been the target of potential antiviral drugs. Subsequent studies have shown that neuraminidase-deficient influenza viruses have been unable to infect their host.[50] Therefore, neuraminidase has been an important target for the development of new antiviral drugs. Recently, 4-guanidino-Neu5Ac2en (GG167) **28** has been synthesized and is one of the most potent influenza virus inhibitors discovered. Known commericially as Zanamivir, this guanidine-containing compound is a potent and highly specific neuraminidase (sialidase) inhibitor and shows significant inhibitory activity *in vivo* against both influenza A and B viruses.[52] Zanamivir **28** has been extensively studied in both mice and ferrets that have been infected with influenza and has recently been approved as a drug for the treatment of influenza by the FDA. When Zanamivir **28** was given clinically through inhalation, it has been shown to significantly reduce the effects of influenza, even after one dosage. Studies have also shown that Zanamivir **28** has a long retention time in the respiratory tract tissues after one dose is administered. This effect may be beneficial since Zanamivir **28** could be administered to at-risk groups thus protecting them from influenza virus infections.



28

Synthetic guanidine-containing products have also been used as other potentially useful drugs and as pesticides.[1] The uses of synthetic guanidine-containing products is diverse and in

addition to their use for medicinal chemistry purposes, have also been used as fire-retardants[53] and as potent sweeteners.[54,55]

1.2 References

(1) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377-409.

(2) Angyal, S. G.; Warburton, W. K. *J. Chem. Soc.* **1951**, 2492-2495.

(3) Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; John Wiley & Sons: New York, 1991; Vol. 2.

(4) Gobbi, A.; Frenking, G. *J. Am. Chem. Soc.* **1993**, *115*, 2362-2372.

(5) Gund, P. *J. Chem. Educ.* **1972**, *49*, 100-103.

(6) Mills, N. S.; Shapiro, J.; Hollingsworth, M. *J. Am. Chem. Soc.* **1981**, *103*, 1263-1264.

(7) Ohwada, T.; Itai, A.; Ohta, T.; Shudo, K. *J. Am. Chem. Soc.* **1987**, *109*, 7036-7041.

(8) Wiberg, K. B. *J. Am. Chem. Soc.* **1990**, *112*, 4177-4182.

(9) Alder, R. W.; Bryce, M. R.; Goode, N. C.; Miller, N.; Owen, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2840-2847.

(10) Staab, H. A.; Saupe, T. *Angew. Chem.* **1988**, *100*, 895-909.

(11) Huang, S. M.; Huang, Y. C. *J. Chromatogr.* **1988**, *429*, 235-253.

(12) Pauling, L. *The Nature of Chemical Bond*; Cornell University Press: Ithaca, NY, 1960.

(13) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433-6442.

(14) Jubian, V.; Veronese, A.; Dixon, R. P.; Hamilton, A. D. *Angew. Chem. Int. Ed.* **1995**, *24*, 1237-1239.

(15) Sanchez-Quesada, J.; Seel, C.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1996**, *118*, 277-278.

(16) Russell, V. A.; Evans, C. C.; Li, W.; Ward, M. D. *Science* **1997**, *276*, 575-578.

(17) Perreault, D. M.; Cabell, L. A.; Ansyln, E. V. *Bioorg, Med. Chem.* **1997**, *5*, 1209-1220.

(18) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609-1646.

(19) Flocco, M. M.; Mowbray, S. L. *J. Mol. Biol.* **1994**, *235*, 709-717.

(20) Mitchell, J. B. O.; Thornton, J. M.; Singh, J. *J. Mol. Biol.* **1992**, *226*, 251-262.

(21) Kozak, A.; Grottel, M.; Koziol, A. E.; Pajak, Z. *J. Phys. C* **1987**, *20*, 5433-5447.

(22) Haas, D. J.; Harris, D. R.; Mills, H. *Acta Crystallogr.* **1965**, *19*, 676-679.

(23) Adams, J. M.; Small, R. W. H. *Acta Crystallogr.* **1974**, *B30*, 2191-2193.

(24) Pajak, Z.; Grottel, M.; Koziol, A. E. *J. Chem. Soc., Faraday Trans. 2* **1982**, *78*, 1529-1538.

(25) Kanamori, K.; Roberts, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 4698-4701.

(26) Botto, R. E.; Schwartz, J. H.; Roberts, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 23-25.

(27) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *Journal of Organic Chemistry* **1998**, *63*, 3804-3805.

(28) Berlinck, R. G. S. In *Progress in the Chemistry of Organic Natural Compounds*; Springer Verlag, 1995, pp 119-295.

(29) Matsumura, K. *Nature* **1995**, *378*, 563-564.

(30) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339-365.

(31) Yasumoto, T.; Yotsu, M.; Endo, A.; Murata, M.; Naoki, H. *Pure Appl. Chem.* **1989**, *61*, 505-508.

(32) Yunes, J. S. *J. Venom. Anim. Toxins* **1997**, *3*, 97-100.

(33) Mueller, A. L.; Roeloffs, R.; Jackson, H.; Cordell, G. A., Ed.; Academic Press, 1995; Vol. 46, p 63.

(34) Schulz, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 314-326.

(35) Raditsch, M.; Geyer, M.; Kalbitzer, H. R.; Jahn, W.; Ruppersberg, J. P.; Witzemann, V. *Eur. J. Biochem.* **1996**, *240*, 416-426.

(36) Ohtani, I.; Moore, R. E.; Runnegar, M. T. C. *J. Am. Chem. Soc.* **1992**, *114*, 7941-7942.

(37) Harada, K.; Ohtani, I.; Iwamoto, K.; Suzuki, M.; Watanabe, M. F.; Watanabe, M.; Terao, K. *Toxicon* **1994**, *32*, 73-84.

(38) Harman, R. E.; Ham, E. A.; Bolhofer, W. A.; Brink, N. G. *J. Am. Chem. Soc.* **1958**, *80*, 5173-5178.

(39) Nakamura, M.; Yoshida, K.; Yoshida, M.; Kunimoto, S.; Takeuchi, T.; Ohno, T. *J. Antibiot.* **1995**, *48*, 1362-1363.

(40) Capon, D. J.; Ward, R. H. R. *Annu. Rev. Immunol.* **1991**, *9*, 649-678.

(41) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brosse, C. D.; Mai, S.; Truneh, A.; Carte, B. *J. Org. Chem.* **1995**, *60*, 1182-1188.

(42) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814-1819.

(43) Gentry, A. H.; Cook, K. *J. Ethnopharmacology* **1984**, *11*, 337-343.

(44) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913-2916.

(45) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159-7160.

(46) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535-1539.

(47) Kobayashi, J. i.; Inaba, K.; Tsuda, M. *Tetrahedron* **1997**, *53*, 16679-16682.

(48) Glezen, W. P. *Epidermiol. Rev.* **1982**, *4*, 25-44.

(49) Monto, A. S.; Iacuzio, I. A.; LaMontague, J. R. *J. Infect. Dis.* **1997**, *176*, 51-53.

(50) Babu, Y. S.; Chand, P.; Bantai, S.; Kotian, P.; Dehghani, A.; El-kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Elliott, A. J.; Parker, C. D.; Ananth, S. L.; Horn, L. L.; Laver, G. W.; Montgomery, J. A. *J. Med. Chem.* **2000**, *43*, 3482-3486.

(51) Hayden, F. G.; Couch, R. B. *Rev. Med. Virol.* **1992**, *2*, 89-96.

(52) Fenton, R. J.; Morley, P. J.; Owens, I. J.; Gower, D.; Parry, S.; Crossman, L.; Wong, T. *Antimicrobial Agents and Chemotherapy* **1999**, *43*, 2642-2647.

(53) Horacek, H.; Grabner, R. *Polym. Degrad. Stab.* **1996**, *54*, 205.

(54) Tetin, S. Y.; Linthicum, D. S. *Biochemistry* **1996**, *35*, 1258-1260.

(55) Guddat, L. W.; Shan, L.; Anchin, J. M.; Linthicum, D. S.; Edmunson, A. B. *J. Mol. Biol.* **1994**, *236*, 247-249.

Chapter 2

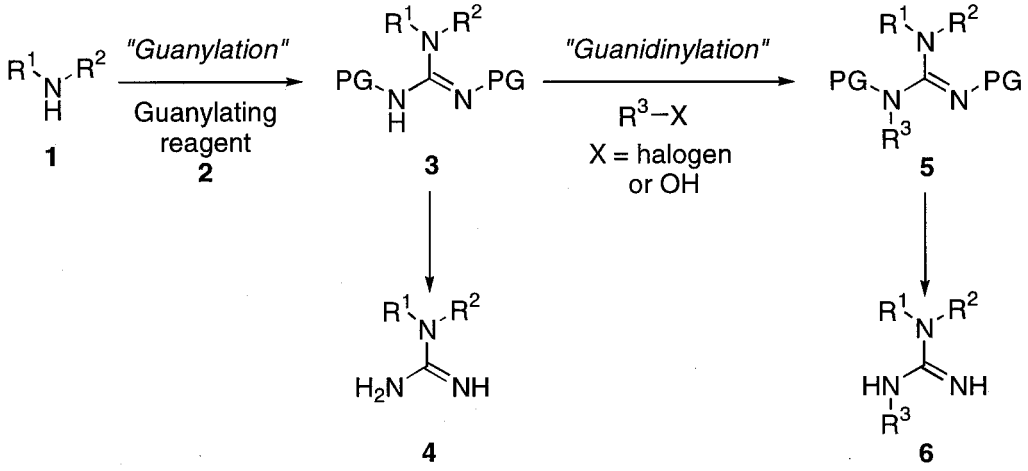
Phase-Transfer Catalyzed Alkylation of Guanidines by Alkyl Halides Under Biphasic Conditions: A Convenient Protocol for the Synthesis of Highly Functionalized Guanidines

2.1 Introduction

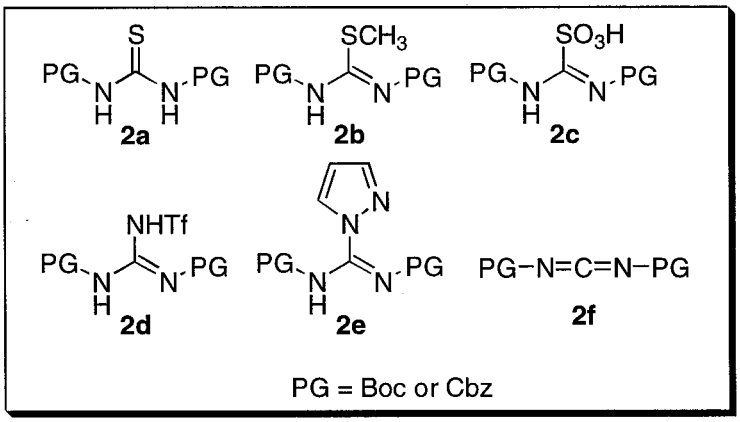
2.1.1 General Introduction

Natural and synthetic guanidine-containing natural products display a diverse array of biological activity, from the anti-HIV properties of the batzelladine marine-alkaloids[1,2] and the potent influenza inhibitors of the synthetic zanamivir antiviral drugs,[3] to the potent toxicity of the puffer fish extract, tetrodotoxin.[4] As a result of the prevalence and diverse biological activity of both natural and synthetic guanidine-containing compounds, there has been considerable interest in creating efficient methods to create these compounds. Many synthetic methods are available for the synthesis of guanidine-containing compounds by reaction of a 1° or 2° amine **1** with a wide range of guanylating agents **2a-2f** (Scheme 2.1). It should be noted that there is little agreement in the literature as to the terminology for transformation of amine **1** into guanidine **3** (Scheme 2.1).[5] Many terms have been used for the conversion of amine **1** to guanidine **3**, the most popular terms for this conversion are *guanylation*, *guanidinylation*, and *guanidination*.[5] The conversion of amine **1** into guanidine **3** formally involves the attachment of a $-C(=NH)NH_2$ group, which was traditionally referred to as a *guanyl* group.[5] However, the term *guanyl* was replaced by the term *amidino*,[6] which has since been officially replaced by the term *carbamimidoyl*.[5] Therefore, the conversion of amine **1** to guanidine **3** should formally be referred to as a *carbamimidoylation*; however, this arduous term has rarely been used in the literature.[7] Since the term *carbamimidoylation* has rarely been utilized, the term *guanylation* will be used for the purposes of this thesis to represent the conversion of amine **1** to guanidine **3**. Additionally, methods for the functionalization of guanidine **1** to yield the more substituted guanidine **3** have been utilized in the literature; however, the terminology for this transformation has also not been standardized. Conversion of **3** to the more highly-substituted guanidine **5**, for the purposes of this thesis, will be referred to as a *guanidinylation* since the *guanidino* functionality ($-NH(C=NH)NH_2$) is reacted with an alkyl halide or alkyl alcohol moiety (Scheme 2.1). Alternately, conversion of **3** to the more substituted guanidine **5** could be referred to as an *alkylation of a guanidine* (i.e. for the case where R^3 = alkyl, Scheme 2.1). For intermolecular reactions, the usage of the terms *guanidinylation* versus *alkylation of a guanidine* will depend on the degree of complexity associated with the guanidine and alkyl components. The term *guanidinylation* is more concise in representing the conversion of **3** to the more highly substituted guanidine **5** and this terminology will be used throughout this thesis. The use of this

terminology was recently proposed by our research group in order to draw attention to these two distinct classes of reactions, as well as to standardize the usage of these terms.[8] Methods for guanidine syntheses shown here are divided based on the type of reaction utilized.



Common Guanylating Reagents



Scheme 2.1

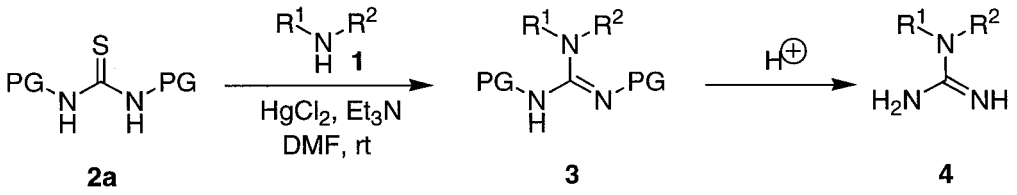
2.1.2 Guanylation Reactions

Guanylation reactions are the most utilized methods for synthesizing guanidine-containing compounds. Typically, these methods involve the reaction of a 1° or 2° amine **1** with an electrophilic amidine species of general structure **2a-2f** (Scheme 2.1). Guanylation reactions will be examined and are grouped based on the methods used to perform the conversion of amine **1** to guanidine **3** (Scheme 2.1)

2.1.2.1 N^1,N^2-Disubstituted Thiourea as a Guanylating Reagent

2.1.2.1.1 The $HgCl_2$-Promoted Guanylation Reaction

One method for the conversion of amine **1** to guanidine **3** is the $HgCl_2$-promoted guanylation of thiourea **2a** with amine **1**. Originally developed by Kim and co-workers, this $HgCl_2$-promoted guanylation is an efficient method for the formation of guanidines starting from relatively unreactive amines.[9] Prior to this method, guanidines were usually formed from amidinesulfonic acids; however, the use of unreactive amines were either ineffective or provided low yields of the desired guanidine. With this method, $HgCl_2$ promotes the reaction between N^1,N^2-bis-(Boc or Cbz-protected)-thioureas **2a** and amines **1** (Scheme 2.2). Once guanylation is complete, the protecting groups can be removed to yield mono-substituted terminal guanidines **4**. This method is well suited for the guanylation of unreactive amines, such as aromatic amines or sterically hindered amines, and has been extensively used for the synthesis of terminal guanidines. Kim and co-workers[9] believed the reactive intermediate in this protocol was a bis-Boc-carbodiimide, which was formed *in situ* and undergoes guanylation even with deactivated amines. Subjecting the bis-Boc-thiourea **2a** to the reaction conditions, a less polar compound is rapidly formed. Additionally, spectroscopic data obtained from this intermediate supported the formation of the bis-Boc-carbodiimide as the intermediate.



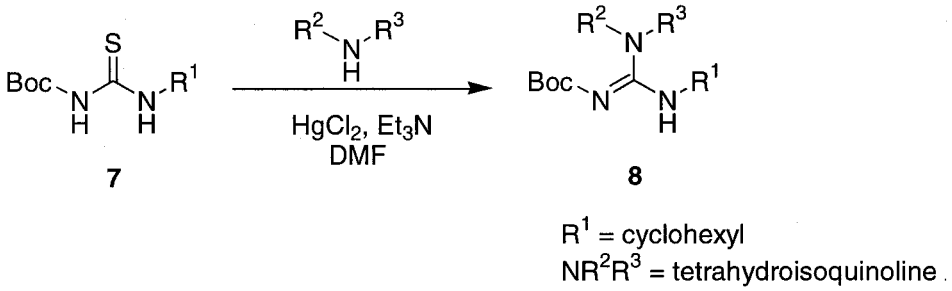
2a **3** **4**

PG = Boc or Cbz

Scheme 2.2

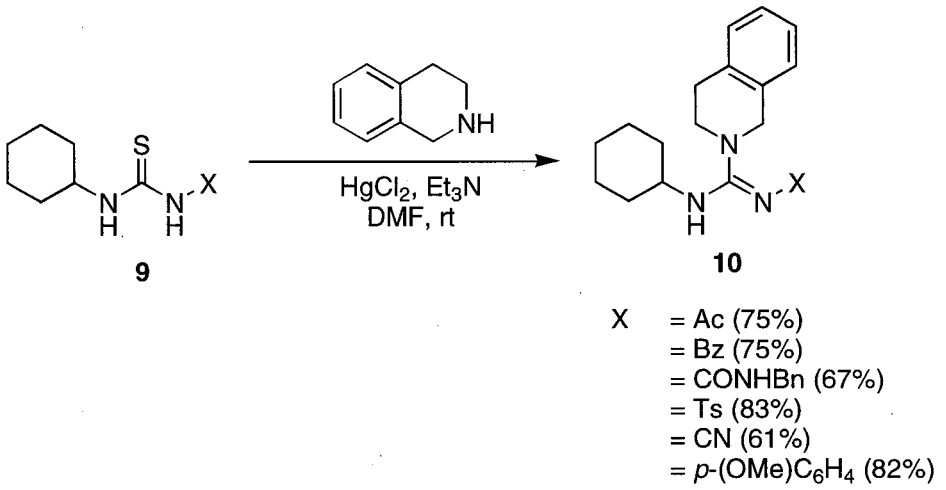
The use of the bis-Boc or Cbz-protecting groups with guanylating agent **2a** in the $HgCl_2$ process, play a more important role than simply acting as protecting groups.[10] The synthesized guanidine bearing the electron-withdrawing carbamate (Boc or Cbz) protecting groups can be easily purified using standard techniques due to their reduced polarity and basicity, unlike unprotected guanidines, which must be purified using non-standard techniques.

Having shown that bis-Boc or Cbz-protecting groups are necessary for the conversion of thiourea **2a** to guanidine **3**, the scope of the reaction was subsequently expanded by Ko and co-workers.[10] Mono-Boc protected thioureas **7** (N^1-Boc-N^2-substituted thioureas) were synthesized and Ko and co-workers have shown that the $HgCl_2$ process does occur with this substrate, making the synthesis of substituted internal guanidines **8** possible (Scheme 2.3).



Scheme 2.3

Ko and co-workers have also shown that the Boc-protecting group is not necessary for the conversion of thiourea **2a** to guanidine **3**. In fact, other electron-withdrawing groups, which replace the Boc-protecting group, such as N^1-carbonyl-, N^1-cyano-, N^1-sulfonyl-, and N^1-aryl-N^2-cyclohexyl thioureas **9**, were successfully converted into their corresponding guanidine compounds **10** (Scheme 2.4).



Scheme 2.4

However, the $HgCl_2$-mediated process was only successful with thioureas containing N^1-conjugated substituents (Scheme 2.4); therefore, bis-alkyl thioureas were unreactive (Figure 2.1). Additionally, terminal thioureas, small-ring thioureas, and thioureas lacking an NH proton on each of the nitrogens also failed (Figure 2.1). The use of the $HgCl_2$-mediated guanylation reaction using thioureas has been used extensively and remains a popular route to the synthesis of guanidine-containing compounds.[11-14]

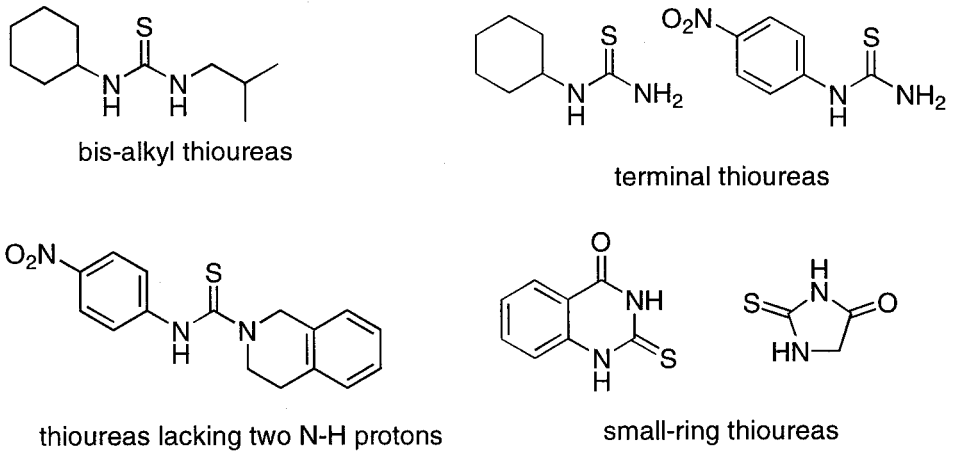
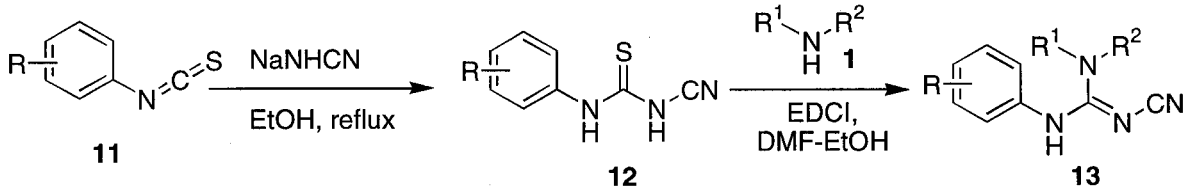


Figure 2.1 Representative Unsuccessful Thioureas

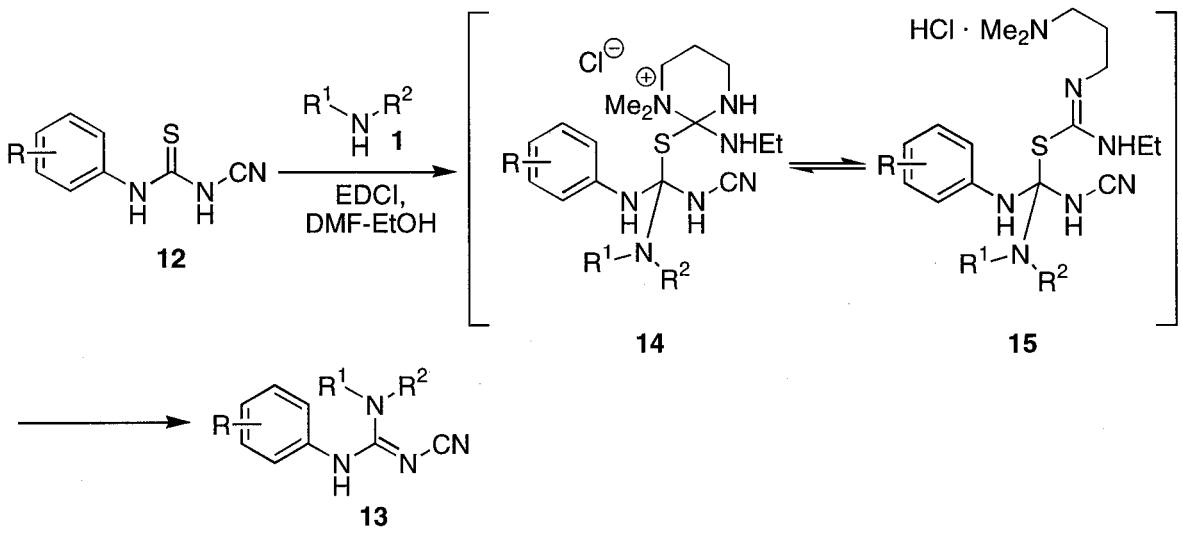
2.1.2.1.2 The EDCI-Promoted Guanylation Reaction

The use of dicyclohexylcarbodiimide (DCC) has been reported for the conversion of a thiourea into a cyanoguanidine;[15] however, Atwal and co-workers[16] treated a variety of thioureas with DCC and amines and obtained low yields of the desired guanidine products. The difficulty encountered with separating the guanidine from the DCC by-product, dicyclohexylthiourea, prompted Atwal and co-workers to replace DCC with the water-soluble EDCI. When a variety of isothiocyanates **11** were treated with sodium cyanamide an intermediate thiourea **12** was obtained, which was reacted with EDCI and an amine **1** to give the desired cyanoguanidine product **13** (Scheme 2.5).



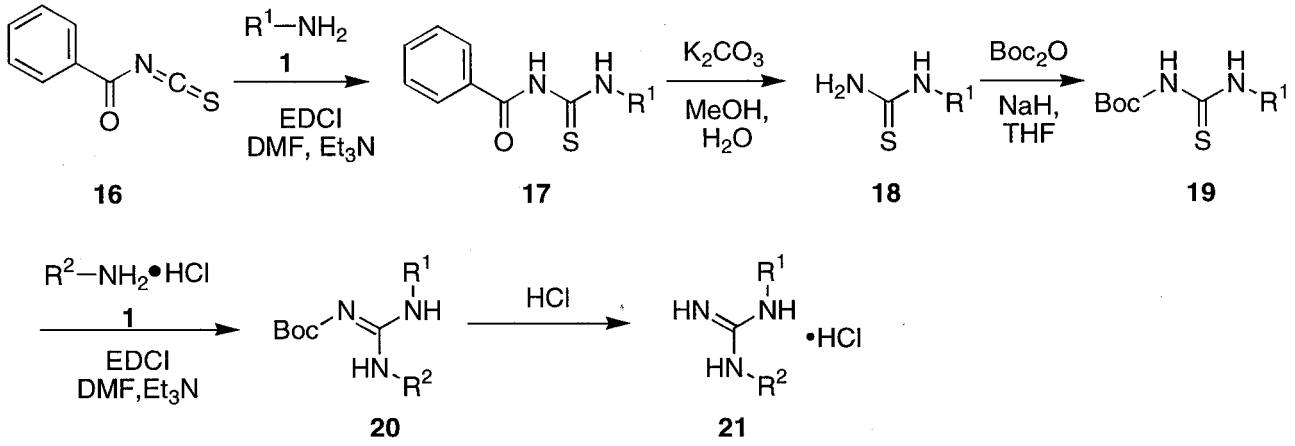
Scheme 2.5

Atwal and co-workers also investigated the mechanism for this reaction and it was necessary to have simultaneous addition of amine **1** and EDCI in order for the reaction to proceed. When amine **1** and EDCI were added separately, no reaction was observed. Based on these observations, a mechanism was proposed in which the amine **1** and EDCI enable the formation of a tetrahedral intermediate **14** and **15**, or an equilibrium mixture, forming the desired cyanoguanidine **13** (Scheme 2.6).



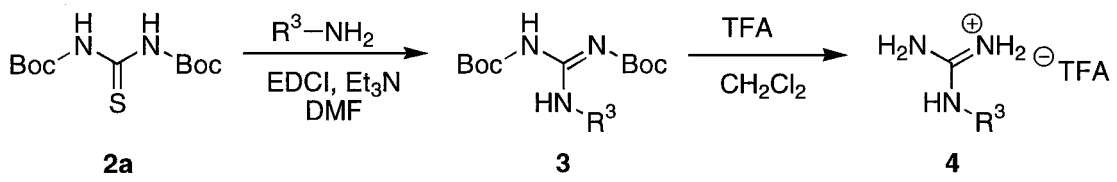
Scheme 2.6

Inspired by the report from Atwal,[16] which described the synthesis of cyanoguanidines from cyanothioureas, Poss and co-workers[17] examined the preparation of acylguanidines from acylthioureas. Poss and co-workers synthesized *N*-Boc-thioureas **19** in a 3 step procedure by treating an amine **1** with benzoyl isothiocyante **16** to yield the benzoyl thiourea **17**, which was deacylated and the subsequent thiourea **18** was reacylated with Boc_2O to give the desired *N*-Boc-thiourea **19** (Scheme 2.7). Guanylation was then performed by combining the *N*-Boc-thiourea **19** with an amine hydrochloride **1** in the presence of EDCI, yielding the desired Boc-protected guanidine **20** (Scheme 2.7). Removal of the Boc group was achieved by treating guanidine **20** with acid to provide the unprotected guanidine **21** as the hydrochloride salt (Scheme 2.7).



Scheme 2.7

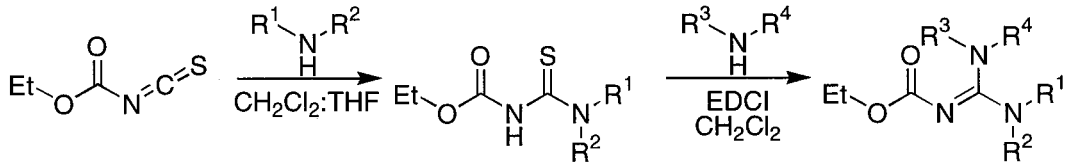
Additionally, this methodology was expanded to the preparation of mono-substituted guanidines **4** (after deprotection) by using the bis-Boc-thiourea **2a** as the guanylating agent (Scheme 2.8).



2a **3** **4**

Scheme 2.8

Hamilton and co-workers[18] have expanded the EDCI-protocol to enable the synthesis of N^1,N^2-multisubstituted guanidines through the use of carbamoyl isothiocyanates **22** (Scheme 2.9). The carbamate increases the reactivity of the isothiocyanate allowing even hindered amines to be easily reacted yielding the thiourea **23**. A second amine could then be coupled with the thiourea **23**, using EDCI as the coupling agent, to yield N^1,N^2-disubstituted guanidines or N^1,N^1,N^2-trisubstituted guanidines **24**. With this procedure only limited purification procedures were necessary and the di- or tri-substituted guanidines **24** could be obtained either stepwise or through a one-pot synthesis.

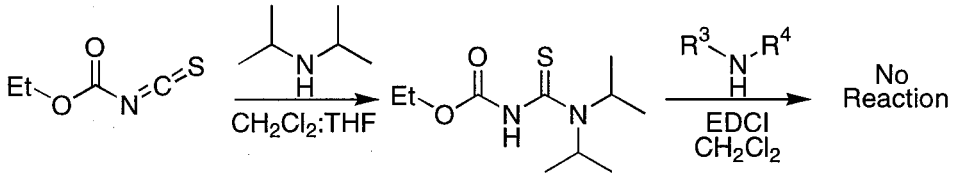


22 **23** **24**

Scheme 2.9

Reaction of a 2° amine, such as diisopropylamine, with the carbamate-protected isothiocyanate **22** gave quantitative yields of the desired thiourea **23a**; however, this thiourea **23a** could not undergo reaction with either a 1° or a 2° amine to yield a N^1,N^2,N^2-trisubstituted guanidine or a N^1,N^1,N^2,N^2-tetrasubstituted guanidine (Scheme 2.10). Either the lack of an NH proton at N^2 (R^2 = H) prevents addition of an amine to the thiourea **23a**, presumably by inhibiting the formation of a carbodiimide, or increased steric bulk around the thiourea **23a** prevents addition. An identical series of reactions using the exact same isothiocyanate **22** and

amines was repeated by Anslyn and co-workers, who additionally showed that the formation of guanidine **24** could also be achieved with Mukaiyama's reagent and $HgCl_2$.[19]

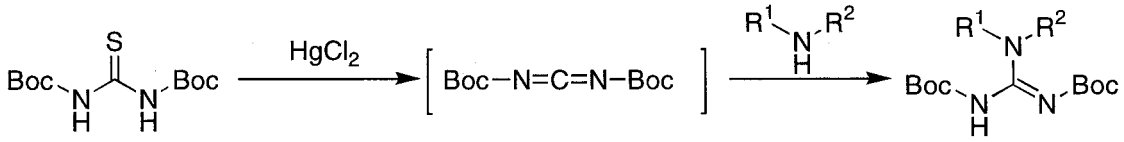


22 **23a**

Scheme 2.10

2.1.2.1.3 The Mukaiyama-Promoted Guanylation Reaction

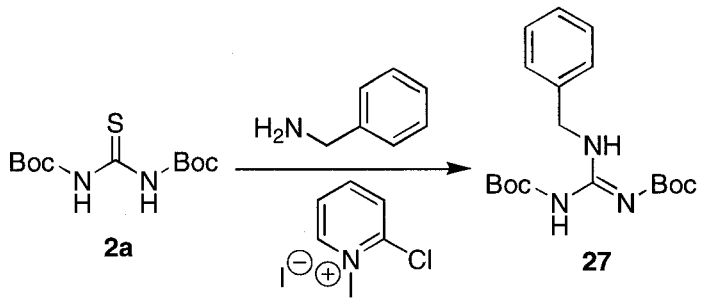
It has been hypothesized that the ease of formation of guanidine **3** (Scheme 2.11) with the $HgCl_2$-mediated guanylation procedure was a result of formation of the bis-Boc-carbodiimide **25**,[9] which is a highly electrophilic intermediate.



2a **25** **3**

Scheme 2.11

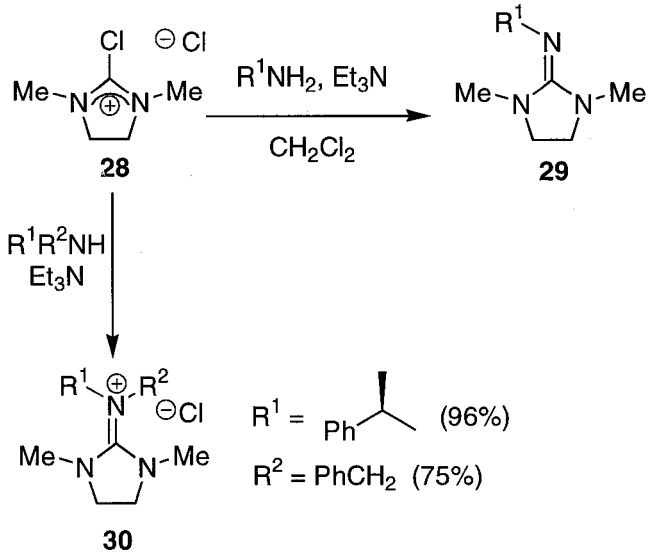
However, the $HgCl_2$-mediated guanylation process was not applicable to solid phase guanylation.[20] As a result, Lipton and co-workers searched for other reagents known to promote the formation of carbodiimides from thioureas, in order to avoid the use of toxic mercuric salts.[21] Mukaiyama's reagent[22] **26** was known to promote the formation of carbodiimides and was also compatible with amines, making it an attractive coupling reagent for guanylation. Lipton and co-workers treated bis-Boc-thiourea **2a** with Mukaiyama's reagent **26** and benzylamine to yield the desired guanidine **27** in 91% yield (Scheme 2.12). They have also successfully performed the guanylation procedure with a variety of amines, as well as guanylating a variety of resin-bound amines. In general, the use of Mukaiyama's reagent provides an alternate approach to the mercuric chloride guanylation protocol. Additionally, Lipton and co-workers noted that Mukaiyama's reagent yields a variety of guanidines including ones synthesized from relatively unreactive amines. The use of Mukaiyama's reagent also eliminates the environmental hazards associated with the use of heavy metal salts.



Scheme 2.12

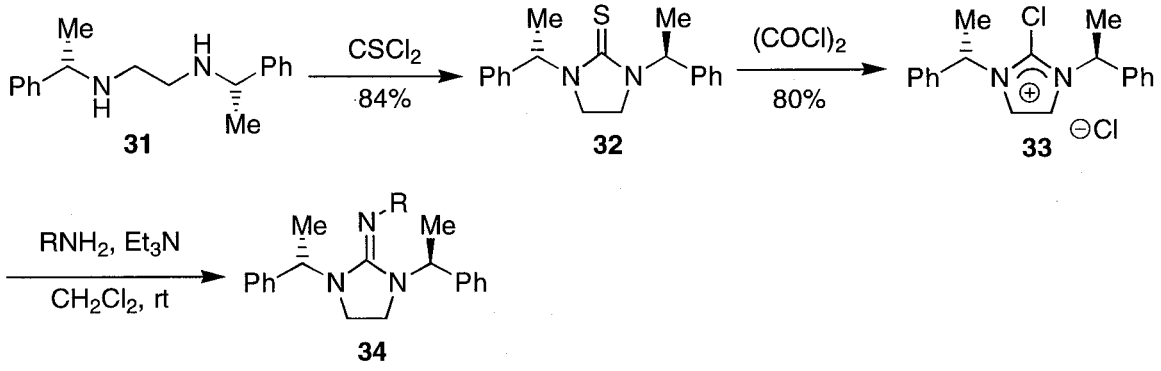
2.1.2.1.4 The DMC-Promoted Guanylation Reaction

An interesting guanylation procedure has been developed by Ishikawa and co-workers[23-28] for the synthesis of substituted guanidine compounds. In a sequential series of three publications, Ishikawa shows that 2-chloro-1,3-dimethylimidizolinium chloride (DMC) **28** can be utilized as either a guanylating agent or a reagent that promotes a guanylation reaction between an amine and a thiourea derivative. In the first publication, Ishikawa uses DMC **28** and its derivatives as guanylating agents that were reacted with a variety of amines yielding the desired iminoimidazolidine derivatives (Scheme 2.13). As an example, 1,3-dimethyl-2-iminoimidazolidines **29** were prepared by treating DMC **28** with a primary amine. When a secondary amine was used instead of the primary amine, guanidinium salts **30** were obtained in good to excellent yields.



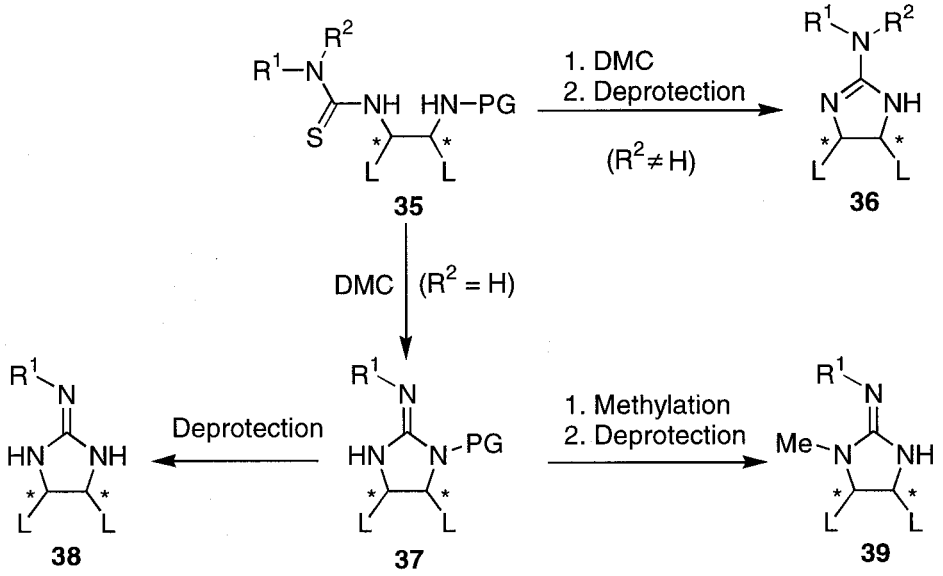
Scheme 2.13

In addition, Ishikawa and co-workers synthesized a variety of DMC derivatives from their corresponding thiourea compounds, which were then treated with amines to yield the guanidine-containing compounds. For this procedure, *N*,*N*'-bis[(*S*)-1-phenylethyl]-ethylenediamine **31** was reacted with thiophosgene to yield the cyclic thiourea **32**. Treatment of the thiourea **32** with oxalyl chloride gave 1,3-bis[(*S*)-phenylethyl]-2-chloroimidazolinium chloride **33**, which was reacted with a variety of amines to yield the desired cyclic guanidine **34** (Scheme 2.14)



Scheme 2.14

DMC has also been utilized as a coupling reagent by Ishikawa and co-workers,[24,25] who have shown that chiral guanidines could be synthesized using this DMC-promoted protocol. A chiral amino-thiourea **35** was treated with DMC, followed by deprotection, to yield the desired chiral cyclic guanidine in excellent yields (Scheme 2.15). When $R^2 \neq H$, the chiral cyclic guanidine **36** was obtained; however, when $R^2 = H$, the chiral cyclic guanidine **37** was isolated. Intermediate **37** could be deprotected to give guanidine **38**. Alternately, intermediate **37** could be methylated, followed by deprotection, to give the corresponding methyl-substituted guanidine **39**.



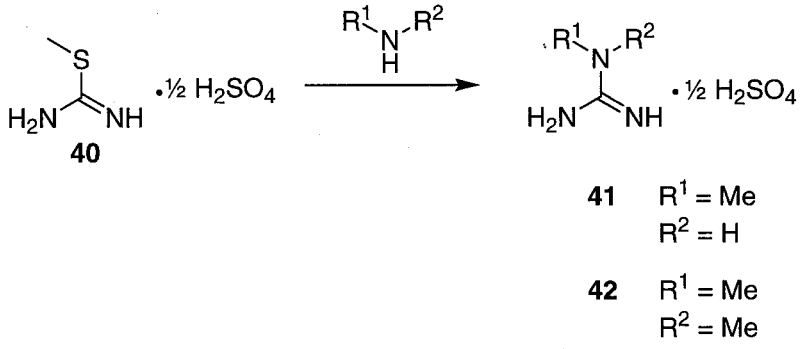
Scheme 2.15

2.1.2.2 N^1,N^2-Bis-Carbamate Protected *S*-Methyl Isothiourea as a Guanylating Reagent

2.1.2.2.1 The Guanylation Reaction in the Absence of an Activating Metal Salt

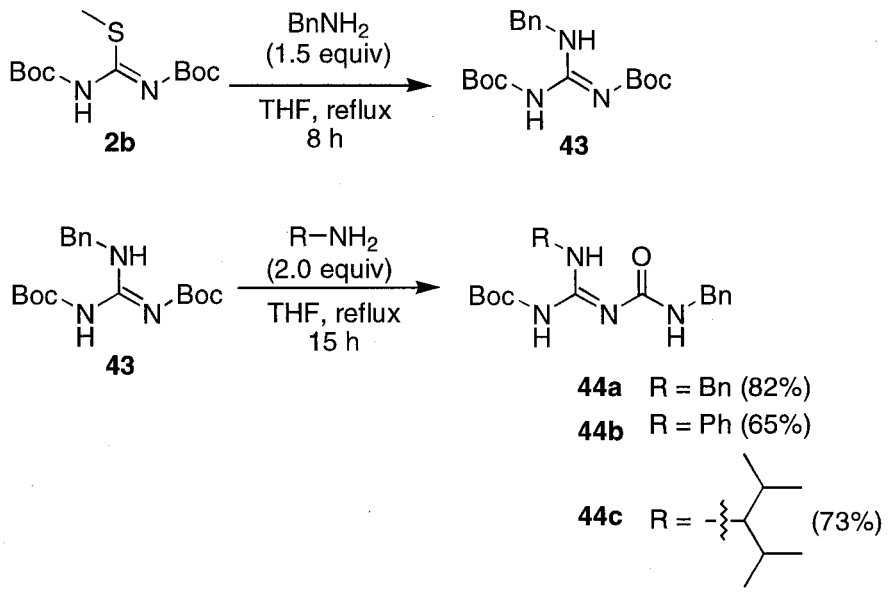
The use of *S*-methyl isothiourea guanylating agents (**40**) to produce guanidines has been extensively utilized in the literature.[29-34] In 1921, Arndt[35] reported the synthesis of a new reagent: *S*-methyl isothiourea sulfate **40** (Scheme 2.16). Arndt noted that this reagent provided methyl mercaptans upon heating in a dilute alkali solution, with carbodiimide produced as the by-product. Phillips and co-workers[36] benefited from this observation and reasoned that amines would undergo reaction with the *S*-methyl isothiourea guanylating reagent **40** providing a new method for the synthesis of alkylguanidines. An aqueous solution of *S*-methyl isothiourea sulfate

40 was refluxed with methylamine or dimethylamine to provide the desired methylguanidine sulfate **41** or N^1,N^1-dimethylguanidine sulfate **42** in excellent yield (Scheme 2.16). This protocol was expanded by Smith[37] to include the synthesis of N^1-arylguanidines by refluxing the *S*-methyl isothiourea sulfate **40** with aniline (2.0 equiv) in THF.



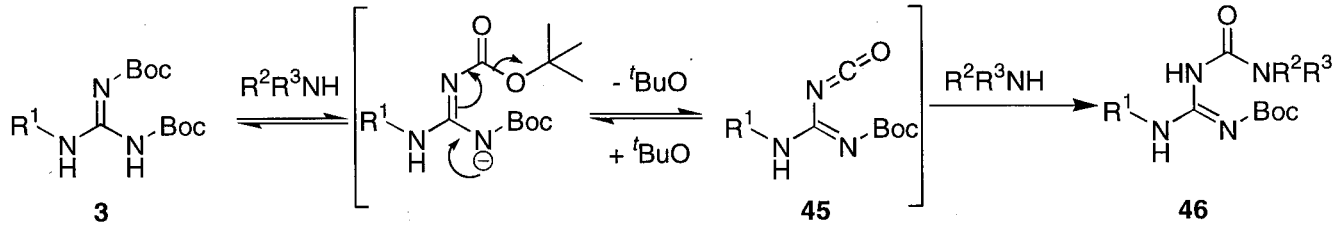
Scheme 2.16

Heavy-metal salts, such as mercury salts and silver salts, have been used as co-reagents in the guanylation of amines with *S*-methyl isothiourea derivatives and this is discussed in Section 2.1.2.2.2 of this thesis. However, due to the cost of silver salts and the toxicity associated with mercury compounds, numerous guanylation reactions are performed under refluxing conditions in the absence of these heavy metals.[38] The presence of electron-withdrawing groups, such as a Boc or Cbz, at the N^1,N^2-positions, such as **2b**, greatly facilitate the formation of guanidines, along with the use of nucleophilic amines. Rault and co-workers[39] heated N^1,N^2-bis-Boc-*S*-methyl isothiourea **2b** with benzyl amine to afford the desired bis-Boc-protected benzyl guanidine **43** (Scheme 2.17). However, an interesting side reaction was noted when N^1,N^2-bis-Boc-benzylguanidines **43** were heated for a prolonged period with an excess of an amine. When N^1,N^2-bis-Boc-benzylguanidines **43** was heated to reflux with benzyl amine (2.0 equiv) for 15 h, the amidinourea compound **44a** was formed in 82% yield (Scheme 2.17). When poorly nucleophilic amines, such as aniline, or the bulky diisopropyl amine was treated with N^1,N^2-bis-Boc-protected benzylguanidine **43** the desired amidinourea compounds (**44b** and **44c**) were formed in 65% and 73% yield, respectively (Scheme 2.17).



Scheme 2.17

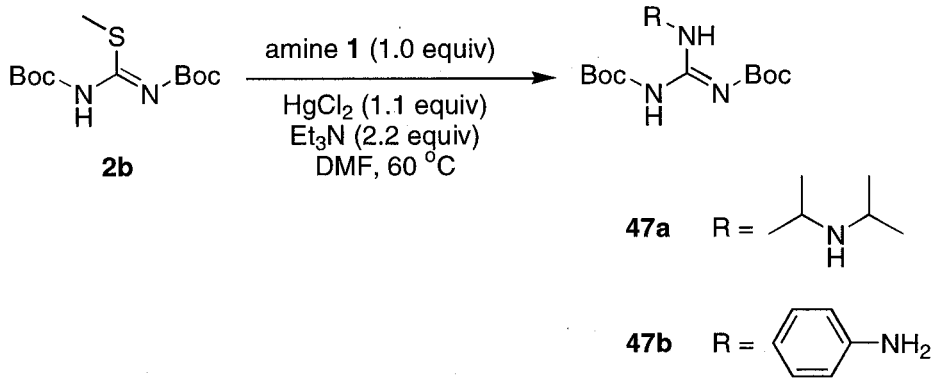
While aminolysis of certain carbamates is possible,[40] it is well documented that the Boc protecting group is resistant to nucleophilic attack.[41] Rault and co-workers noted that Lamothe[42] reported the conversion of Boc-protected amines into ureas through a proposed isocyanate intermediate **45**. Rault and co-workers used a similar mechanism to that proposed by Lamothe to explain the cleavage of the Boc-protecting group from **3** to form the amidinourea compounds **46** (Scheme 2.18).



Scheme 2.18

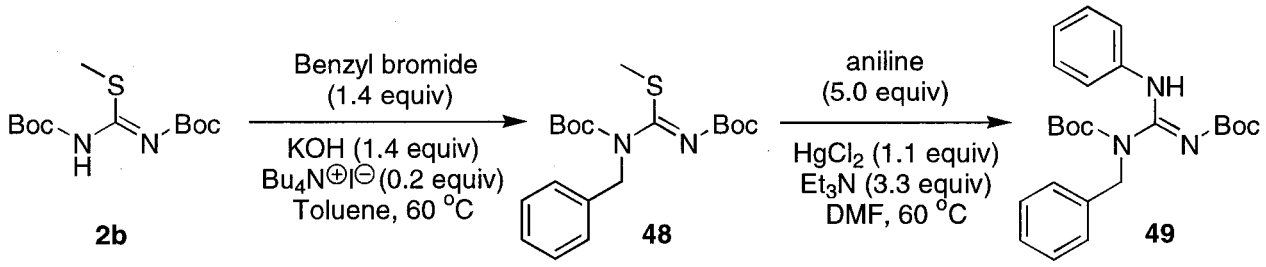
2.1.2.2.2 The Heavy Metal-Promoted Guanylation with S-Methyl Isothiourea

Heavy metals, such as mercuric salts and silver salts, have been used in conjunction with bis-carbamate-*S*-methyl isothiourea compounds **2b** (typically Boc or Cbz) to yield monosubstituted guanidine compounds **47a**, **47b** (Scheme 2.19). Capitalizing on Chandrakumar's synthesis[43] of Cbz-protected guanidines using mercury chloride as a co-reagent, Cammidge and co-workers[44] successfully extended this protocol to include the use of bis-Boc-*S*-methyl isothiourea **2b** (Scheme 2.19). A variety of monosubstituted guanidines were synthesized using this protocol, including challenging guanidine products achieved from aromatic **47b** and sterically hindered amines **47a** (Scheme 2.19).



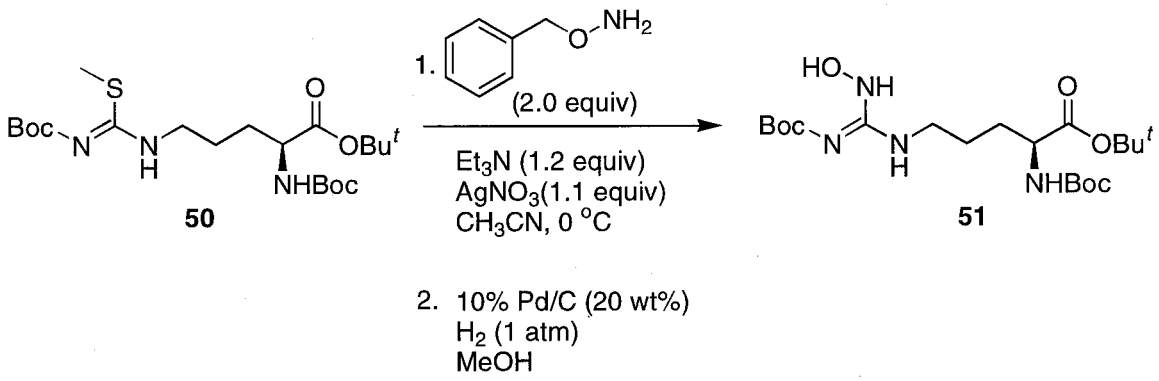
Scheme 2.19

According to Cammidge and co-workers,[44] TLC and spectroscopic monitoring of the reaction mixtures showed the formation of an intermediate, which they presumed to be the carbodiimide. Cammidge and co-workers also alkylated the bis-Boc-*S*-methyl isothiourea **2b** with benzyl bromide in the presence of KOH and Bu_4NI to give **48** (Scheme 2.20). Treatment of **2b** with aniline in the presence of $HgCl_2$ (2.2 equiv) yielded the disubstituted guanidine **49**. This result indicates a carbodiimide is not formed in this guanylation reaction and instead a mercury-activated complex is likely being formed, since formation of a carbodiimide from compound **48** is not possible. This indicates that guanylation of **2b** proceeds through the formation of an activated complex with mercury and not through the carbodiimide intermediate.



Scheme 2.20

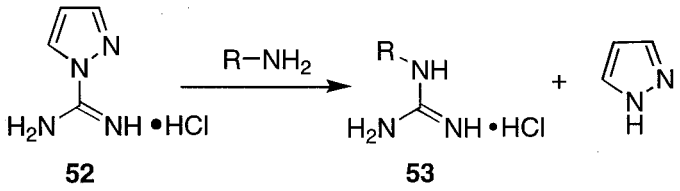
Feldman has successfully performed a guanylation reaction by using silver salts as a co-reagent.[45] Stirring the mono-Boc-guanidine **50** with *o*-benzylhydroxylamine (2.0 equiv), Et_3N (1.2 equiv), and $AgNO_3$ (1.1 equiv) in CH_3CN gave the desired hydroxyarginine derivative **51**, after hydrogenolysis of the benzyl group (Scheme 2.21). Although no mechanistic information was reported, a mechanism similar to that occurring with mercuric salts is likely, in which the silver salts activate the *S*-methyl moiety, aiding in an addition/elimination mechanism.



Scheme 2.21

2.1.2.3 Pyrazole Carboxamidines as Guanylating Reagents

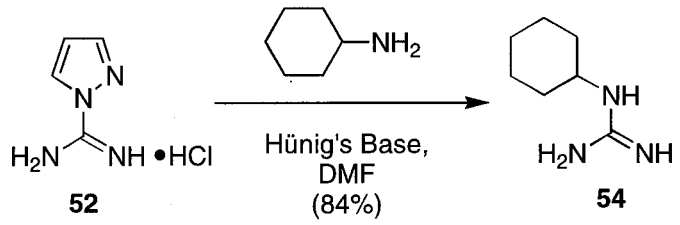
The use of 1*H*-pyrazole-1-carboxamidine hydrochloride **52** had previously been utilized for the synthesis of guanidines in moderate yields[46] (Scheme 2.22). However, Bernatowicz and co-workers[47] reported on the scope and limitations of **52** as a guanylating reagent for the conversion of amines to monosubstituted guanidines **53**.



52 **53**

Scheme 2.22

Treatment of **52** with an amine, such as cyclohexylamine, Hünig's base and DMF as the solvent provided the desired guanidine **54** in moderate to excellent yields (84% yield for cyclohexylamine guanidine **54**) (Scheme 2.23). In general, Bernatowicz found this protocol was useful for the guanylation of sterically unhindered primary and secondary aliphatic amines.

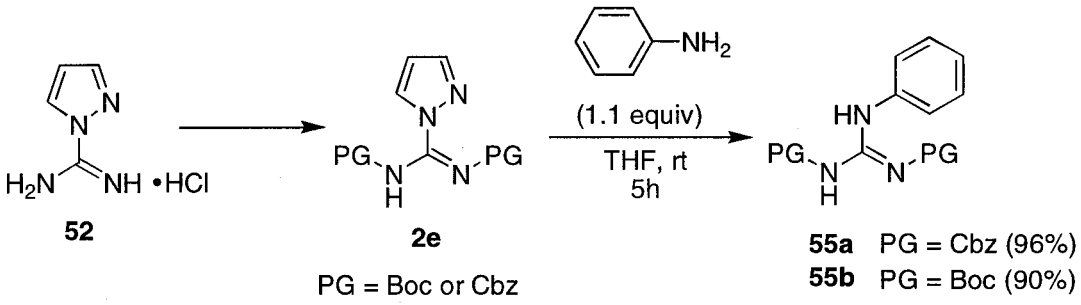


52 **54**

Scheme 2.23

This protocol was later expanded by Bernatowicz and co-workers[48] by using the bis-(Boc or Cbz) derivatives **2e** as the guanylating reagent (Scheme 2.24). With these amidine derivatives **2e**, the presence of the two electron-withdrawing carbamate groups at positions in conjugation with the reaction centre, the electrophilicity of the amidino carbon relative to the unprotected derivatives **52** is increased. As a result, both the bis-Cbz and bis-Boc derivatives **2e** were considerably more reactive than the corresponding unprotected 1*H*-pyrazole carboxamidine **52**. Treatment of the unprotected 1*H*-pyrazole carboxamidine **52** with aniline failed to yield the desired guanidine; however, the bis-Cbz and bis-Boc derivatives **2e** reacted readily with non-

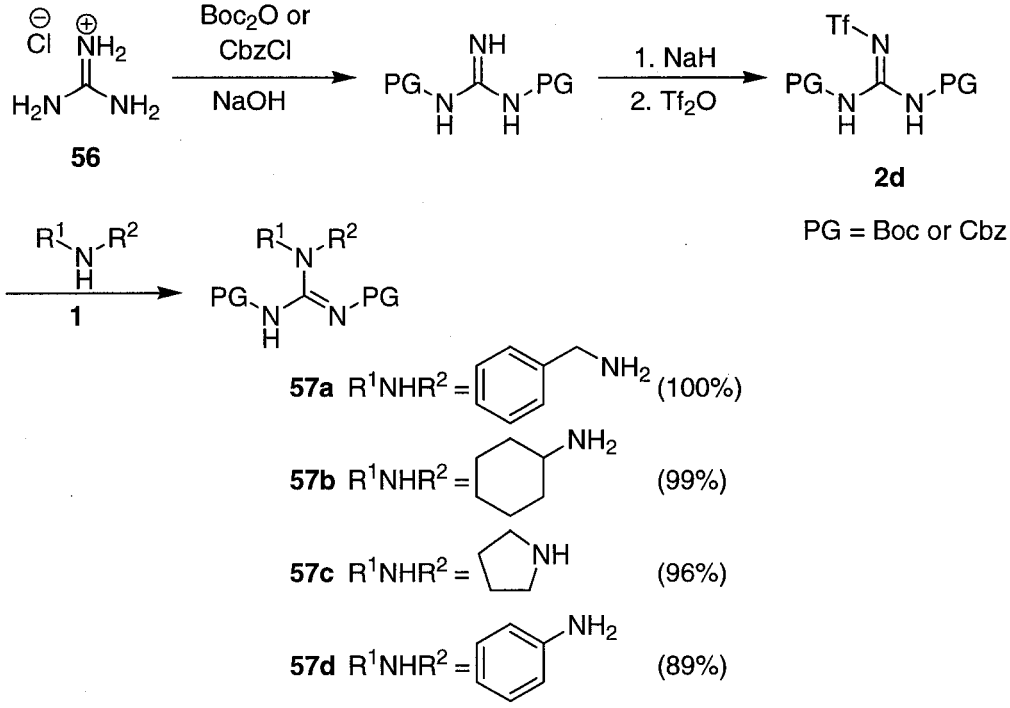
nucleophilic amines, such as aniline, to provide the desired guanidines **55a** and **55b** (Scheme 2.24). The N^1,N^2-bis-carbamate-pyrazole carboxamidine compounds **2e** as guanylating reagents have been used extensively for the synthesis of guanidine compounds.[49,50]



Scheme 2.24

2.1.2.4 Diprotected Triflylguanidines

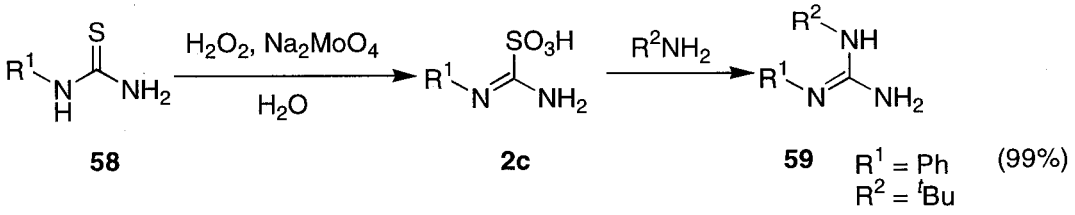
In 1998, Goodman and co-workers[51] developed a new and efficient class of guanylating reagents: N^1,N^2-bis-Boc-N^3-triflylguanidine and N^1,N^2-bis-Cbz-N^3-triflylguanidine **2d** (Scheme 2.25). These stable crystalline solids were easily prepared from guanidine hydrochloride **56** and displayed high reactivity with unhindered primary amines, such as benzylamine **57a** (100%) and cyclohexylamine **57b** (99%). Additionally, secondary amines and aromatic amines reacted more slowly compared to primary amines; however, excellent yields were obtained with the guanylation of pyrrolidine **57c** (96%) and aniline **57d** (89%) using the bis-Boc-derived guanidine **2e** as the guanylating agent under prolonged reaction times. Sterically hindered amines, such as diisopropylamine, were problematic and failed to yield the desired guanidine compound even under prolonged reaction times under refluxing conditions. These new guanylating reagents have received considerable attention in the literature and the authors anticipate their widespread use in the synthesis of protected guanidines.[52-59]



Scheme 2.25

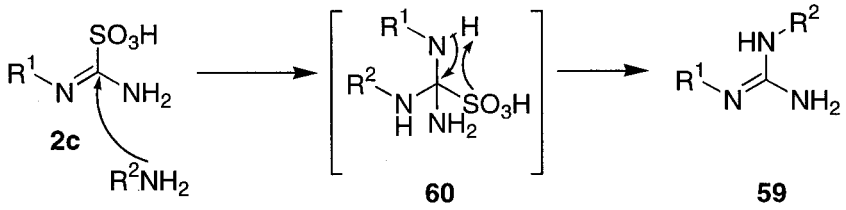
2.1.2.5 Aminoimino-Methanesulfonic Acids

The commercial synthesis of guanidine-containing compounds usually employs the use of *S*-methylisothiourea salts (as discussed in section 2.1.2.2). However, the by-product of this reaction is methyl mercaptan, a noxious gas detectable to 1 ppb by humans.[59] Commercial facilities that use this process are required to convert the methyl mercaptan to an environmentally acceptable by-product. As a result of the problems associated with the use of *S*-methylisothiourea salts, Maryanoff and co-workers[60] developed a process in which thioureas **58** are oxidized to sulfonic acid derivatives **2c** that can undergo guanylation reactions with a variety of amines (Scheme 2.26).



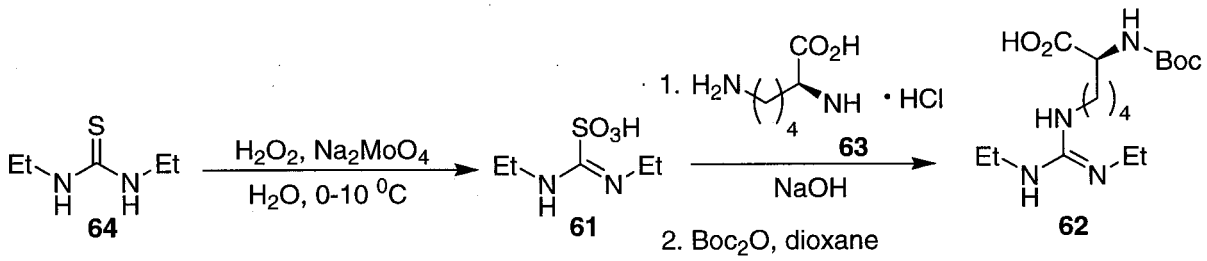
Scheme 2.26

The guanylation of amines with the sulfonic acid derivative **2c** was monitored by IR spectroscopy and no carbodiimide absorption was observed, leading Maryanoff to believe the reaction follows an addition/elimination mechanism with a tetrahedral intermediate **60** (Scheme 2.27).



Scheme 2.27

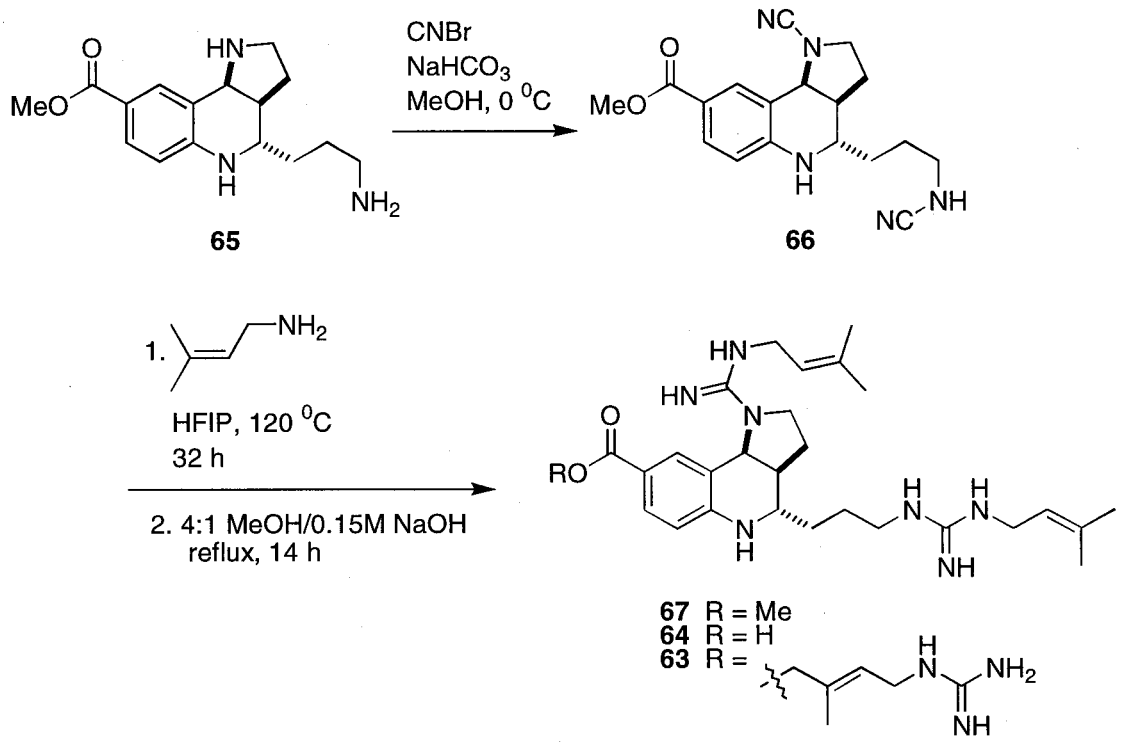
Inspired by the work of Maryanoff,[60] Arzeno and co-workers[61] found that (ethylamino)(ethylimino)-methanesulfonic acid **61** provided large quantities of Boc-diethylhomoarginine **62** from lysine **63** (Scheme 2.28). Arzeno was interested in obtaining dialkyl arginine analouges due to earlier reports that the incorporation of these compounds into peptides can have beneficial effects in terms of biological activity.[62] The methanesulfonic acid derivative **61** was obtained through the oxidation of the N^1,N^2-diethyl thiourea **64** with H_2O_2 and sodium molybdate as the catalyst. The product was isolated by filtration and was treated with the lysine derivative **63** to give the desired compound **62**.



Scheme 2.28

2.1.2.6 Guanidines Synthesized from Cyanamides

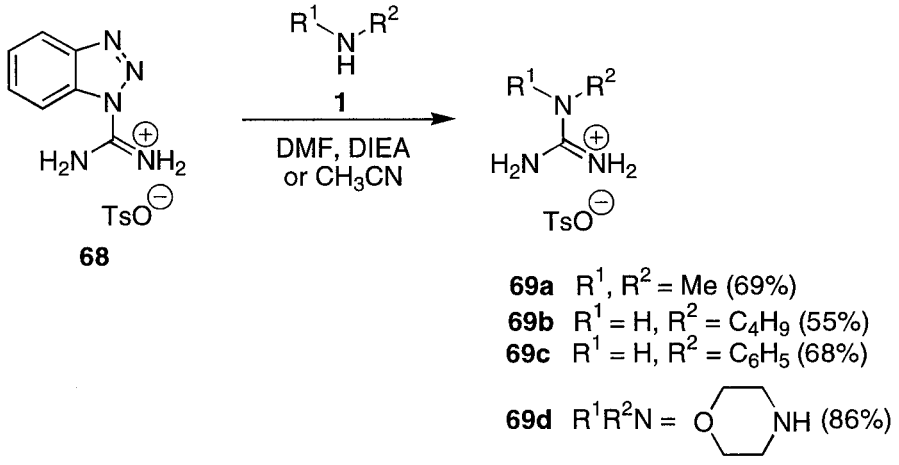
Nucleophilic attack of an amine with a cyanamide derivative is one of the earliest methods employed for the synthesis of guanidine-containing compounds.[63] However, this method is still utilized by many research groups. Snider and co-workers have been interested in the total synthesis of (±)-Martinelline **63** and (±)-Martinellic acid **64** (Scheme 2.29). The pyrroloquinoline core structure of these non-peptide antagonists for the bradykinin B_1 and B_2 receptors was recently reported[64] and the subsequent total synthesis of (±)-Martinellic acid **64** was accomplished.[65] Interestingly, Snider and co-workers reacted the triamine **65** with cyanogen bromide (2.2 equiv) to yield the bis-cyanamide **66**. Heating the bis-cyanamide **66** with 3-methyl-2-buten-1-amine in a sealed tube (120 °C) for 32 h. using a highly polar solvent, hexafluoro-2-propanol, yielded the desired methyl martinellate product **67**. Hydrolysis of the methyl ester under basic conditions gave martinellic acid **64** (Scheme 2.29).



Scheme 2.29

2.1.2.7 Miscellaneous Guanylation Reactions

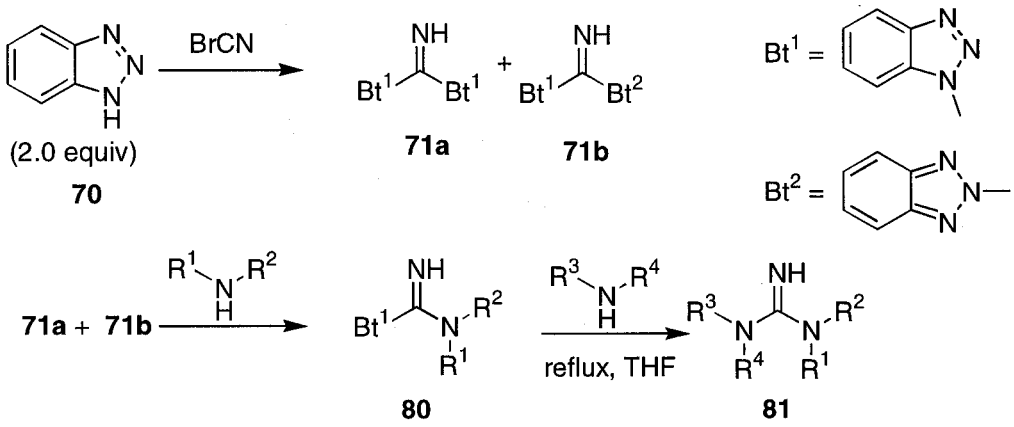
Guanylation procedures grouped in this section, although useful, have not been utilized as extensively as the other guanylation methods discussed in the preceding sections of this thesis. These methods are valuable and provide additional procedures for the synthesis of guanidine-containing compounds from amines. One such method employs the conversion of amines to guanidines utilizing benzotriazole methodology. Katritzky and co-workers[66] utilized benzotriazole-1-carboxamidinium tosylate **68** to yield monosubstituted guanidines **69a-c** from amines **1** (Scheme 2.30). This protocol is general for a variety of primary and secondary amines, including non-nucleophilic aromatic amines, such as aniline, and yields range from 55% to 86% (Scheme 2.30). Reactions are performed in either DMF, in the presence of Hünig's base, or in CH_3CN with the desired guanidine collected by filtration.



Scheme 2.30

Katritzky and co-workers later expanded this benzotriazole methodology to the use of bis-(benzotriazol-1-yl)methanimine which allows for the synthesis of tri- and tetrasubstituted guanidines (Scheme 2.31).[67] Benzotriazole **70** (2.0 equiv) was reacted with cyanogen bromide to obtain a mixture of di(1*H*-benzotriazol-1-yl)methanimine **71a** and 1*H*-benzotriazol-1-yl(2*H*-benzotriazol-2-yl)metanimine **71b**. The first benzotriazole moiety was displaced by the addition of an amine to the mixture of isomers **71a** and **71b**. The addition of the first amine to compound **71a** and **71b** lowers the electrophilicity of the methanimine carbon in compound **80** such that addition of a second amine at room temperature does not occur. However, under refluxing

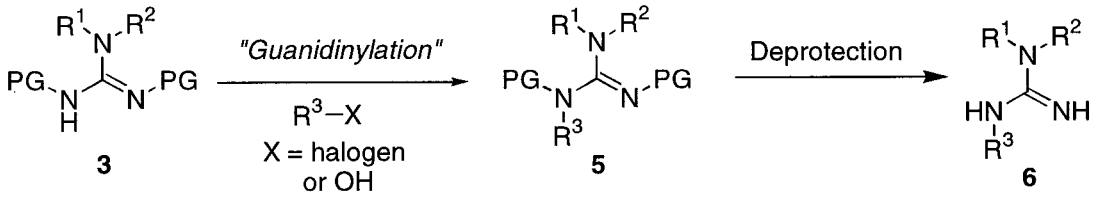
conditions in THF the remaining benzotriazole group was displaced to give the tri- or tetrasubstituted guanidines **81** in good yield (Scheme 2.31).



Scheme 2.31

2.1.3 Guanidinylation Reactions

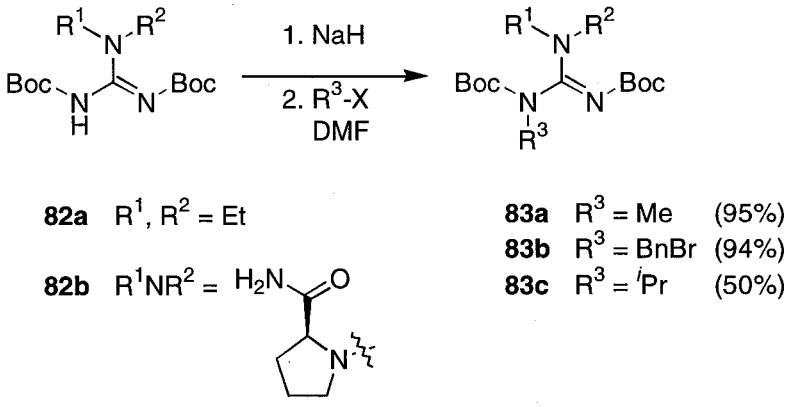
As seen in the previous sections, there are numerous guanylation methods available for the synthesis of guanidine-containing compounds. However, to the best of our knowledge, there are only two common methods used for the functionalization of guanidines of general structure **3** (Scheme 2.32). The first method was developed by Ko and co-workers[68] and involves the deprotonation of guanidine **3** (PG = Boc) with NaH followed by reaction with an alkyl halide to give the functionalized guanidine **5**. The second method was developed by Kozikowski and co-workers[69] and allows guanidine **3** to be reacted with a variety of primary or secondary alcohols, under the Mitsunobu conditions, to give functionalized guanidines **5**. These two methods will be discussed in detail in the following sections.



Scheme 2.32

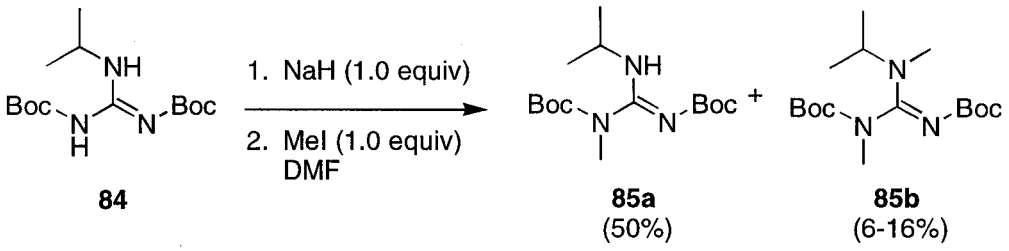
2.1.3.1 The Sodium Hydride Method

Ko and co-workers speculated the N-H proton of the bis-Boc-protected guanidines **3** was fairly acidic, due to the delocalization ability of the resulting negative charge by the two Boc-carbamate functionalities. It was speculated that alkylation of the resulting conjugate base would then be possible, leading to functionalized internal guanidines (after Boc deprotection) of general structure **5**. Initially, the N^2,N^3-bis-Boc-N^1,N^1-diethyl-guanidine compound **82a** and the proline-derived guanidine **82b** were examined. Alkylations with **82a** proceeded smoothly using simple alkyl halides such as methyl iodide and benzyl bromide; however, reactions using sterically-hindered amines, such as 2-iodopropane required long reaction times and gave low yields (Scheme 2.33).



Scheme 2.33

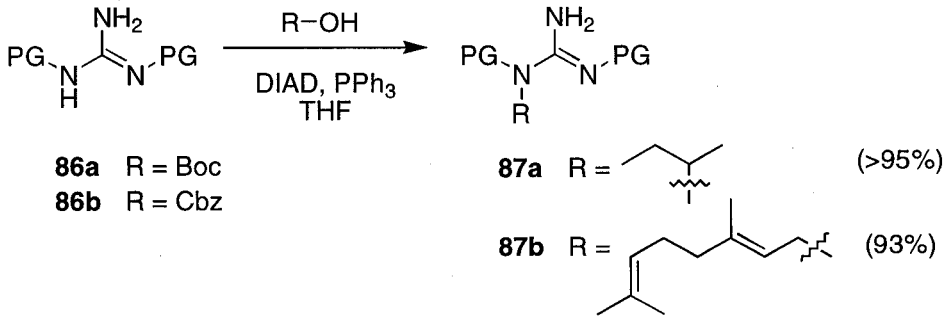
Alkylations of a primary amine-derived guanidine, such as isopropyl guanidine **84**, was problematic due to regioselectivity issues. The BocNH- proton should be slightly more acidic compared to the RNH- proton, since the negative charge of the former conjugate base is delocalized through the carbamate functionality, as well as through the guanidine. However, the acidities of these two protons are comparable. Treatment of **84** with NaH (1.0 equiv) and methyl iodide (1.0 equiv) yielded the desired methylated compound **85a**, however, the yield for the reaction was moderate (50%). The bis-alklyated product **85b** (6-16%) was also isolated, along with unreacted starting material (Scheme 2.34). This method is versatile for the guanidinylation of simple alkyl halides; however, it has limitations with more functionalized alkyl halides. Additionally, the strongly basic conditions used are not tolerated by base-sensitive functional groups.



Scheme 2.34

2.1.3.2 The Mitsunobu Method

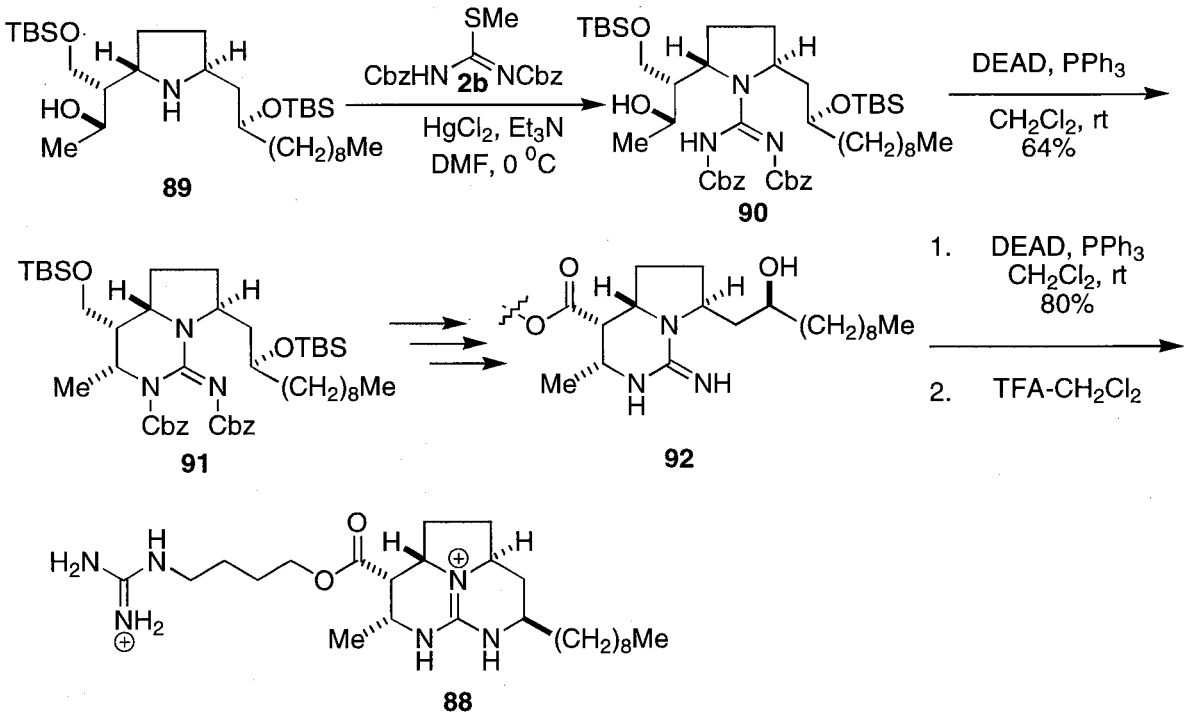
An alternate method to the sodium hydride route was reported by Kozikowski and co-workers.[69] This method utilized N^1,N^2-bis-(Boc or Cbz)-guanidines **86a** and **86b** as nucleophiles in the Mitsunobu protocol. This protocol is relatively mild with primary and secondary alcohols undergoing guanidinylation readily. Alcohols such as 1-butanol and geraniol gave excellent yields of the desired guanidines **87a** and **87b** (Scheme 2.35).



Scheme 2.35

An interesting example of a guanidinylation reaction using the Mitsunobu protocol was recently reported by Nagasawa and co-workers.[70] This report exemplified the effectiveness of the Mitsunobu protocol by utilizing this procedure twice on advanced intermediates in their synthesis of (±)-batzelladine D (**88**) (Scheme 2.36). In the first instance, the advanced amine derivative **89** was subjected to a guanylation procedure using bis-Cbz-*S*-methylisothiourea **2b**, promoted by mercuric chloride. The obtained guanidine **90** was then subjected to the Mitsunobu protocol to obtain the bicyclic guanidine **91** in 64% yield. This bicyclic guanidine **91** was further

functionalized in a number of steps to yield guanidine **92**. The Mitsunobu reaction was employed for the second time by Nagasawa and co-workers to give a stereocontrolled synthesis of the tricyclic guanidine in 80% yield, followed by removal of the Boc-protecting groups to yield (±)-batzelladine D (**88**) (Scheme 2.36). Walker and co-workers[71] have reported a $pK_a \leq 11$ is necessary for the conjugate acid of the nucleophilic component in the Mitsunobu reaction, making the conversion of **92** to **88** by Nagasawa interesting since the bicyclic guanidine **92** does not fall in this range, although the success of this reaction may be due to the intramolecular nature of the reaction.



Scheme 2.36

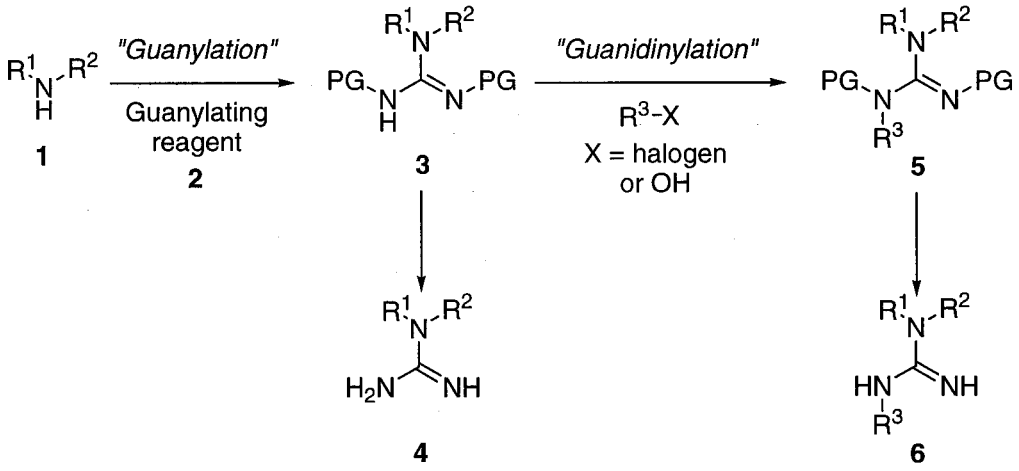
In addition to the examples previously examined, the Mitsunobu reaction has been a popular method for the guanidinylation of a variety of alcohols and continues to be a well used method for the synthesis substituted guanidines.[72-79]

2.2 Results and Discussion

Substituted guanidines are synthetically challenging functionalities that are contained within a variety of natural and synthetic molecules. The high basicity and polarity, and consequent water solubility of many guanidines, provides considerable practical challenges to the synthesis of guanidine-containing compounds. Additionally, guanidines can have multiple substitution patterns, with zero to five possible sites for substitution, allowing for a variety of alkyl and aryl substituents to be incorporated. These considerations make the synthetic planning of complex guanidines difficult, both synthetically and strategically. As a result of these limitations, new methods for guanidine synthesis are still necessary in order to expand the scope of the previously described guanylation and guanidinylation procedures. As shown previously, there are a large number of guanylation methods available for the synthesis of guanidine-containing compounds (conversion of **1** to **3**, Scheme 2.37). However, to the best of our knowledge, there are only two methods available for the functionalization of protected guanidines of general structure **3** (Scheme 2.37). The sodium hydride method was previously described (Section 2.1.3.1) and involves the deprotonation of guanidine **3** (PG = Boc or Cbz) with sodium hydride followed by reaction with an alkyl halide to give functionalized guanidine **3** (Scheme 2.37). Although this protocol is effective with alkyl halides, such as methyl iodide and benzyl bromide, difficulties were encountered with unreactive alkyl halides, such as *n*-butyl bromide. Additionally, the highly basic conditions employed are often not conducive to base-sensitive functional groups, such as esters. The Mitsunobu method was also previously described (Section 2.1.3.2) and has been utilized extensively by many research groups. Although this method works well with a variety of alcohols, it requires expensive stoichiometric coupling reagents, which are sometimes problematic to remove on purification. Since only the NaH and Mitsunobu methods were available for the functionalization of guanidine **3**, it was apparent that additional protocols were needed for this transformation.

Herein a mild and efficient protocol for the guanidinylation of various alkyl halides and mesylates in a biphasic medium containing an aqueous solution of KOH, an organic solvent, and a catalytic amount of a phase-transfer catalyst is described. This protocol was scaleable to yield multi-gram quantities of highly functionalised and protected guanidines **5** that were easily purified. The results given in this section were performed in conjunction with David Powell, a co-author on this published protocol.[80] Only substituted guanidine products synthesized and characterized by myself are reported in the experimental section (Section 2.3); however, for

clarity, some examples synthesized by David Powell will be listed in the current section of this thesis.

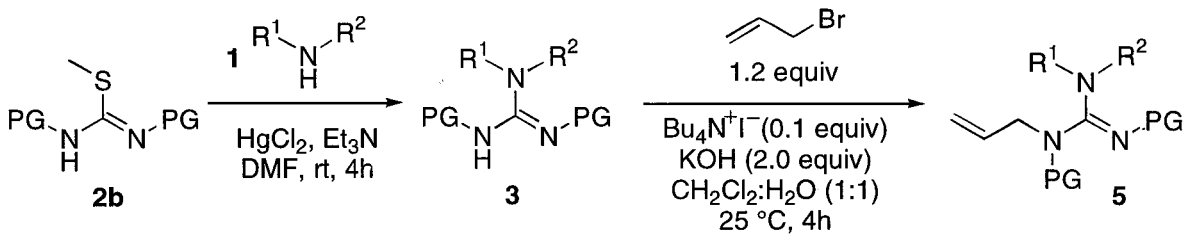


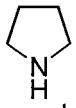
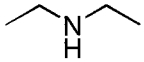
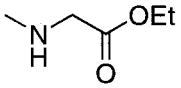
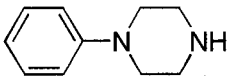
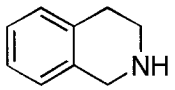
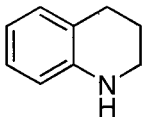
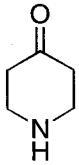
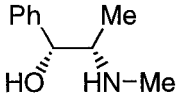
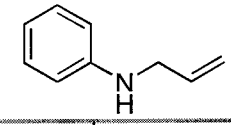
Scheme 2.37

2.2.1 Guanidinylation Reactions with Allyl Bromide Using a Variety of Guanidine Nucleophiles

The reaction of a variety of guanidine nucleophiles of differing complexity was examined with allyl bromide using this biphasic protocol. The guanidines **3** were prepared in good to excellent yields (Table 2.1) by guanylation of the necessary amines **1** with N^1,N^2-di-(Boc or Cbz)-*S*-methylisothiourea **2b** in the presence of a mercury (II) salt promoter (Table 2.1). The protected guanidines were then alkylated with allyl bromide (1.2 equiv) in the presence of the phase-transfer catalyst Bu_4NI (10 mol%) and KOH (2.0 equiv) in a 1:1 mixture of H_2O and CH_2Cl_2. After the biphasic mixture was stirred vigorously for 4 h, the solutions were diluted with an equal volume of H_2O and CH_2Cl_2 and the layers were separated. The organic phases were then concentrated *in vacuo* and purified through a short silica gel column, to remove the remaining phase-transfer catalyst. This simple procedure yielded the desired substituted guanidines **5** in high purity.

Table 2.1 Phase-Transfer Catalyzed Coupling of Guanidines with Allylbromide



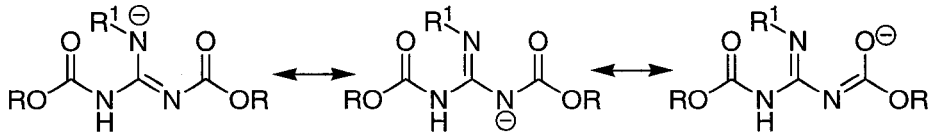
Entry	R^1-NH-R^2	PG	Compound 3	Yield 3 (%)[a]	Compound 5	Yield 5 (%)[a]
1		Boc	**3a**	96	**5a**	89
2		Cbz	**3b**	80	**5b**	87
3	NH_3[b]	Boc	**3c**	99	**5c**	94
4		Boc	**3d**	88	**5d**	90
5		Boc	**3e**	87	**5e**	78[c]
6		Boc	**3f**	86	**5f**	87
7		Boc	**3g**	86 (91)[d]	**5g**	96 (79)[d] (97)[e] (97)[f]
8		Boc	**3h**	89	**5h**	96
9		Boc	**3i**	87	**5i**	91
10		Boc	**3j**	78	**5j**	78 (64)[g]
11		Boc	**3k**	69	**5k**	91

[a] Isolated yield. [b] Guanylation carried out in the absence of $HgCl_2$. [c] Reaction carried out for 2h. [d] Reaction carried out on a 12.0 g (31.2 mmol) scale. [e] Yield with Bu_4NBr as the PTC. [f] Yield with Bu_4NCl as the PTC. [g] Yield of corresponding HCl salt after deprotection of both Boc groups.

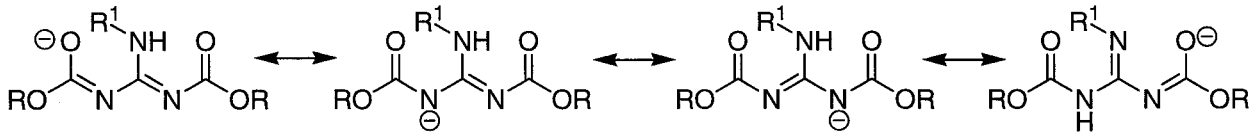
This procedure is applicable to both the Boc- and Cbz-protected pyrrolidine derived guanidines, since **3a** and **3b** were readily allylated under the reaction conditions to give the desired substituted guanidines **5a** and **5b** in 89% and 87% yields, respectively (Table 2.1, entries 1-2). In the guanidinylation reactions reported by Kozikowski and co-workers,[81] the Mitsunobu protocol was utilized for the alkylation of N^1,N^2-di-Boc-guanidine **3c** with a variety of alcohols. The biphasic protocol also works with guanidine **3c** and treatment with allylbromide afforded the regioselectively allylated guanidine **5c** in 94% yield (Table 2.1, entry 3). Therefore, this mild biphasic protocol provides an alternate method for the synthesis of monosubstituted guanidines than the previous method developed by Kozikowski and co-workers.[81] Subjecting N^1,N^2-di-Boc-guanidine **3c** to an excess of allylbromide (5.0 equiv) for extended reaction times (24 h) and with heating (50 °C), gave only the monoalkylated guanidine **5c**. A variety of N^1,N^2-di-Boc-N^3,N^3-disubstituted guanidines were also subjected to this biphasic protocol to give the desired substituted guanidines in high yield and were obtained in high purity by purification through a short column to remove the phase-transfer catalyst (Table 2.1, entries 4-11). The biphasic protocol is mild and tolerant to a wide range of functional groups present on the guanidine, including esters (Table 2.1, entry 5), amines (Table 2.1, entries 3 and 6), ketones (Table 2.1, entry 9), alcohols (Table 2.1, entry 10), and alkenes (Table 2.1, entry 11).

This protocol was easily adapted to larger scales, as illustrated by the allylation of the tetrahydroisoquinoline-derived guanidine **3g**, which was performed on a 12.0 gram (31.2 mmol) scale (Table 2.1, entry 7). Aqueous workup and purification of **5g** through a short column of silica gel gave the desired product in 79% yield. The Boc-protecting groups were then removed by stirring **5g** with 1M HCl to yield the trisubstituted guanidine **6g** as the HCl salt in 90% yield.

This protocol does have its limitations and this is exemplified in the reaction of 1° amine-derived guanidines **5l** (Scheme 2.39) with alkyl halides under the biphasic conditions. Alkylation of the conjugate base of **3** would pose a regioselectivity challenge, since the acidities of RNH- and carbamate-NH- are expected to be comparable. The acidity of RNH- is expected to be slightly less than the carbamate-NH-, since the negative charge of the latter experiences more resonance stabilization (Scheme 2.38).



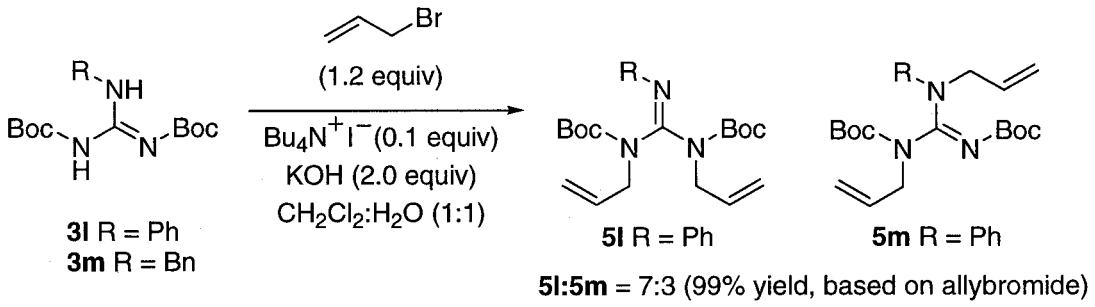
Resonance Structures from Deprotonation at R^1NH



Resonance Structures from Deprotonation at the Carbamate-NH

Scheme 2.38

When 1° amine-derived guanidines **3l** and **3m** were treated under the biphasic protocol with allylbromide (1.2 equiv), as expected, a mixture of diallylated compounds were obtained. For example, reaction of N^1,N^2-di-Boc-N^3-phenylguanidine **3l** with allylbromide (1.2 equiv) gave a separable mixture of diallylated compounds **5l** and **5m** in a 7:3 ratio, as well as unreacted guanidine starting material **3l** (Scheme 2.39).



5l:5m = 7:3 (99% yield, based on allybromide)

Scheme 2.39

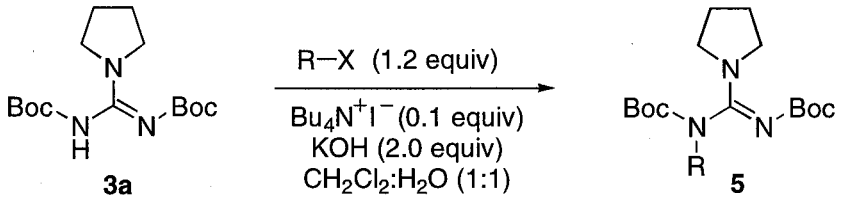
Additionally, N^1,N^2-di-Boc-N^3-benzylguanidine **3m** was treated with allylbromide in multiple reactions in an attempt to synthesize the monoallylated guanidine (Scheme 2.39). The benzylguanidine **3m** was treated with varying equivalents of allylbromide (1.2-5.0 equiv) and different reaction conditions, such as cooling to 0 °C with slow addition of allylbromide; however, all attempts to synthesize the monoallyated product were unsuccessful. Instead, a mixture of diallylated products in a similar ratio to that obtained with the phenylguanidine **3l** was obtained, although these compounds could not be separated. These results were similar to

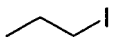
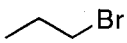
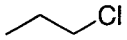
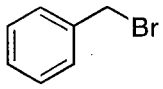
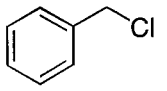
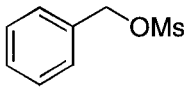
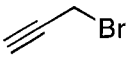
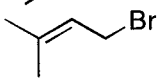
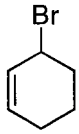
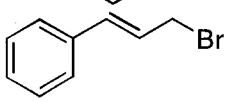
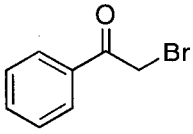
previous studies where reaction of 1° amine-derived guanidines **3** with allyl alcohols under Mitsunobu conditions, gave mixtures of diallylated compounds.[82] In addition, problems were encountered with selective alkylation of 1° amine-derived guanidines **3** with alkyl halides using the sodium hydride protocol, by Ko and co-workers.[83]

2.2.2 Guanidinylation Reactions of a Variety of Electrophiles with Pyrrolidine-Derived Guanidines

Having shown that a variety of guanidine nucleophiles successfully guanidinlyated allylbromide in good to excellent yields (Table 2.1), the tolerance of various electrophiles was then examined under the biphasic protocol. The N^1,N^2-di-Boc-N^3-pyrrolidineguanidine **3a** was used as the model substrate with a range of electrophiles (Table 2.2). Saturated alkyl halides, such as iodomethane (Table 2.2, entry 1) and bromopropane (Table 2.2, entry 3) were cleanly guanidinylated by **3a** to give the desired substituted guanidines **5o** and **5p** in 95% and 81% yield, respectively. Secondary alkyl bromides could also be guanidinylated regioselectively to yield the isopropyl and cyclohexenyl guanidines in 60% and 78% yields, respectively (Table 2.2, entries 5 and 11). In contrast, secondary alkyl bromides in the sodium hydride method reported by Ko and co-workers[83] gave only elimination products, rather than alkylation products.

Table 2.2 Phase-Transfer Catalyzed Alkylation of N^1,N^2-Di-Boc-N^3-pyrrolidine-1-carboxamidine **3a** with Various Electrophiles.



Entry	R—X	Time (h)	Temp (°C)	Compound 5	Yield (%)[a]
1	CH_3I	5	25	**5o**	95[b]
2		12	50	**5p**	77[b]
3		12	50	**5p**	81
4		48	50	**5p**	0[b,c]
5		48	50	**5q**	60[b]
6		4	25	**5r**	95
7		12 (10)	25 (50)	**5r**	88 (89)[d]
8		16	25	**5r**	92[e]
9		4	25	**5s**	92
10		4	25	**5t**	99
11		25	25	**5u**	78[b]
12		4	25	**5v**	95
13		4	25	**5w**	82

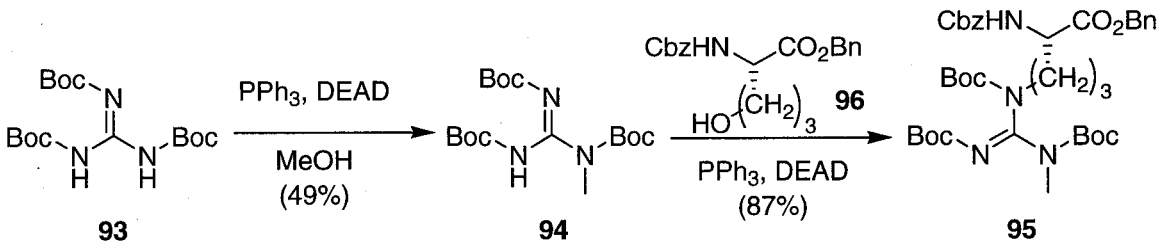
[a] Isolated yield. [b] 2.2 equiv of electrophile used. [c] Starting material isolated [d] Reaction carried out in a biphasic mixture of toluene:water (1:1) [e] Benzyl mesylate must be prepared and used immediately to avoid decomposition at rt, but may be stored for extended periods (> 3 months) at 0 °C.

For large-scale syntheses from a commercial standpoint, the use of alkyl chlorides over the more costly alkyl bromides is highly desirable. The biphasic protocol was therefore tested with alkyl chlorides, such as benzyl chloride, as the electrophilic component. It was gratifying to observe that biphasic alkylation of **3a** with benzyl chloride ($2.27/mol) proceeded under similar conditions and yield (Table 2.2, entry 7) as with the more expensive benzyl bromide ($39.80/mol) (Table 2.2, entry 6).[84] However, the guanidinylation procedure was not successful with unreactive alkyl chlorides, such as 1-chloropropane (Table 2.2, entry 4). Since non-chlorinated solvents, such as toluene, are often preferred industrially, the use of toluene as a co-solvent in the biphasic protocol was examined. Guanidine **3a** was heated with benzyl chloride in a biphasic mixture of toluene and water at 50 °C for 10 h in the presence of the phase-transfer catalyst and KOH, giving the desired benzylated guanidine **5r** in 89% yield (Table 2.2, entry 7). The guanidinylation procedure was expanded to include the use of mesylates (Table 2.2, entry 8), which were easily synthesized from the corresponding alcohols. The use of mesylates is an important expansion in the scope of this reaction since this protocol now provides an alternative method to the Mitsunobu reaction. Alcohols used exclusively in the Mitsunobu procedure can now be easily converted to the corresponding mesylate and subjected to the biphasic guanidinylation procedure, eliminating troublesome purification procedures associated with the Mitsunobu protocol. Clean alkylation of guanidine **3a** was also achieved with propargyl bromide (Table 2.2, entry 9) and 4-bromo-2-methyl-2-butene (Table 2.2, entry 10). Reaction at the secondary carbon of 3-bromocyclohexene (Table 2.2, entry 11), as with 2-bromopropane (Table 2.2, entry 5), was slower than displacement at a 1° carbon; therefore, longer reaction times were required. This difference in regioselectivity at 1° and 2° sites may also be responsible for the regioselective alkylation of cinnamyl bromide (Table 2.2, entry 12), which undergoes guanidinylation at the sterically favoured S_N2 site, rather than the electronically favoured S_N2' site.

The use of other phase-transfer catalysts, such as Bu_4NBr and Bu_4NCl, afforded products in similar yields to those obtained with Bu_4NI. Treatment of tetrahydroisoquinoline-derived guanidine **3a** with allyl bromide, using either Bu_4NBr or Bu_4NCl as the phase-transfer catalyst, afforded **5g** in similar yields compared to those obtained using Bu_4NI as the phase-transfer catalyst (Table 2.1, entry 7). Phase-transfer catalysis conditions have been used to prepare alkyl iodides via a Finkelstein reaction[85] and whether such a process was occurring under the biphasic conditions was examined. Reaction of guanidine **3a** and 1-chloropropane did not occur under refluxing biphasic conditions, with either Bu_4NCl or Bu_4NI as the phase-transfer catalyst, even

after 24 h (Table 2.2, entry 4). In contrast, treatment of **3a** with 1-iodopropane under the same conditions, using Bu_4NI as the phase-transfer catalyst, gave **5p** in 77% yield (Table 2.2, entry 2). Since alkylation of **3a** using Bu_4NI as the phase-transfer catalyst failed with 1-chloropropane, but was successful using 1-iodopropane, an *in situ* Finkelstein reaction does not occur under these biphasic reaction conditions.

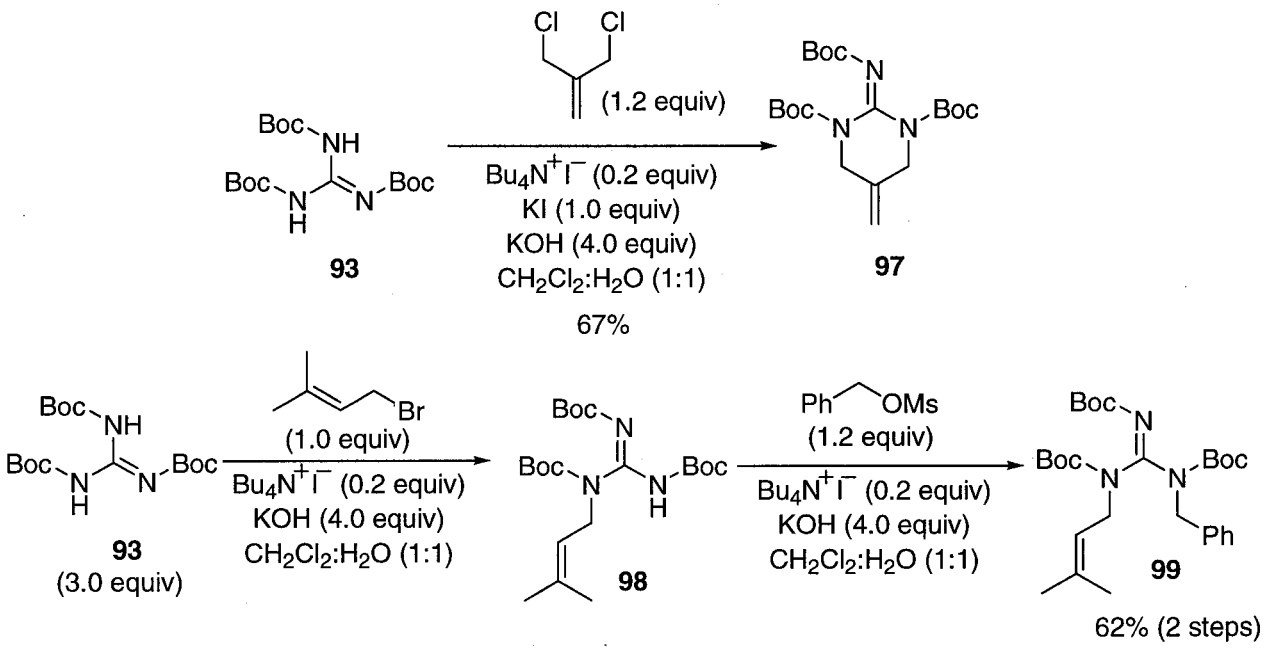
Recently, Goodman and co-workers have demonstrated that N^1,N^2,N^3-tri-Boc-guanidine **93** acts as a nucleophile for the guanidinylation of alcohols under the Mitsunobu conditions (Scheme 2.40).[86] Many biologically interesting guanidines contain two different alkyl groups in an N^1,N^2-substitution pattern. By using **93**, Goodman has shown that access to differentially alkylated guanidines **95** is now possible through two subsequent Mitsunobu reactions. The synthesis of ω-methylarginine **95**, an important inhibitor of nitric oxide synthethase, was achieved by using the tri-Boc guanidine **93** (Scheme 2.40). Goodman and co-workers converted the tri-Boc reagent **93** into the *N*-methyl derivative **94** by reacting **93** with MeOH, PPh_3, and DEAD. This *N*-methyl derivative **94** was then used in the second Mitsunobu step with alcohol **96** to yield the desired dialkylated guanidine **95** in 87% yield.



Scheme 2.40

Substrate **93** can similarly be alkylated with alkyl halides using the newly developed biphasic reaction conditions. For example, N^1,N^2,N^3-tri-Boc-guanidine **93**, prepared using a slightly modified procedure, was treated with 1 equivalent of 3-chloro-2-chloromethyl-1-propene in the presence of 1 equivalent of KI, to the give the cyclic guanidine **97**, resulting from tandem-intermolecular and intramolecular alkylation (Scheme 2.41). Alkylation of the tri-Boc-guanidine **93** with 2 different electrophiles was possible using a two-step procedure. Thus, reaction of 3 equivalents of the tri-Boc-guanidine **93** with 1 equivalent of prenyl bromide gave the alkylated guanidine **98**. After purification to remove the excess tri-Boc-guanidine **93**, reaction of **98** with

1.2 equivalents of benzyl mesylate gave the differentially dialkylated guanidine **99** in 62% yield, over the 2 step procedure (Scheme 2.41)



Scheme 2.41

2.2.3 Conclusions

An efficient method of the guanidinylation of *N*-dicarbamate-protected guanidines using a variety of alkyl halides was established. Under this procedure, the acidic *N*-carbamate hydrogen is deprotonated using biphasic conditions, with a catalytic amount of a tetrabutylammonium salt, as the phase-transfer catalyst, and then subsequently alkylated to yield highly functionalised guanidines. This protocol provides an alternate method for the alkylation of protected guanidines from those currently utilised. In addition, the need for stoichiometric amounts of costly or highly reactive coupling reagents is circumvented. An attractive feature of this methodology is that few by-products are generated and upon completion of the reaction, simple aqueous workup followed by filtration through a short column of silica gel, to remove the remaining phase-transfer catalyst, gives high yields of the desired products. Furthermore, less expensive benzyl chlorides serve as effective electrophiles. Replacement of dichlormethane with toluene as the organic solvent gives comparable results and is ideal for commercial preparation of substituted guanidines. Finally, the differentiation in terminology for two distinct classes of reactions, guanylations and guanidinylations, was proposed. The use of this terminology draws

attention to these two distinct reactions and avoids confusion in the literature with the nomenclature of these reactions.

2.3 Experimental Section

2.3.1 Chemical Characterization

Melting points were determined using a Fisher-Johns melting point apparatus. Infrared spectra were obtained from a Perkin-Elmer Spectrum 1000 series FTIR as KBr disks for solid samples and neat for liquid samples using KBr plates. Nuclear magnetic resonance spectra were obtained using either a 300 MHz Varian Mercury or 400 MHz Varian Unity spectrometer (^{1}H NMR) and a 400 MHz Varian Unity spectrometer operating at 100 MHz (^{13}C NMR) and all signals are reported in ppm (δ). All ^{1}H NMR spectra were referenced to an internal standard (TMS) when using deuteriochloroform as the solvent. The ^{13}C-NMR spectra were obtained using deuteriochloroform and residual solvent peaks were referenced to δ 77.0 ppm. ^{1}H NMR spectra are listed in the experimental section as follows: chemical shift (ppm), (number of protons, multiplicity, coupling constants). Line broadening is apparent in some NMR spectra and is due to rotamers around the carbamate nitrogen. Low-resolution mass spectral data were obtained from Dr. Alex Young at the University of Toronto using a Bell and Howell 21-490 spectrometer. High-resolution mass spectral data were also obtained from Dr. Alex Young using an AEI MS3074 spectrometer.

2.3.2 General Procedures

All reagents, unless otherwise stated, were used as received from commercial suppliers. Toluene was distilled from sodium metal/benzophenone ketyl under an atmosphere of argon. Dichloromethane was distilled from calcium hydride under an atmosphere of argon prior to use. DMF was distilled from 4 Å molecular sieves under reduced pressure. Where appropriate, reactions were conducted under an inert atmosphere in flame dried or oven-dried glassware. Reactions were monitored by TLC using 1.5 cm x 5 cm aluminium plates pre-coated with silica gel 60, 0.2 mm thick (F_{254}, E. Merck). The TLC plates were viewed under a U.V. lamp (254nm/366nm). Flash chromatography was performed using silica gel 60 (0.040-0.063 nm, 230-400 mesh A.S.T.M.) with reagent grade solvents.

General Procedure A: Procedure for the Synthesis of Guanidines 3.

To a solution of amine **1** (3.00 mmol), N^1,N^2-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea **2b** (960 mg, 3.30 mmol) and triethylamine (1.25 mL, 9.00 mmol) in anhydrous DMF (10 mL) was added $HgCl_2$ (891 mg, 3.30 mmol). The suspension was stirred at rt for 4 h and then concentrated *in vacuo*. The crude reaction mixture was taken up in Et_2O (40 mL), filtered through a pad of celite on a sintered glass funnel, washed with saturated aqueous NH_4Cl (50 mL), H_2O (50 mL), brine (50 mL), and dried over $MgSO_4$. The mixture was concentrated *in vacuo* and purified by flash chromatography to yield the guanidine product **3**.

General Procedure B: Procedure for the Biphasic, Phase-Transfer Catalyzed Synthesis of Guanidines 5.

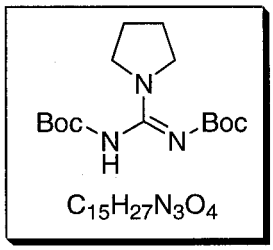
A biphasic solution of guanidine **3** (0.50 mmol), tetrabutylammonium iodide (18 mg, 0.05 mmol), and KOH (56 mg, 1.0 mmol) in a 1:1 mixture of CH_2Cl_2:H_2O (5 mL) was treated with the alkyl halide or alkyl mesylate (0.60–1.0 mmol, depending on the electrophile, see Table 2.2). The reaction was stirred at 25-50 °C (depending on the electrophile, see Table 2.2) for 2-4 h and then the reaction mixture was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product **5** was purified by flash chromatography through a short column of silica gel.

General Procedure C: Procedure for the Deprotection of N^1,N^2-bis(*tert*-butoxycarbonyl)-Guanidines 6.

A solution of the guanidine **5** (0.25 mmol) in 1M aqueous HCl (2 mL) and dioxane (2 mL) was stirred at rt for 4 h or until all of the starting material was consumed, as monitored by TLC. The reaction was concentrated *in vacuo* and purified by flash chromatography to give the unprotected guanidine as the HCl salt.

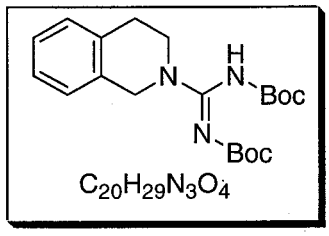
2.3.3 Experimental Procedures

N^1,N^2-Bis(*tert*-butoxycarbonyl)-pyrrolidine-1-carboxamidine (3a):



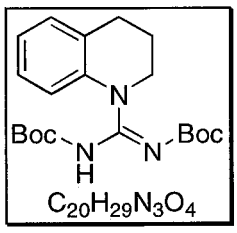
The product was synthesized using General Procedure A and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to yield an off-white solid in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (1H, br s), 3.48 (4H, br s), 1.95-1.79 (4H, m), 1.41 (18H, s); MS (EI) *m/e* 314 (19, MH^+), 201 (29), 184 (60), 70 (41), 57 (100); HRMS (EI) *m/e* (M^+) calcd 313.2002, found 313.1999. This compound has been previously characterized. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804-3805.

N^1,N^2-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine (3g):



The product was synthesized using General Procedure A and was purified by flash chromatography (80% hexanes:20% EtOAc) to yield a clear oil in 86% yield. R_f = 0.28 (80% hexanes:20% EtOAc); IR (neat) ν 3104, 2978, 1747, 1614, 1415, 1366, 1299, 1146, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (1H, bs), 7.19-7.09 (4H, m), 4.71 (2H, bs), 3.77 (2H, bs), 2.97 (2H, t, *J* = 6.0 Hz), 1.51 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 134.6, 132.7, 128.3, 126.7, 126.3, 126.2, 82.2, 79.4, 48.8, 45.0, 28.6, 28.2, 28.1 (2 quaternary carbons not observed); MS (EI) *m/e* 375 (6, M^+), 319 (19), 263 (61), 246 (32), 219 (40), 174 (27), 132 (87), 131 (29), 59 (30), 57 (100); HRMS (EI) *m/e* (M^+) calcd 375.2158, found 375.2141.

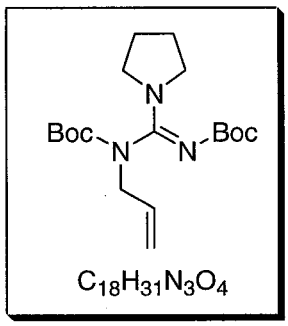
N^1,N^2-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-quinoline-1-carboxamidine (3h):



The product was synthesized using General Procedure A and was purified by flash chromatography (80% hexanes:20% EtOAc) to yield a white powder in 89% yield. R_f = 0.38 (80% hexanes:20% EtOAc); mp 159-161 °C (80% hexanes:20% EtOAc); IR (KBr) ν 3211, 2951, 2246, 1750, 1634, 1574, 1602, 1493, 1391, 1303, 1243, 1162, 1131 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 9.96 (1H, br s), 7.25-6.91 (4H, m), 3.89 (2H, t, *J* = 6.5 Hz), 2.77 (2H, t, *J* = 6.5 Hz), 2.03-1.91 (2H, m), 1.52 (9H, br s), 1.19 (9H, br s); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 154.5, 139.8, 132.6, 129.4, 128.6, 126.7, 126.2, 124.4, 120.8, 116.9, 114.1, 46.5, 41.9, 28.0 (br), 26.8, 23.8, 22.1; MS (EI)

m/e 375 (45, M^+), 319 (28), 274 (13), 262 (10), 245 (53), 218 (50), 200 (62), 175 (66), 158 (29), 132 (100); HRMS (EI) *m/e* (M^+) calcd 375.2158, found 375.2156.

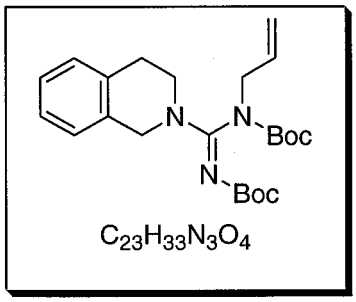
N^1-Allyl-N^1,N^2-bis(*tert*-butoxycarbonyl)pyrrolidine-1-carboxamidine (5a):



$C_{18}H_{31}N_3O_4$

The product was synthesized using General Procedure B and was purified by flash chromatography (50% hexanes:50% Et_2O) to yield a clear oil in 89% yield. R_f = 0.22 (50% hexanes:50% Et_2O); IR (neat) ν 2976, 1720, 1597, 1455, 1366, 1243, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz), 5.21 (1H, dd, *J* = 17.0, 1.0 Hz), 5.12 (1H, dd, *J* = 10.0, 1.0 Hz), 4.23 (1H, bs), 3.63-3.43 (5H, m), 1.87 (4H, bs), 1.46 (9H, s), 1.45 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.0, 152.2, 133.0, 118.9, 81.3, 78.8, 49.9, 48.0, 47.6, 28.2, 28.1, 25.2, 24.8; MS (EI) *m/e* 354 (MH^+, 10), 353 (M^+, 9), 253 (16), 224 (21), 197 (54), 152 (19), 97 (23), 72 (22), 70 (49), 57 (100); HRMS (EI) *m/e* (M^+) calcd 353.2315, found 353.2306.

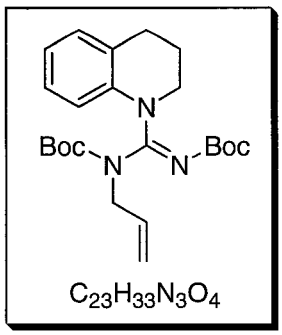
N^1-Allyl-N^1,N^2-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine



$C_{23}H_{33}N_3O_4$

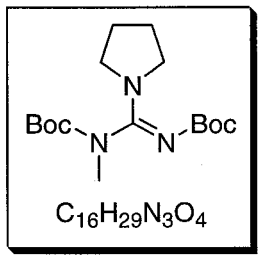
(5g): The product was synthesized using General Procedure B and was purified by flash chromatography (50% hexanes:50% Et_2O) to yield a clear oil in 96% yield. R_f = 0.32 (50% hexanes:50% Et_2O); IR (neat) ν 2977, 1720, 1600, 1454, 1366, 1268, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.12 (4H, m), 5.91-5.86 (1H, m), 5.25 (1H, d, *J* = 17.0 Hz), 5.16 (1H, d, *J* = 10.0 Hz), 4.88-4.08 (4H, m), 3.80-3.52 (2H, m), 2.90-2.88 (2H, m), 1.51-1.43 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 153.5, 152.1, 134.8, 133.6, 132.3, 128.2, 126.3, 119.5, 81.5, 79.1, 50.0, 47.6, 43.3, 29.1, 28.0 (2 quaternary carbons not observed); MS (EI) *m/e* 415 (4, M^+), 259 (22), 144 (22), 132 (58), 86 (31), 84 (40), 57 (100); HRMS (EI) *m/e* (M^+) calcd 415.2471, found 415.2480.

N^1-Allyl-N^1,N^2-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-quinoline-1-carboxamidine (5h):



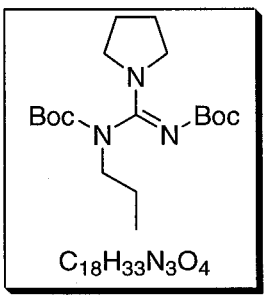
The product was synthesized using General Procedure B and was purified by flash chromatography (80% hexanes: 20% EtOAc) to yield a clear, colourless oil in 96% yield. R_f = 0.41 (80% hexanes: 20% EtOAc); IR (neat) ν 2971, 2922, 2253, 1718, 1620, 1577, 1496, 1454, 1391, 1366, 1243, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.01 (4H, m), 5.84 (1H, ddt, J = 17.0, 10.5, 6.5 Hz), 5.10-5.06 (2H, m), 4.18-3.42 (4H, br m) 2.75 (2H, br t, *J* = 6.0 Hz), 1.99 (2H, bs), 1.43 (9H, s), 1.41 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 133.3, 128.6, 126.3, 124.6, 122.1, 118.0, 82.1, 79.7, 50.8, 46.9, 28.1, 26.7, 23.6 (4 quaternary carbons not observed); MS (EI) *m/e* 416 (20, MH^+), 415 (38, M^+), 259 (26), 215 (20), 134 (22), 133 (100), 132 (35); HRMS (EI) *m/e* (M^+) calcd 415.2471, found 415.2465.

N^1,N^2-Bis(*tert*-butoxycarbonyl)pyrrolidine-N^1-methyl-1-carboxamidine (5o):



The product was synthesized using General Procedure B and was purified by flash chromatography (70% hexanes:30% EtOAc) to yield a clear oil in 95% yield. R_f = 0.10 (70% hexanes:30% EtOAc); IR (neat) ν 2935, 1717, 1680, 1595, 1474, 1454, 1363, 1282, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.50 (2H, bs), 3.41 (2H, bs), 2.96 (3H, s), 1.91 (4H, bs), 1.48 (9H, s), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 81.3, 78.9, 48.0, 47.2, 28.3, 28.1, 25.3, 24.9 (2 quaternary carbons not observed); MS (EI) *m/e* 327 (11, M^+), 271 (17), 215 (44), 198 (33), 170 (17); HRMS (EI) *m/e* (M^+) calcd 327.2158, found 327.2149.

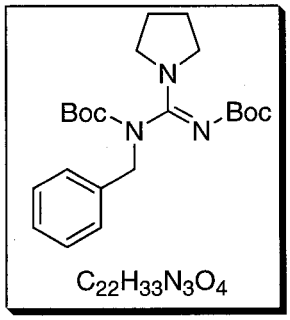
N^1,N^2-Bis(*tert*-butoxycarbonyl)-N^1-(1-propyl)pyrrolidine-1-carboxamidine (5p):



The product was synthesized using General Procedure B and was purified by flash chromatography (50% hexanes:50% Et_2O) to yield a light yellow oil in 81% yield. R_f = 0.15 (50% hexanes:50% Et_2O); IR (neat) ν 2974, 1718, 1596, 1453, 1366, 1242, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.55-3.42 (5H, m), 2.99 (1H, bs), 1.88 (4H, bs), 1.57-1.50 (2H, m), 1.45 (18H, s), 0.85 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 153.2, 152.2, 81.0, 78.7, 49.3, 48.1, 47.5, 28.3, 28.1, 25.3, 24.9, 22.3, 11.4; MS (EI) *m/e* 355 (12, M^+), 299 (10), 243 (15), 226 (19), 201 (22), 157 (19), 143 (31), 142 (50), 141 (46), 140 (40), 129

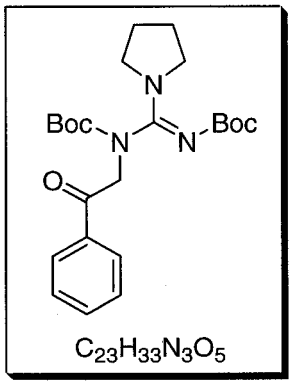
(36), 97 (27), 86 (43), 84 (84), 70 (95), 57 (100); HRMS (EI) *m/e* (M^+) calcd 355.2471, found 355.2474.

N^1-Benzyl-N^1,N^2-bis(*tert*-butoxycarbonyl)pyrrolidine-1-carboxamidine (5r):



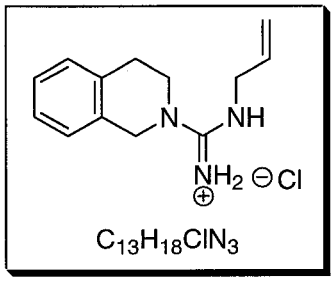
The product was synthesized using General Procedure B and was purified by flash chromatography (50% hexanes:50% Et_2O) to yield a yellow oil in 95% yield. R_f = 0.30 (50% hexanes:50% Et_2O); IR (neat) ν 2975, 1718, 1596, 1454, 1366, 1274, 1165, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m), 4.97 (1H, bs), 4.09 (1H, bs), 3.44 (2H, bs), 3.21 (1H, bs), 2.76 (1H, bs), 1.80-1.75 (4H, m), 1.48 (9H, s), 1.46 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.1, 152.3, 136.8, 129.2, 128.4, 127.7, 81.4, 78.8, 50.8, 47.9, 47.4, 28.3, 28.2, 25.0, 24.7; MS (EI) *m/e* 403 (M^+, 25), 347 (23), 291 (26), 274 (32), 247 (43), 230 (28), 202 (43), 156 (28), 143 (21), 106 (97), 97 (34), 91 (64), 70 (91), 57 (100); HRMS (EI) *m/e* (M^+) calcd 403.2471, found 403.2462.

N^1,N^2-Bis(*tert*-butoxycarbonyl)-N^1-(2-oxo-2-phenyl-ethyl)-pyrrolidine-1-carboxamidine



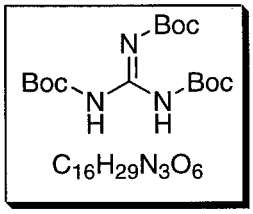
(5w): The product was synthesized using General Procedure B and was purified by flash chromatography (80% hexanes:20% EtOAc) to yield a clear, viscous oil in 82% yield. R_f = 0.22 (80% hexanes:20% EtOAc); IR (neat) ν 3267, 3211, 2978, 1788, 1729, 1701, 1511, 1366, 1250, 1208, 1138 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.92-7.83 (2H, m), 7.61-7.39 (3H, m), 5.34-5.28 (1H, m), 4.40-4.34 (1H, m), 3.61-3.46 (4H, m), 2.05-1.81 (4H, bs), 1.55-1.38 (18H, m); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 193.6, 192.9, 159.6, 159.3, 154.2, 152.3, 151.2, 150.1, 149.3, 135.0, 133.5, 128.7, 127.7, 85.1, 82.0, 78.7, 54.4, 53.6, 49.6, 48.5, 48.3, 28.3, 28.0, 25.2, 24.9; MS (EI) *m/e* 431 (5, M^+), 358 (5), 331 (8), 302 (8), 274 (13), 258 (23), 231 (32), 214 (19), 206 (21); HRMS (EI) *m/e* (M^+) calcd 431.2420, found 431.2427.

N^1-Allyl-N^2-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine hydrochloride (6g):



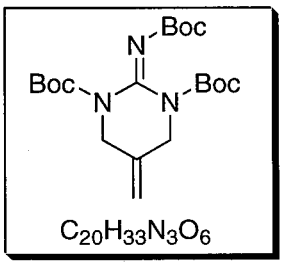
The product was synthesized using General Procedure C and was purified by flash chromatography (90% CH_2Cl_2:10% MeOH) to yield a white powder in 90% yield as the HCl salt. R_f = 0.30 (90% CH_2Cl_2:10% MeOH); mp 163-164 °C (90% CH_2Cl_2:10% MeOH); IR (KBr) ν 3295, 3133, 2922, 1648, 1606, 1454 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.23 (4H, m), 5.93 (1H, ddt, J = 17.0, 10.5, 5.0 Hz), 5.26 (2H, m), 4.86 (2H, s), 4.61 (2H, s), 3.97 (2H, m), 3.67 (2H, t, J = 6.0 Hz), 3.00 (2H, t, J = 6.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 157.4, 136.0, 134.1, 133.0, 129.3, 128.7, 128.1, 127.5, 117.4, 48.6, 45.6, 45.4, 29.5; MS (EI) *m/e* 216 (18, MH^+), 215 (62, M^+), 200 (18), 186 (8), 174 (11), 159 (7), 142 (5) 132 (100); HRMS (EI) *m/e* (M^+, free guanidine) calcd 215.1422, found 215.1419.

N^1,N^2,N^3-Tris-(*tert*-butoxylcarbonyl)-guanidine (93):



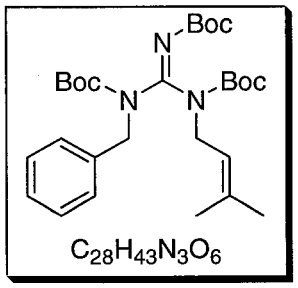
The product was obtained as a white solid (72%). R_f = 0.27 (70% hexanes: 30% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.62-8.10 (2H, br s), 1.51 (27H, s); MS (EI) *m/e* 360 (10, MH^+), 304 (15), 248 (27), 192 (54), 148 (45), 57 (100); HRMS (EI) *m/e* (MH^+) calcd 360.2135, found 360.2139. This compound has been previously characterized, see: Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432-8439.

N^1,N^2,N^3-Tris-(*tert*-butoxylcarbonyl)-4,6-dihydro-5-methylene-pyrimidine (97): To a biphasic solution of CH_2Cl_2: H_2O (1:1) (3 mL) was added 3-chloro-2-chloromethyl-1-propene (45 μL, 0.39 mmol), KI (54 mg, 0.33 mmol), KOH (55 mg, 0.98 mmol), and Bu_4NI (24 mg, 0.07 mmol). The mixture was stirred vigorously at rt and then a solution of the tri-Boc-guanidine **93** (117 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) was added dropwise over a 1 h period. After 16 h, the mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (80% hexanes:20% EtOAc with 1% Et_3N) gave the product as a white solid (89 mg, 67%). R_f = 0.39 (70% hexanes:30% EtOAc); mp 109-110 °C (70% hexanes:30% EtOAc); IR (KBr) ν 2978, 2929, 1753, 1725, 1690, 1644, 1454, 1370, 1314,



1254, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (2H, s), 4.27 (4H, s), 1.49 (27H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 151.5, 148.0, 140.5, 108.6, 83.4, 79.8, 47.6, 28.2, 28.0; MS (EI) *m/e* 412 (8, MH^+), 360 (4), 312 (4), 260 (35), 204 (52), 148 (71), 130 (44), 104 (16), 57 (100); HRMS (EI) *m/e* (MH^+) calcd 412.2448, found 412.2459.

N^1-Benzyl-N^1,N^2,N^3-tris-(*tert*-butoxycarbonyl)-N^2-(3-methyl-but-2-ene) (99): To a biphasic solution of CH_2Cl_2 (1.5 mL) and H_2O (1.5 mL) was added the tri-Boc-guanidine **93** (375 mg, 1.04 mmol) followed by KOH (58 mg, 1.04 mmol) and Bu_4NI (26 mg, 0.07 mmol). The mixture was stirred vigorously and then 4-bromo-2-methyl-2-butene (40 μL, 0.35 mmol) was added. After 16 h, the mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The mixture was passed over a small plug of silica gel (90% hexanes: 10% EtOAc) to remove the phase-transfer catalyst and excess tri-Boc-guanidine **93**.



The tri-Boc-prenyl-guanidine **98** was stirred in a biphasic mixture of CH_2Cl_2 (1.5 mL) and H_2O (1.5 mL). To this mixture was added KOH (53 mg, 0.95 mmol) and Bu_4NI (23 mg, 0.06 mmol). Benzyl mesylate (88 mg, 0.47 mmol) was then added and the mixture was stirred vigorously at rt. After 16 h, the mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 90% hexanes: 10% EtOAc with 1% Et_3N) gave the product (112 mg, 62% yield) as a clear oil. R_f = 0.11 (90% hexanes:10% EtOAc); IR (neat) ν 2978, 2936, 1736, 1722, 1644, 1454, 1387, 1370, 1250, 1222, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38-7.22 (5H, m), 5.23-5.18 (1H, m), 4.79 (2H, s), 4.14 (0.5 H, d, *J* = 6.5 Hz), 4.03 (1.5 H, d, *J* = 6.5 Hz), 1.70 (0.7H, br s), 1.65 (2.3H, br s), 1.61 (1H, br s), 1.59 (2H, br s), 1.48 (9H, s), 1.47 (9H, s), 1.35 (9H, s); ^{13}C NMR (100 MHz, CD_3CN, rotamers) δ 159.0, 153.1, 152.9, 150.5, 139.0, 136.9, 136.2, 129.3, 128,4, 128.1, 120.4, 83.8, 82.8, 81.7, 52.3, 47.0, 46.8, 28.5, 28.4, 28.2, 26.0, 18.2; MS (EI) *m/e* 518 (20, MH^+), 517 (5, M^+), 496 (9), 418 (12), 361 (12), 305 (28), 283 (10), 261 (35), 239 (15), 214 (20), 170 (16), 126 (16), 106 (20), 84 (49), 57 (100); HRMS (EI) *m/e* (M^+) calcd 517.3152, found 517.3168.

2.4 References

(1) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brosse, C. D.; Mai, S.; Truneh, A.; Carte, B. *J. Org. Chem.* **1995**, *60*, 1182-1188.

(2) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814-1819.

(3) Fenton, R. J.; Morley, P. J.; Owens, I. J.; Gower, D.; Parry, S.; Crossman, L.; Wong, T. *Antimicrobial Agents and Chemotherapy* **1999**, *43*, 2642-2647.

(4) Matsumura, K. *Nature* **1995**, *378*, 563-564.

(5) Jones, J. H. *J. Peptide Sci.* **2002**, *8*, 285-287.

(6) *Nomenclature of Organic Chemsitry*; IUPAC and Butterworths: London, 1969.

(7) Maehr, H.; Yarmchuk, L.; Leach, M. *J. Antibiot.* **1976**, *29*, 221-226.

(8) Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.*, in press.

(9) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7667-7680.

(10) Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291-5304.

(11) Cunha, S.; Costa, M. B.; Napolitano, H. B.; Lariucci, C.; Vencato, I. *Tetrahedron* **2001**, *57*, 1671-1675.

(12) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 3138-3141.

(13) Zhang, J.; Shi, Y.; Stein, P.; Atwal, K.; Li, C. *Tetrahedron Lett.* **2002**, *43*, 57-59.

(14) Jirgensons, A.; Kums, I.; Kauss, V.; Kalvins, I. *Synth. Commun.* **1997**, *27*, 315-322.

(15) Hansen, E. T.; Petersen, H. J. *Synth. Commun.* **1984**, *14*, 1275-1283.

(16) Atwal, K. S.; Ahmed, S. Z.; O'Reilly, B. C. *Tetrahedron Lett.* **1989**, *30*, 7313-7316.

(17) Poss, M. A.; Iwanowicz, E., J.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933-5936.

(18) Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566-1568.

(19) Manimala, J. C.; Anslyn, E. V. *Tetrahedron Lett.* **2002**, *43*, 565-567.

(20) Harada, K.; Ohtani, I.; Iwamoto, K.; Suzuki, M.; Watanabe, M. F.; Watanabe, M.; Terao, K. *Toxicon* **1994**, *32*, 73-84.

(21) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540-1542.

(22) Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 575-576.

(23) Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770-7773.

(24) Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7774-7778.

(25) Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7779-7785.

(26) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 5832-5835.

(27) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984-6988.

(28) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6989-6992.

(29) Nizi, E.; Botta, M.; Corelli, F.; Manetti, F.; Messina, F.; Maga, G. *Tetrahedron Lett.* **1998**, *39*, 3307-3310.

(30) Lal, B.; Gangopadhyay, A. K. *Tetrahedron Lett.* **1996**, *37*, 2483-2486.

(31) Xue, C.-B.; DeGrado, W. F. *Tetrahedron Lett.* **1995**, *36*, 55-58.

(32) Wang, X.; Thottathil, J. *Tetrahedron: Asymmetry* **2000**, *11*, 3665-3669.

(33) Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357-8367.

(34) Durand, P.; Peralba, P.; Renaut, P. *Tetrahedron* **2001**, *57*, 2757-2760.

(35) Arndt, F.; Milde, E.; Eckert, G. *Ber.* **1921**, *54B*, 2236-2242.

(36) Phillips, R.; Clarke, H. T. *J. Am. Chem. Soc.* **1923**, 1755-1757.

(37) Smith, G. B. L. *J. Am. Chem. Soc.* **1929**, 476-479.

(38) Cherouvrier, J.-R.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2002**, *43*, 3581-3584.

(39) Miel, H.; Rault, S. *Tetrahedron Lett.* **1998**, *39*, 1565-1568.

(40) Bounkham, T. *Synthesis* **1997**, 1189-1194.

(41) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; John Wiley & Sons, Inc.: Toronto, 1999.

(42) Lamothe, M.; Perez, M.; Colovray-Gotteland, V.; Halazy, S. *Synlett* **1996**, 507-508.

(43) Chandrakumar, N. S. *Synth. Commun.* **1996**, *26*, 2613-2616.

(44) Guo, Z.-X.; Cammidge, A. N.; Horwell, D. C. *Synth. Commun.* **2000**, *30*, 2933-2943.

(45) Feldman, P. L. *Tetrahedron Lett.* **1991**, *32*, 875-878.

(46) Bredereck, H.; Effenberger, F.; Hajek, M. *Chem. Ber.* **1965**, *98*, 3178-3179.

(47) Bernatowicz, M. S.; Youling, W.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497-2502.

(48) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389-3392.

(49) Ghosh, A. K.; Hol, W. G. J.; Fan, E. *J. Org. Chem.* **2001**, *66*, 2161-2164.

(50) Drake, B.; Patek, M.; Lebl, M. *Synthesis* **1994**, 579-582.

(51) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804-3805.

(52) Baker, T. J.; Luedtke, N. W.; Tor, Y.; Goodman, M. *J. Org. Chem.* **2000**, *65*, 9054-9058.

(53) Tamaki, M.; Han, G.; Hruby, V., J. *J. Org. Chem.* **2001**, *66*, 1038-1042.

(54) Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133-1136.

(55) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432-8439.

(56) Luedtke, N. W.; Baker, T. J.; Goodman, M.; Tor, Y. *J. Am. Chem. Soc.* **2000**, *122*, 12035-12036.

(57) Jacobson, K. A.; Gao, Z.-G.; Chen, A.; Barak, D.; Kim, S.-A.; Lee, K.; Link, A.; Rompaey, P. V.; Calenbergh, S. v.; Liang, B. T. *J. Med. Chem.* **2001**, *44*.

(58) Mamai, A.; Hughes, N. E.; Wurthmann, A.; Madalengoitia, J. S. *J. Org. Chem.* **2001**, *66*, 6483-6486.

(59) Guerreiro, P.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Dellis, P. *Tetrahedron Lett.* **2001**, *42*, 3423-3426.

(60) Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882-1884.

(61) Arzeno, H. B.; Bingenheimer, W.; Morgans, D. J., Jr. *Synth. Commun.* **1990**, *20*, 3433-3437.

(62) Nestor, J. J., Jr.; Ho, T. L.; Simpson, R. A.; Horner, B. L.; Jones, G. H.; McRae, G. I.; Vickery, B. H. *J. Med. Chem.* **1982**, *25*, 795-801.

(63) Franklin, E. C. *J. Am. Chem. Soc.* **1922**, *44*, 486-509.

(64) Snider, B. B.; O'Hare, S. M. *Tetrahedron Lett.* **2001**, *42*, 2455-2458.

(65) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217-4220.

(66) Katritzky, A. R.; Parris, R. L.; Allin, S. M.; Steel, P. J. *Synth. Commun.* **1995**, *25*, 1173-1186.

(67) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080-8082.

(68) Ko, S. Y.; Lerpiniere, J.; Christofi, A. M. *Synlett* **1995**, 815-816.

(69) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977-980.

(70) Ishiwata, T.; Hino, T.; Koshino, H.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Org. Lett.* **2002**, *4*, 2921-2924.

(71) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235-4238.

(72) Fishlock, D.; Guillemette, J. G.; Lajoie, G. A. *J. Org. Chem.* **2002**, *67*, 2352-2354.

(73) Nagasawa, K.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2001**, *42*, 4155-4158.

(74) Beumer, R.; Reiser, O. *Tetrahedron* **2001**, *57*, 6497-6503.

(75) Shin, I.; Lee, M.-r.; Lee, J.; Jung, M.; Lee, W.; Yoon, J. *J. Org. Chem.* **2000**, *65*, 7667-7675.

(76) Osterkamp, F.; Ziemer, B.; Koert, U.; Wiesner, M.; Raddatz, P.; Goodman, S. L. *Chem. Europ. J.* **2000**, *6*, 666-683.

(77) Wang, Q.; Sasaki, N. A.; Potier, P. *Tetrahedron* **1998**, *54*, 15759-15780.

(78) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432-8439.

(79) Acton III, J. J.; Jones, A. B. *Tetrahedron Lett.* **1996**, *37*, 4319-4322.

(80) Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.*, in press.

(81) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977-980.

(82) Tomioka, M. In *Book of Abstracts, 219th National Meeting of the American Chemical Society*; American Chemical Society, Washington, DC: Medi-230: San Francisco, CA, 2000.

(83) Ko, S. Y.; Lerpiniere, J.; Christofi, A. M. *Synlett* **1995**, 815-816.

(84) Listed prices from the Aldrich Chemical Company, 2002, U.S. funds.

(85) Starks, C. M.; Liotta, C. *Phase-Transfer Catalysis: Principles and Techniques*; Academic Press: New York, 1978.

(86) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432-8439.

Chapter 3

Intramolecular Reactions to Generate Cyclic Guanidine-Containing Compounds: Applications Towards Cyclic Guanidine Natural Products

3.1 Introduction

3.1.1 Cyclic Guanidine Natural Products

Compounds containing the guanidine functional group are abundant in nature and have been the focus of several extensive reviews.[1-3] Many guanidine-containing compounds have been isolated from a variety of living organisms, such as terrestrial, marine, and freshwater microorganisms. Additionally, a variety of plants as well as marine and terrestrial invertebrates are a rich source of naturally occurring guanidine compounds. Guanidine-containing compounds isolated from these sources exhibit a wide range of substitution patterns as well as diverse biological activities. Due to the synthetic and medicinal interest in guanidine-containing compounds, a variety of methods have been developed for the synthesis of these biologically active natural products.[1] However, substituted guanidine-containing compounds continue to be synthetically challenging molecules due to their high basicity and polarity. Since guanidines can have multiple substitution patterns, with zero to five possible sites for substitution (Figure 3.1), more synthetic routes need to be developed to add to the reserve of methods currently available.

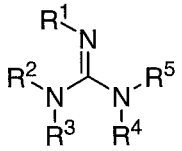


Figure 3.1 Possible Substitution Patterns on Guanidine Functional Groups

An interesting class of guanidine-containing natural products is derived from cyclic guanidines. In these compounds, the guanidine functionality is embedded in the cyclic core of the molecule and compounds containing this motif can exhibit potent biological activities (Figure 3.2).

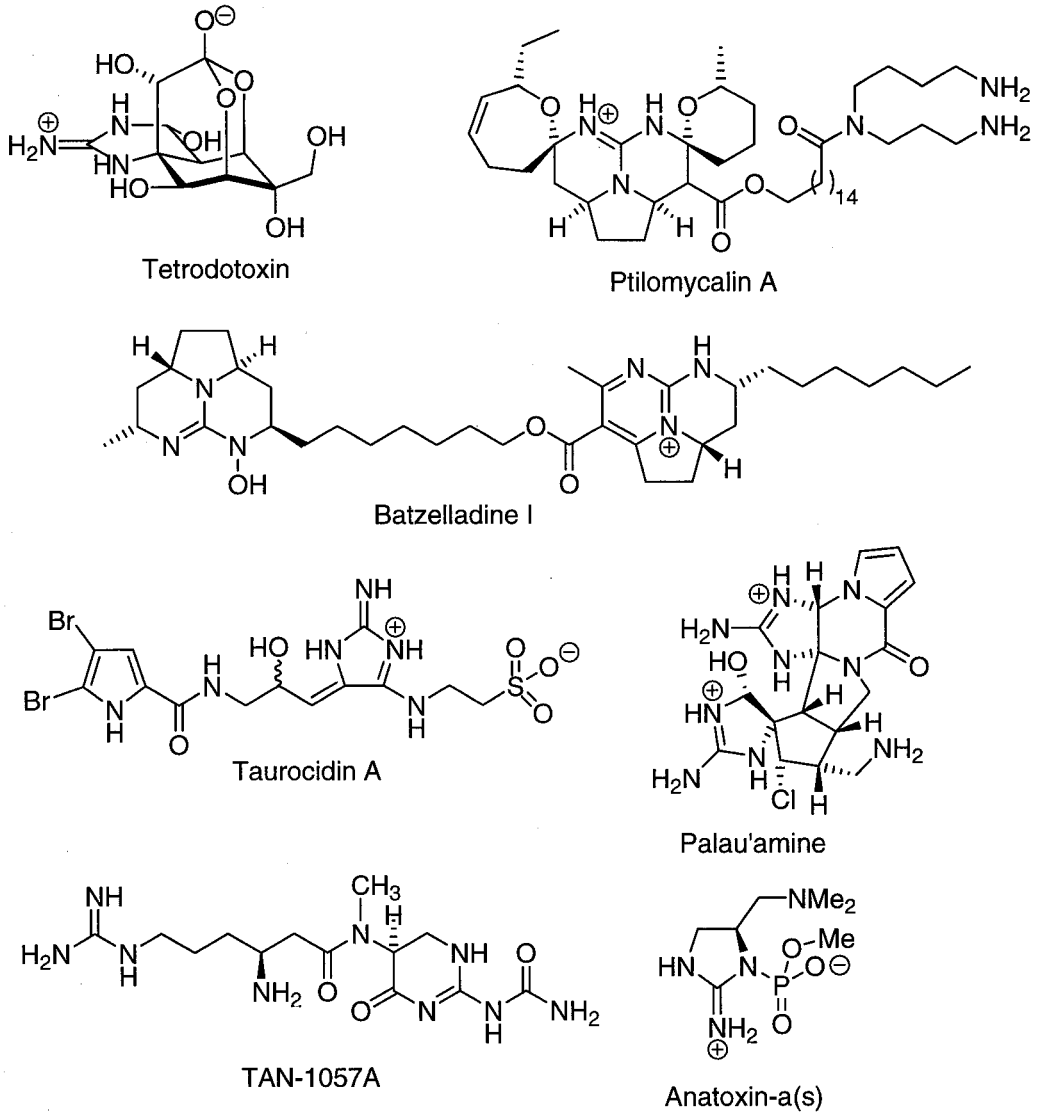
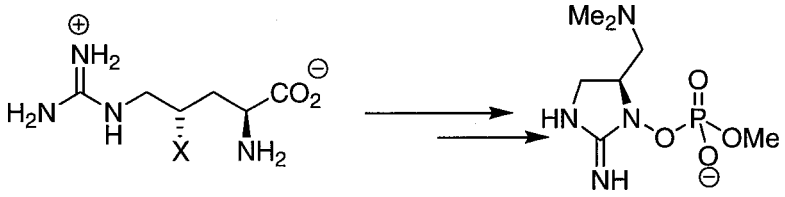


Figure 3.2 Select Examples of Cyclic Guanidine Natural Products

Anantoxin-a(s) **1** is a potent neurotoxin produced by the cyanophyte *Anabaena flos-aquae*. This cyclic guanidine-containing compound has the most potent anticholinesterase activity known, both *in vitro* and *in vivo*, and has been implicated in many animal deaths as a result of consumption of algal-contaminated drinking water.[4-6] Moore and co-workers have extensively examined the biosynthesis of this potent guanidine.[4,5,7] The amino acid, L-arginine **2a**, was added to the cyanophyte, *Anabaena flos-aquae*, and it was shown that anatoxin-a(s) **1** was formed from this amino acid. In addition, (2*S*,4*S*)-4-hydroxyarginine **2b** was added to the cyanophyte and anatoxin-a(s) **1** was also isolated, indicating this arginine derivative is an intermediate in the biosynthetic pathway (Scheme 3.1). Interestingly, a total synthesis of anatoxin-a(s) **1** has not been performed, due in part to the potent toxicity of this compound (LD_{50}

20-40 μg/kg mice).[7] In addition, the apparent stereochemical simplicity of this molecule, containing only one stereocentre, would perhaps make some synthetic groups feel this natural product is not a significantly challenging target. However, the presence of the unique phosphate ester of a cyclic *N*-hydroxyguanidine moiety poses significant challenges to the synthesis of this potent toxin.



2a X = H
2b X = OH

1

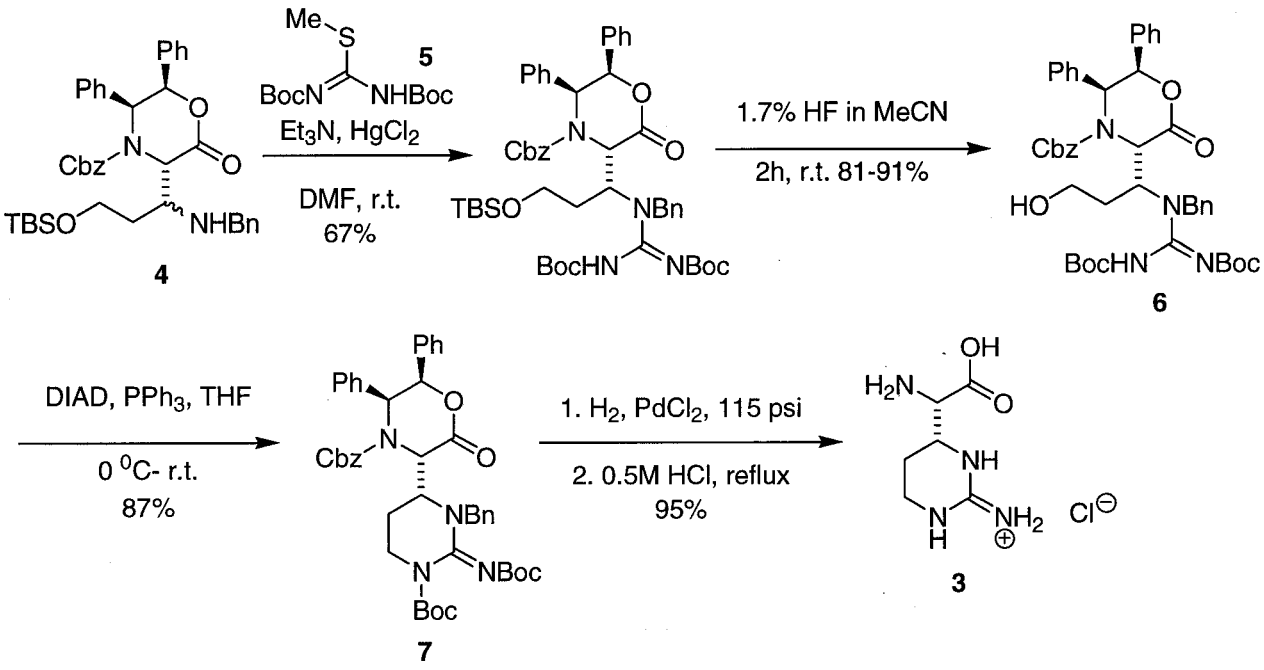
Scheme 3.1

Another interesting cyclic guanidine natural product is batzelladine I (Figure 3.2), which was isolated from the Jamaican sponge *Batzella* by Patil and co-workers.[8,9] Batzelladine I (Figure 3.2) was shown to be a potent inducer of $p56^{lck}$-CD4 dissociation and was one of the first natural products to inhibit the binding of HIV-1 gp120 to human CD4.[8,9] The acquired immunodeficiency syndrome (AIDS) is responsible for a decline in the number of $CD4^+$ cells in the human body, leaving the patient susceptible to infections and complications arising from the deterioration of their immune system. The HIV-1 virus has a high affinity for $CD4^+$ cells caused by binding between the HIV envelope glycoprotein, gp120, and the CD4 surface-receptor protein. Compounds such as batzelladine I (Figure 3.2), inhibit binding of gp120 to the CD4 receptor sites, thereby inhibiting the entry of HIV into the cell and thus preventing HIV replication.

3.1.2 Literature Methods Available for the Synthesis of Cyclic Guanidine Natural Products

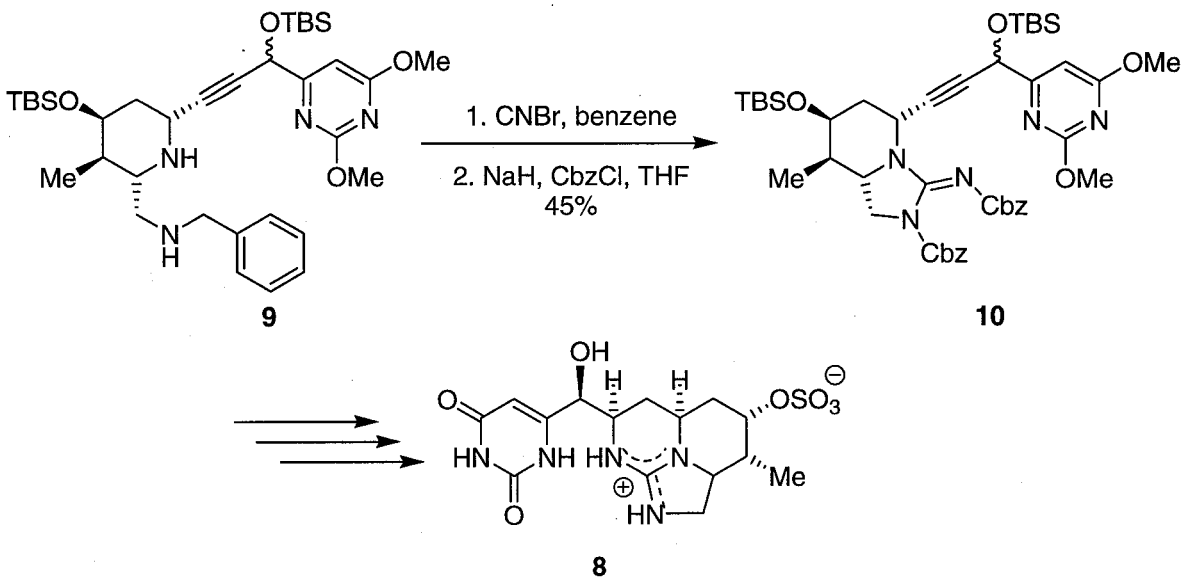
A variety of synthetic methods have been employed for the synthesis of cyclic guanidine natural products.[1-3] Only a brief overview of a handful of these methods will be discussed. The guanidine amino acid (2*S*,2*R*)-capreomycidine (**3**) was an asymmetric synthetic target of Williams and co-workers.[10] The cyclic carbamate **4** was readily synthesized and was then

subjected to the mercury-promoted guanylation procedure with bis-Boc-*S*-methylisothiourea **5**, followed by removal of the TBS protecting group with a solution of HF (1.7%) in MeCN, yielding the desired alcohol **6** (Scheme 3.2). The cyclic guanidine **7** was synthesized via the guanidinylation protocol employing the Mitsunobu reaction (Scheme 3.2), followed by removal of the protecting groups to yield (2*S*,2*R*)-capreomycidine (**3**).



Scheme 3.2

Many methods toward the synthesis of cylindrospermopsin (**8**) have been reported;[11-14] however, the total synthesis of this potent hepatotoxin was only recently achieved (Scheme 3.3).[15] Snider and co-workers synthesized the advanced diamino intermediate **9** in a series of steps, and subjected this intermediate to reaction with cyanogen bromide in order to obtain the desired five-membered guanidine ring **10** (Scheme 3.3). Snider and co-workers completed the total synthesis of cylindrospermopsin **8** with an overall yield of 3.5% over 25 steps.

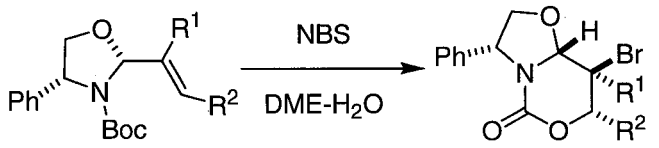


Scheme 3.3

Berlinck discusses further examples of methods used to synthesize cyclic guanidine compounds in a series of reviews.[1-3] In these reviews it is clear that many procedures have been used to synthesize cyclic guanidine compounds. However, due to the structural diversity of these compounds, new methods need to be developed to expand the number of protocols to synthesize these compounds; our research group envisioned two methods for this methodological expansion. The first method was to use iodocyclization reactions to obtain the desired guanidine compounds. The second method was to utilize transition metal-catalyzed allylic cyclization reactions, through the use of π-allyl chemistry, using a suitable olefin and the necessary guanidine component.

3.1.3 Cyclization Reactions Initiated by Iodine: Iodocyclization Reactions

Halocyclization reactions have been well documented in the literature[16] and usually proceed efficiently to yield a product which may be further functionalized through the installed halogen atom (usually bromine or more commonly, iodine). Couty and co-workers have treated α-alkenyl *N*-Boc oxazolidines **11** with NBS which led to the formation of the desired bicyclic product **12** via a bromocyclocarbamation reaction with the carbonyl oxygen of the carbamate acting as the nucleophile (Scheme 3.4).[17,18]

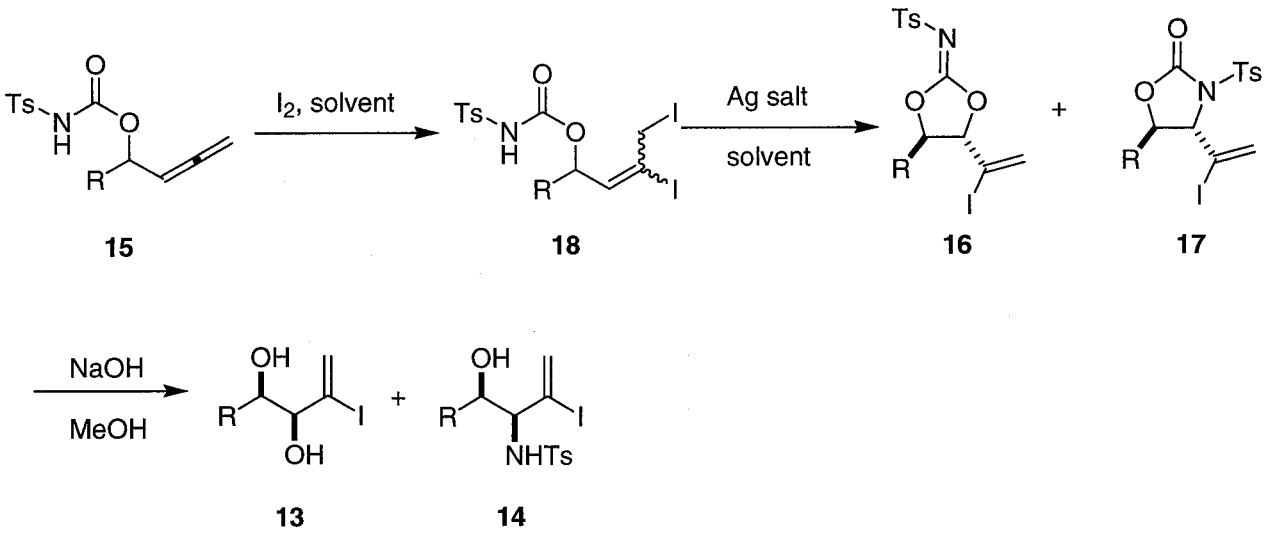


11 **12**

Scheme 3.4

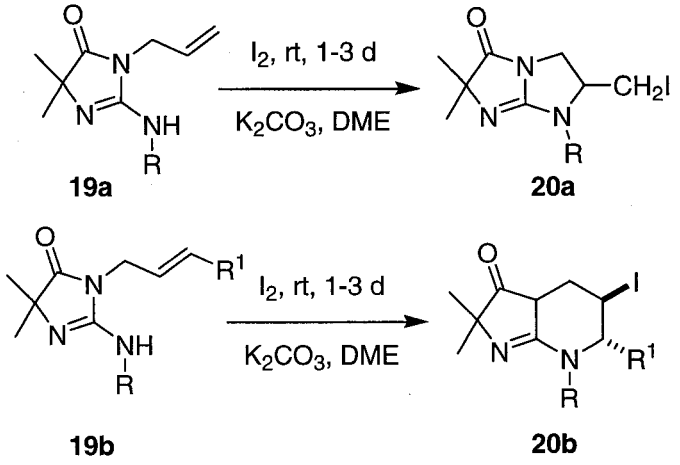
The addition of I_2 or a source of I^+ across an olefin, followed by intramolecular cyclization to yield the desired product is more commonly utilized in halocyclization reactions. An interesting protocol by Friesen and Giroux describing the preparation of *syn*-1,2-diols **13** and *syn*-1,2-amino alcohols **14** via an iodocyclization procedure has been reported (Scheme 3.5).[19] Although the synthesis of *syn*-1,2-amino alcohols via iodocyclization reactions on α-allenic alcohols has already been reported by Friesen,[20-23] as well as other research groups,[24,25] Friesen and Giroux address the regioselectivity of this cyclization and are able to produce both products **13** and **14** (Scheme 3.5). The α-allenic alcohol reagents were converted into *syn*-1,2-amino alcohols **14** by initially forming the *N*-toluenesulfonyl carbamates **15**, followed by iodocyclization with I_2 and a base to form the *trans*-oxazolidinones **16** and **17** (Scheme 3.5). This iodocyclization reaction proceeded through a mixture of the diiodide **18** products, where iodine added selectively to the terminal double bond of the allene. Basic conditions (K_2CO_3) result in the intramolecular S_N2' displacement reaction of iodine with the carbamate nitrogen, yielding the *trans*-oxazolidinone **17**. However, carbamates can act as ambident nucleophiles[26] and the regioselectivity with carbamate reactions depends on the reaction conditions employed. As an example, the intramolecular opening of epoxides with carbamate nucleophiles proceeds through nitrogen under basic conditions in an S_N2 fashion, while the carbonyl oxygen is favoured under Lewis acidic conditions in an S_N1 fashion.[27] Friesen and Giroux reasoned that treatment of the diiodide

intermediates **18** with silver salts would result in nucleophilic trapping of the cationic intermediate by the carbonyl oxygen of the carbamate. It was found that the use of Ag_2CO_3 as the silver source gave excellent regioselectivities (~50:1 of **14**:**13**) in a 50:1 mixture of ether:acetonitrile. Minor differences in the reaction conditions, such as the solvent polarity, play a key role on the S_N2' versus S_N1 regioselective cyclization reactions.



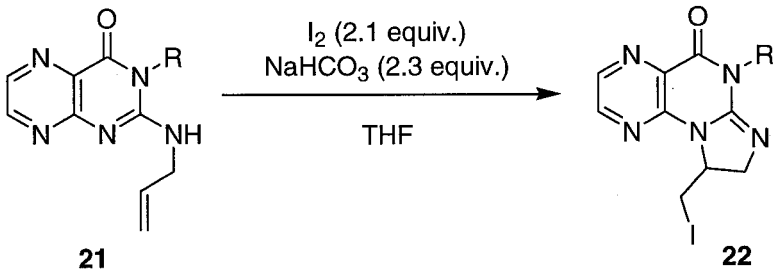
Scheme 3.5

Guanidines, although not utilized as much as carbamates, have been the subject of reported iodocyclization procedures to yield bicyclic guanidine-containing compounds. Noguchi and co-workers have treated imidazolinones **19a** with iodine (2.0 equiv.) in DME at room temperature to give the desired bicyclic guanidines **20a** in good to excellent yield (Scheme 3.6).[28] The 6-*endo* product **20b** could also be achieved as one single diastereomer by altering the substitution pattern on the olefin. The reaction of 3-(*trans*-cinnamyl) and 3-(*trans*-but-2-enyl) **19b** substrates with iodine at room temperature gave the corresponding 6-*endo* bicyclic guanidine (Scheme 3.6). Noguchi and co-workers have used alkynyl substituents instead of olefins for these iodocyclization reactions, producing bicyclic guanidines in good yields.[29]



Scheme 3.6

A report by Eguichi and co-workers also showed that tricyclic guanidines could be formed through iodocyclization reactions.[30] In this report, 2-allylaminopteridin-4-(3*H*)-one derivatives **21** were treated with iodine to yield the desired bicyclic guanidine compound **22** (Scheme 3.7)

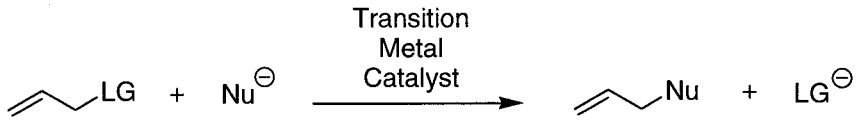


Scheme 3.7

As mentioned earlier, two methods for expanding the reported procedures to synthesize cyclic guanidines were proposed by our group. This first method was the use of iodocyclization reactions with the appropriate substrates. The second method is the use of π-allyl palladium catalyzed cyclization reactions, which is discussed in the following section.

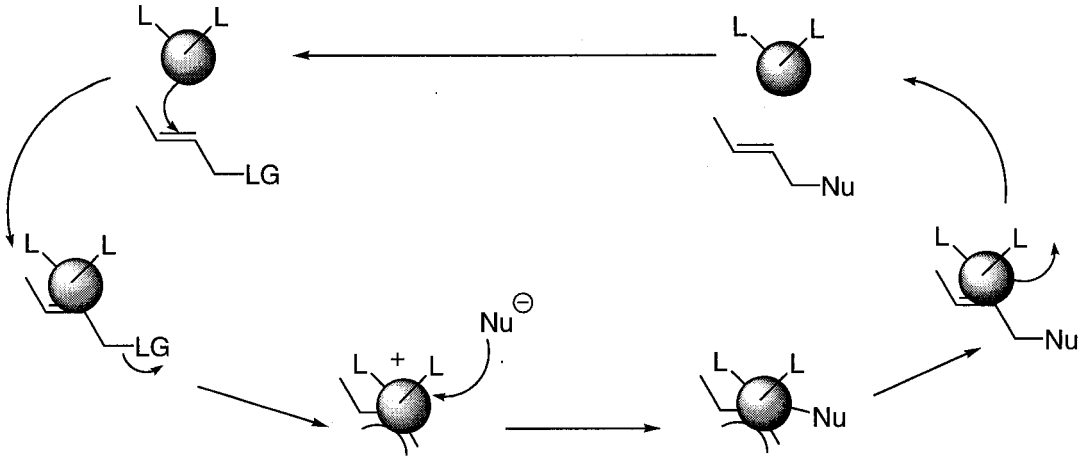
3.1.4 Transition-Metal Catalyzed Allylic Cyclization Reactions

Transition-metal catalyzed allylic alkylation reactions have received a great deal of attention in the literature and the synthetic usefulness of these reactions has been clearly demonstrated since their introduction nearly three decades ago.[31-39] Addition of a nucleophile to an allylic substrate (Scheme 3.8), resulting in displacement of a leaving group from the allyl moiety, has been utilized by numerous research groups.[40] In addition, these reactions have been performed with a wide range of transition-metal complexes, including nickel, palladium, platinum, rhodium, iron, ruthenium, molybdenum, and tungsten.[40]

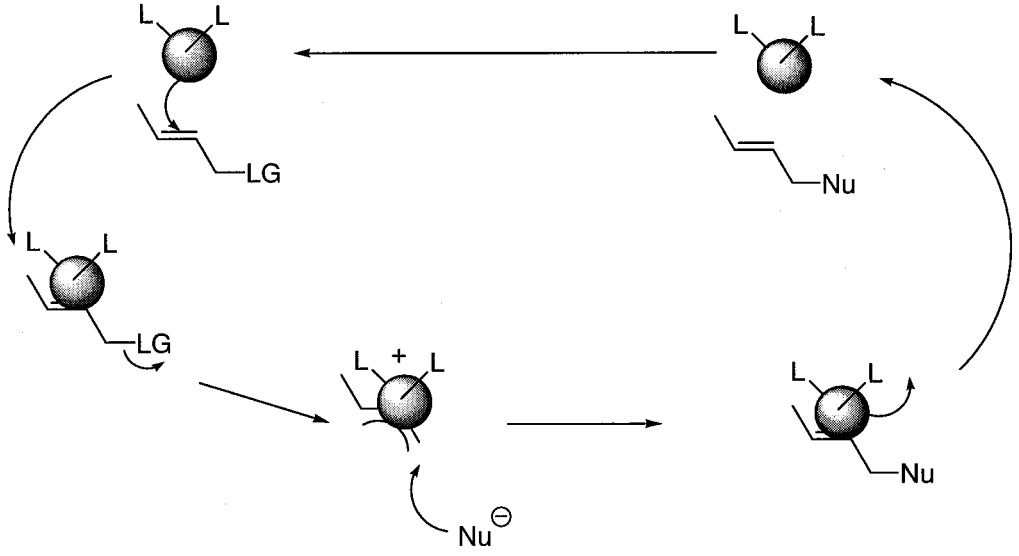


Scheme 3.8

Nucleophilic addition to an allylic substrate (Scheme 3.8) is governed by two general classes of reactions depending on the nature of the nucleophile.[40,41] The first class is observed with 'hard' nucleophiles. When the nucleophile is 'hard', as defined as those derived from conjugate acids whose $pK_a > 25$, the reaction typically proceeds by attachment of the nucleophile to the metal followed by reductive elimination (Scheme 3.9). The second class is observed with 'soft' nucleophiles. When the nucleophile is 'soft', as defined as those that are derived from conjugate acids whose $pK_a < 25$, the reaction proceeds via a different pathway (Scheme 3.10). With this pathway, the bond breaking and making events occur on the face of the π-allyl unit opposite to the transition metal. In other words, these events occur outside of the coordination sphere of the metal; therefore, the leaving group and nucleophile undergo reaction on the π-allyl face opposite to the chiral environment of the ligand. This implies that the chiral ligands must influence the stereochemical outcome of these reactions by transferring their chiral information to the opposite plane of the π-allyl fragment, thus influencing the event that is responsible for controlling the enantioselectivity of the reaction.[40,41]



Scheme 3.9 **Allylic Alkylations with Hard Nucleophiles**



Scheme 3.10 **Allylic Alkylations with Soft Nucleophiles**

3.1.4.1 Enantioselective π-Allyl Reactions Catalyzed by Palladium

Since the first example of an enantioselective palladium-catalyzed allylic substitution reaction by Trost and co-workers,[31] a number of advances have been made. One of the main advances in this area has been the development of reactions where high enantioselectivities may be obtained with a wide range of substrates. More importantly, the enantioselective outcomes of these reactions have been understood as well as predicted. As mentioned earlier, it has been hypothesized that one of the possible reasons for the slow development of these reactions has been that the chiral ligands must reach across the plane of the allyl fragment and transfer their chirality to the event responsible for the enantioselective outcome of the reaction.[40] Adding to the difficulty with these reactions are the five potential sources of enantiodiscrimination in the transition-metal catalyzed allylic alkylations, as outlined by Trost and co-workers.[40] The five potential sources are (a) metal-olefin complexation to enantiotopic faces of the olefin, (b) ionization of enantiotopic leaving groups, (c) enantioface discrimination of the π-allyl complex, (d) nucleophilic attack at the enantiotopic termini of the allyl fragment, and (e) nucleophiles possessing enantiotopic faces (Figure 3.3).

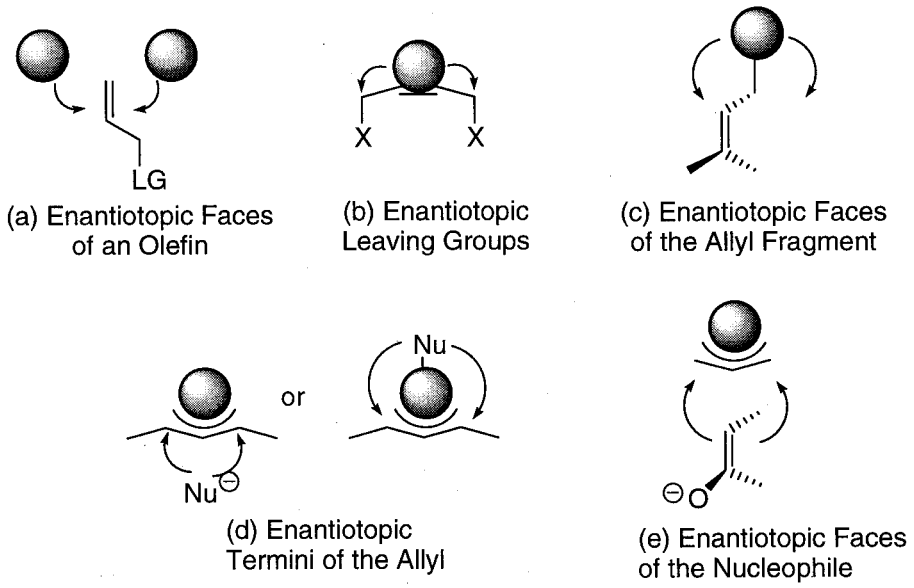
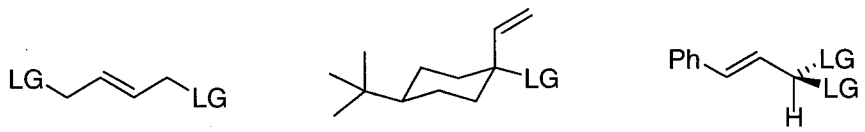


Figure 3.3 Sources of Enantiodiscrimination in Transition-Metal Catalyzed Allylic Alkylations

As shown in Figure 3.3 (a), the complexation of a transition metal to the olefin represents a possible source of stereoselection as the incoming transition metal is forced to choose between enantiotopic faces of the olefin. There is no evidence, however, for selective complexation of a transition metal to the olefin as a source of enantioselection, in terms of allylation reactions. Instead, complexation and subsequent ionization of the corresponding leaving group must be considered simultaneously. As an example, complexation and ionization of **23** - **25** (Figure 3.4) from different faces of the olefin will yield enantiotopic allylic complexes.

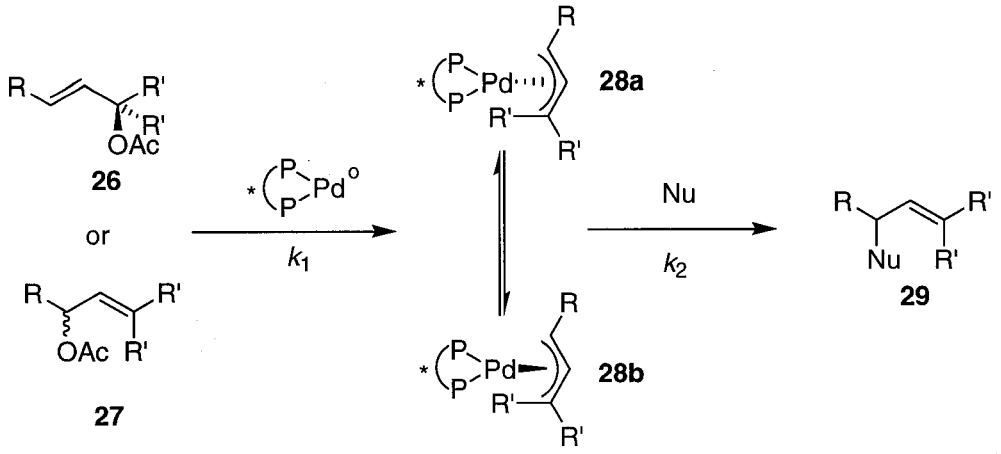


23 **24** **25**

Figure 3.4 Enantiotopic Allylic Complexes Formed From Enantiofacial Ionization

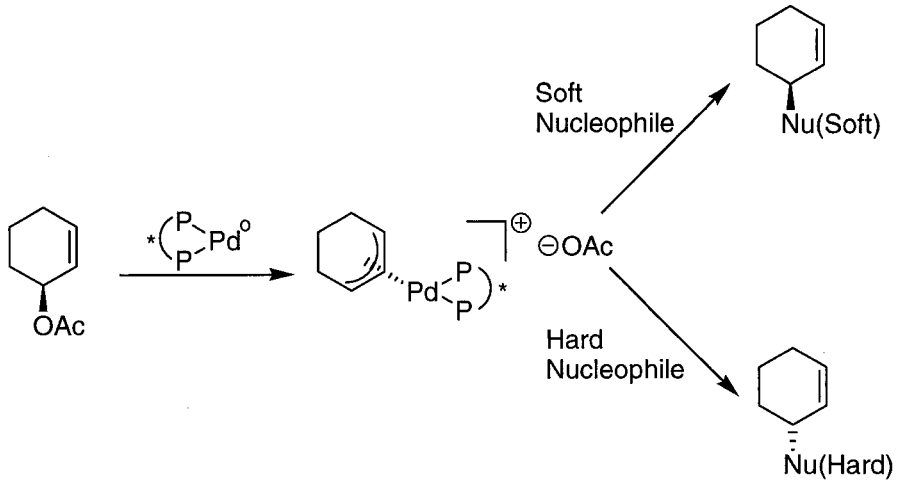
Another important potential source of a stereoselection is illustrated in Figure 3.3 (d). In this case, the nucleophile can attack the η^3-allyl moiety at either end of the enantiotopic allylic termini, resulting in enantiomeric products.

Bosnich and co-workers[42,43] have demonstrated that η^3-allyl intermediates can be formed from chiral allylic acetates **26** as well as from racemic allylic acetates **27** (Scheme 3.11). The major steps in the catalytic allyation reaction are shown below (Scheme 3.11). Bosnich and co-workers have subjected the racemic **27** and chiral allylic acetates **26** to allylation reactions with Pd(*S*,*S*-chiraphos) as the catalyst and sodium dimethyl malonate as the nucleophile. In subsequent experiments (where R and R' = Ph), it was shown that $k_1 >> k_2$; therefore, the oxidative addition step is fast compared to the reaction of the nucleophile with the Pd^{II}-allyl intermediate. In addition, it was shown that Curtin-Hammett conditions were occurring (when R' = aryl). Thus, epimerisation of the η^3-allyl complexes is faster than nucleophilic attack on these Pd^{II} intermediates, making either allylic acetate materials suitable reagents for allylation reactions. If Curtin-Hammett conditions are operating in a reaction, then enantiofacial oxidative addition of Pd° to the allylic starting reagents is irrelevant in determining the enantioselectivity of the allylation reaction. Instead, the enantioselectivity would be determined by preferential reaction of the nucleophile with the two diastereomeric η^3-allyl intermediates **28a** and **28b** (Scheme 3.11).



Scheme 3.11

The ionization of allylic substrates with Pd° normally occurs with inversion of configuration. In other words, the Pd° source adds the allylic substrate from the opposite face of the leaving group (Scheme 3.12). Important differences in the stereochemical outcome of allylation reactions are obtained depending on the nature of the nucleophile (Scheme 3.9 and Scheme 3.10). Soft nucleophiles will attack the allylic substrate from the same face in which the leaving group departed, leading to overall retention of configuration via double inversion (Scheme 3.12). This double inversion mechanism is applicable only to soft (or stabilized) nucleophiles (Scheme 3.10) and examples of these nucleophiles include malonic esters, β-diketones, thiols, amines, amides, carboxylates, and alkoxides. However, a different stereochemical outcome is achieved when hard nucleophiles attack the π-allyl Pd^{II} intermediate. Hard (or unstabilized) nucleophiles (Scheme 3.9), which include Grignard reagents, alkylzinc halides, and hydroborates, first attack the metal and are then transferred to the allyl moiety. The initial ionization step of the allylic substrate occurs with inversion of stereochemistry to give the π-allyl Pd^{II} intermediate, the hard nucleophile then attacks the Pd^{II} intermediate, followed by transfer of the hard nucleophile to the allylic moiety via reductive elimination to yield the allylic substrate with overall inversion of stereochemistry. Therefore, soft nucleophiles lead to allylic substrates with retention of configuration via double inversion, while hard nucleophiles lead to overall inversion of configuration (Scheme 3.12).

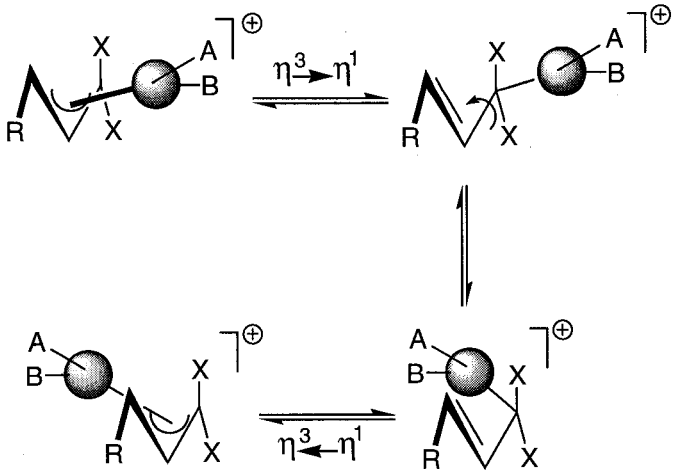


Scheme 3.12

3.1.4.2 Enantiofacial Exchange in the η^3-Allyl Complex

As mentioned earlier, if the η^3-allyl complex is not symmetrical (1,3-disubstituted), enantioselectivity will be governed by the facial selectivity of nucleophilic attack on the π-allyl Pd^{II} complex. The metal is capable of switching between faces of the π-allyl complex via a η^3-η^1-η^3 rearrangement process (Scheme 3.13). Therefore, selective ionization from one enantioface of the allylic substrate may either be detrimental or beneficial to the enantioselective outcome of the allylation reaction. The equilibration of the π-allyl Pd^{II} complexes can be beneficial to the enantioselective outcome of the reaction if nucleophilic attack occurs preferentially on one of the complexes. However, if nucleophilic attack can occur on either of the diastereomeric complexes, then equilibration would be detrimental to the enantioselectivity of the allylation reaction.

There are two important mechanisms for this facial rearrangement process. Compounds possessing identical substrates on at least one of the allylic termini (after ionization) are capable of undergoing facial rearrangement via a η^3-η^1-η^3 mechanism (Scheme 3.13). This mechanism involves a change in hapticity, from an η^3 to an η^1 complex, followed by rotation about the carbon-carbon bond. This mechanism may be detrimental to the enantioselectivity of an allylic reaction by leading to a loss in the stereochemical information achieved in the selective ionization of the olefin moiety.



Scheme 3.13

Figure 3.5 shows some of the substrates that can undergo this η^3-η^1-η^3 exchange mechanism. It is important to note that if this equilibration process is rapid compared to nucleophilic attack, then enantioselectivity for a reaction may be achieved from racemic starting materials, as was shown by Bosnich and co-workers (Scheme 3.11).

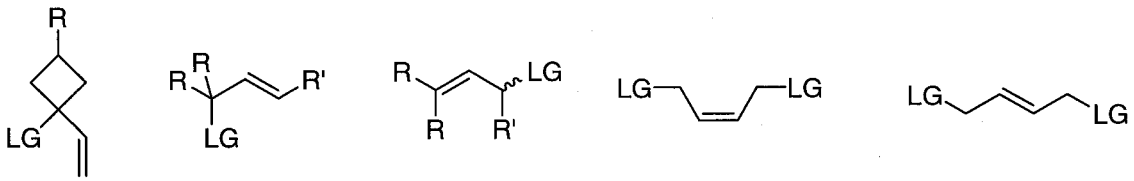


Figure 3.5 Substrates Capable of Racemization Via the η^3-η^1-η^3 Mechanism.

With cyclic substrates or unsymmetrically substituted allyl substrates (Figure 3.6), enantioface exchange of the metal can proceed via a different mechanism than the η^3-η^1-η^3 isomerization process.

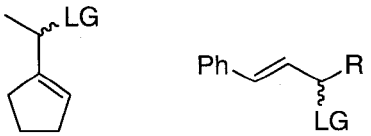
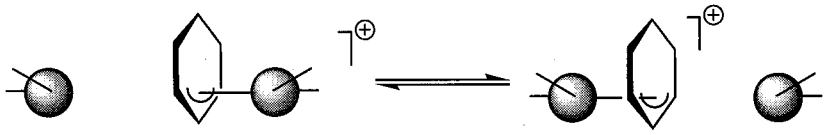


Figure 3.6 Substrates that Racemize Via Enantiofacial Exchange.

The precise mechanism for this process is unclear; however, the following observations have been noted. Isomerization is inhibited by (1) a reactive allylic substrate, (2) a low Pd° concentration, (3) bidentate ligands, and (4) halide ions.[40] In stoichiometric systems, it has been

shown that the rate of diastereofacial exchange in the cationic π-allyl Pd^{II} complexes is dependent on the concentration of Pd°, leading to a mechanism that is dependent on the presence of Pd° (Scheme 3.14).



Scheme 3.14

Substituents present on the π-allyl moiety are assigned as either *syn* or *anti* based on their relative position to the substituent at the C2 position (Figure 3.7). During the course of the allylation reaction, *syn:anti* exchange occurs more rapidly than nucleophilic attack on the π-allyl Pd^{II} complex.

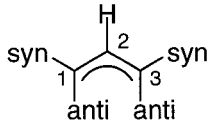
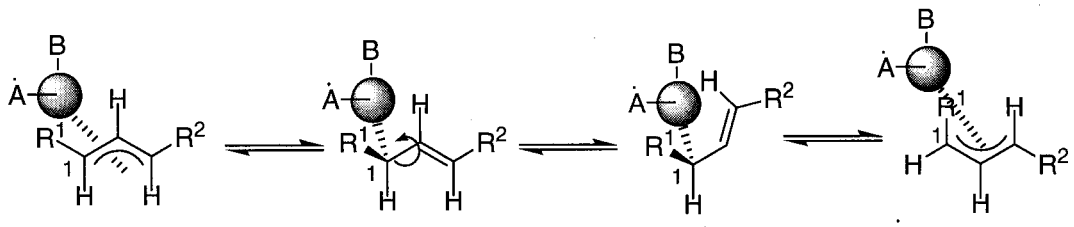


Figure 3.7 Syn and Anti Substituents for Allylic Compounds

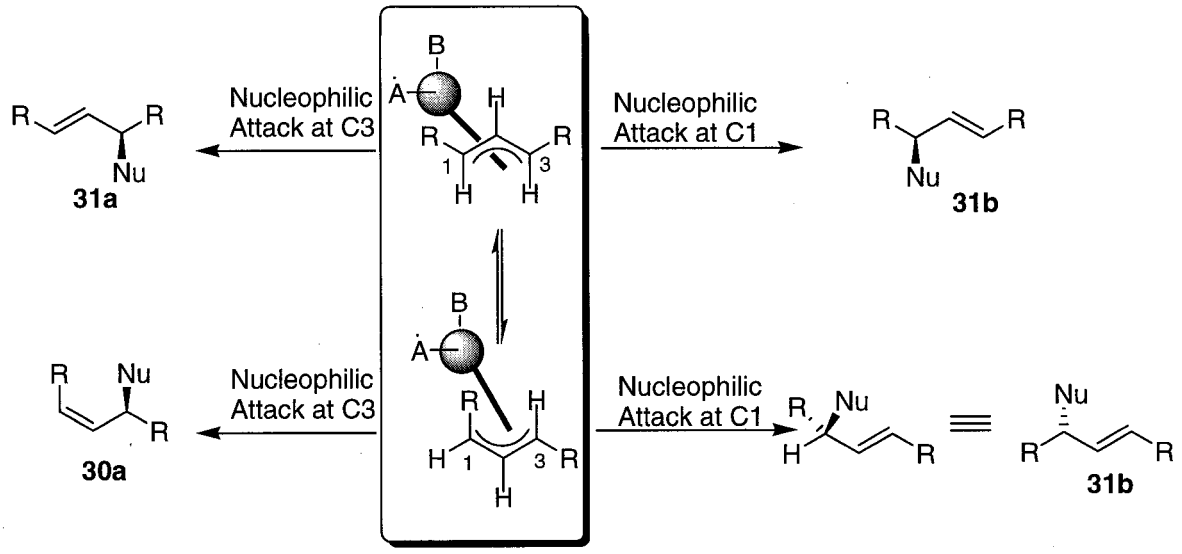
As shown in Scheme 3.13 (η^3-η^1-η^3 exchange scheme), *syn:anti* exchange occurs when identical substitutents are present at one end of the allylic termini. However, *syn:anti* exchange also occurs when the substituents at the *syn* and *anti* positions are different. In both of these cases, the allylic carbons do *not* switch positions. That is, the C1 is *trans* to ligand B and remains *trans* to ligand B after *syn:anti* exchange has occurred.[40] Additionally, the C2 carbon was originally pointing upwards, however, it points downwards after *syn:anti* exchange has occurred (Scheme 3.15). In other words, the palladium has migrated from one face of the π-allyl moiety to the other face. The difference between Scheme 3.13 and Scheme 3.15 occurs in the unsymmetrical case where substituent R^1 at C1 (*trans* to ligand B) changes from a *syn* to *anti* orientation (Scheme 3.15).



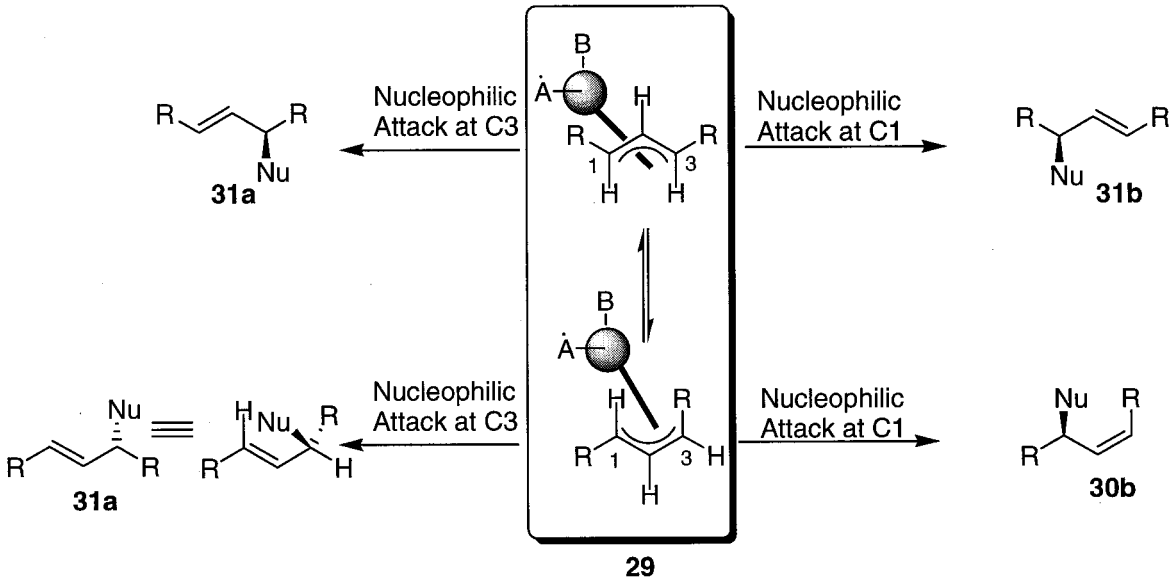
Scheme 3.15

When substituents in the *syn* and *anti* positions are different, interesting stereochemical consequences arise. As an example, with the allyl moiety **29**, when both R groups are identical, the enantioselectivity obtained from these symmetrical π-allyl substrates is not governed by the facial selectivity of nucleophilic attack. However, *syn:anti* isomerization will lead to different diastereomeric products (Scheme 3.16). Shown below are all the possible products resulting from such *syn:anti* isomerization processes. The top half of this scheme shows the products formed by the formation of a σ-Pd bond with the C1 carbon. Rotation about the C1-C2 carbon gives the *syn:anti* isomerized product. Interestingly, the *cis*-olefin products can be obtained from this isomerization process as shown by the formation of **30a** and **30b** (Scheme 3.16).

Products Resulting From *Syn:Anti* Isomerisation Via a σ-Pd Bond at C1



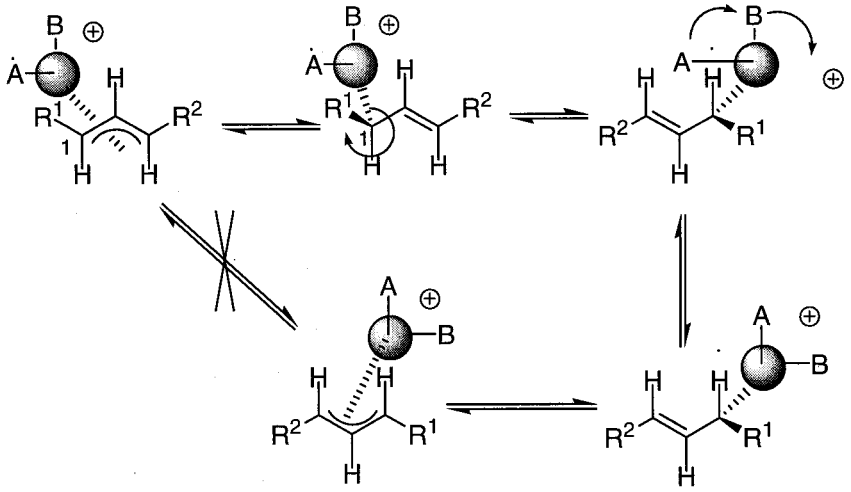
Products Resulting From *Syn:Anti* Isomerisation Via a σ-Pd Bond at C3



Scheme 3.16

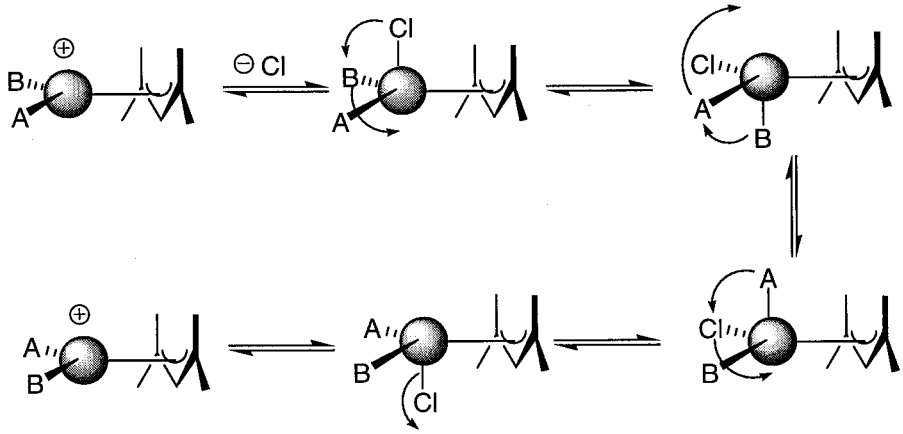
Another isomerization process is possible with π-allyl complexes resulting in apparent allyl rotation. There have been no reported accounts or evidence supporting the simplest mechanism, which has the allyl moiety simply rotating about palladium-allyl axis to yield the isomeric product. The mechanism most likely follows a process in which the allyl hapticity changes from η^3 to η^1, followed by rotation about the carbon-palladium bond. During this

process, the square-planar geometry of the complex must change to open up a coordination site *trans* to ligand B and the complex then reforms the η^3-allyl complex (Scheme 3.17).[40]



Scheme 3.17

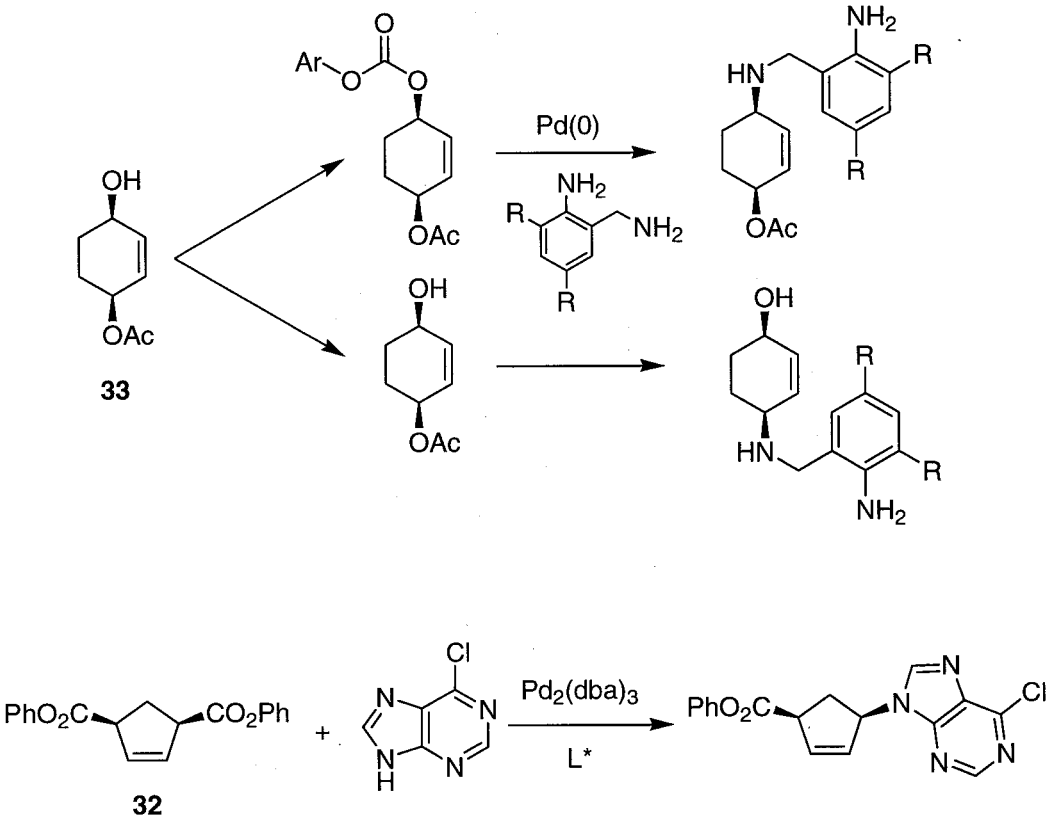
Isomerization that occurs via apparent allyl exchange has been examined extensively and many research groups have found that addition of catalytic amounts of chloride ions greatly accelerates this isomerization process.[44-46] Therefore, the use of (π-allyl)palladium chloride dimer as the catalyst source may not be used interchangeably with halide-free catalysts, such as $Pd_2(dba)_3 \cdot CHCl_3$. Since chloride ions present in a catalytic amount increase the rate of apparent allyl exchange, these ions must be accounted for in the mechanistic pathway. Such a mechanism was proposed by Åkermark and Vitagliano,[47] where a pseudorotation mechanism accounts for the acceleration of the apparent allyl rotation process (Scheme 3.18).



Scheme 3.18

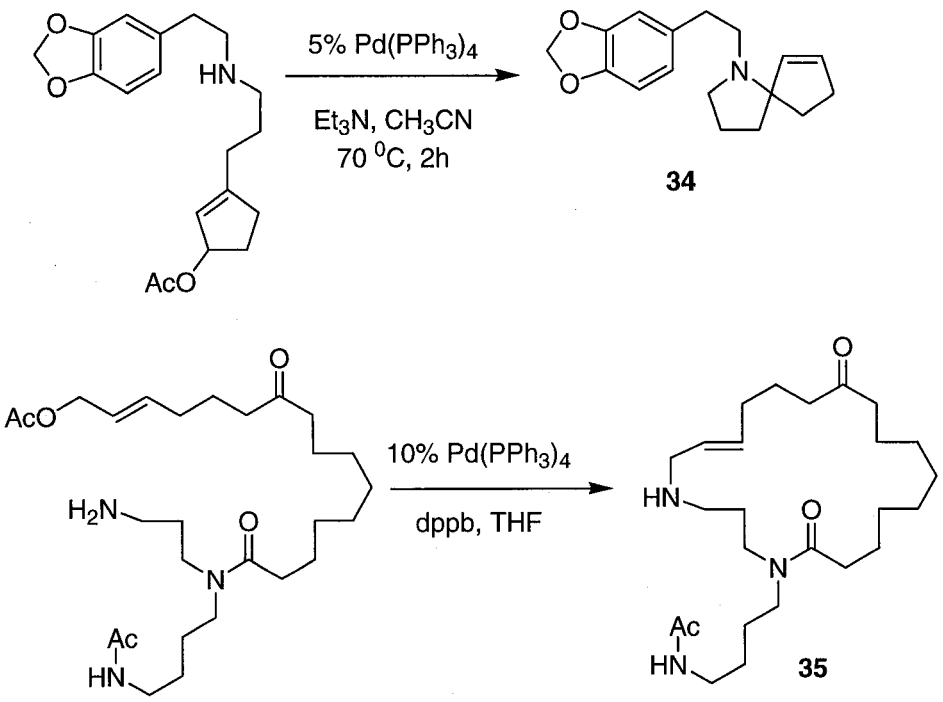
3.1.4.3 Pioneering Aminopalladation Reactions

Asymmetric induction in the Pd-catalyzed allylic amination procedure is efficient and is tolerated by a variety of functional groups. Because of the difference in reactivity of various allylic functional groups (Cl > OCO_2R > OAc >> OH),[48] diols can be aminated at either allylic position (Scheme 3.19).[49] In addition, Pd-catalyzed allylic amination procedures have been extensively used for the desymmetrisation of meso-allylic substrates **32**,[50] as well as highly functionalized cyclohexenes **33** (Scheme 3.19).[51,52]



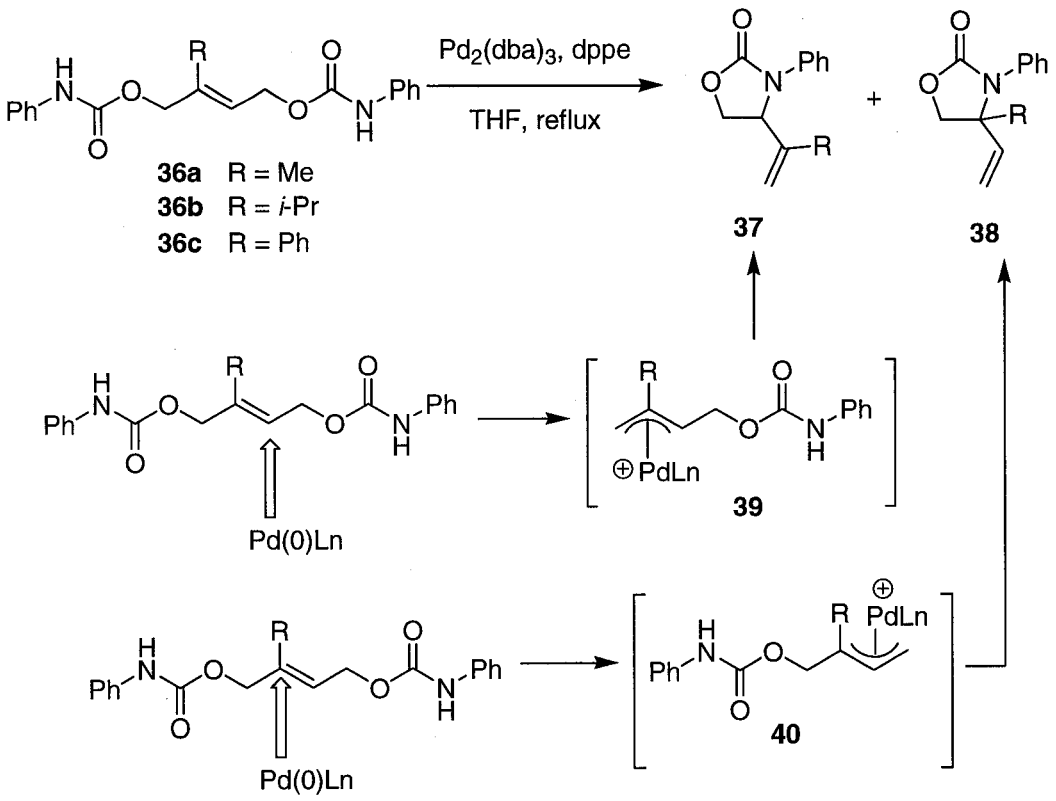
Scheme 3.19

Intramolecular amination reactions are also effective and have been used to give a wide range of spiro **34** as well as macrocylcic systems **35** (Scheme 3.20).[53,54] Palladium-catalyzed allylic aminations are well-established procedures and have been the subjects of many reports.[55]



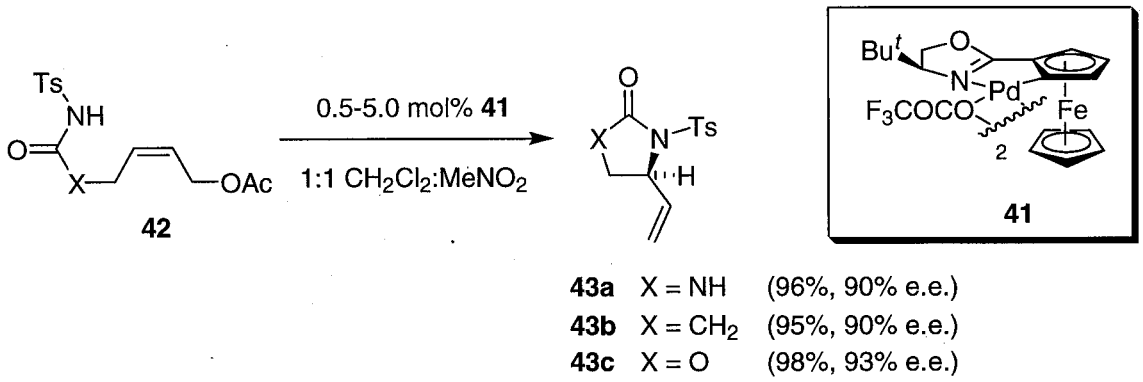
Scheme 3.20

Hayashi and Ito have shown that carbamates are effective nucleophiles, as well as leaving groups, for palladium-catalyzed cyclization reactions to yield 4-vinyl-2-oxazolidones **36** (Scheme 3.21).[56] A variety of dicarbamates were synthesized and subjected to cyclization procedures. The methyl **36a**, isopropyl **36b**, and phenyl **36c** derivatives were synthesized to examine the regioselectivity of the cyclization procedure (Scheme 3.21). It was found that oxazolidone **37**, which has the substituent on the vinyl group, was formed preferentially over the regioisomer **38** with the ratio of **37**:**38** being 89:11, 96:4, and 99:1. The major isomer **37** would be obtained from the formation of the π-allyl intermediate **39**, which led the authors to speculate that oxidative addition of the dicarbamates to palladium(0) occurs by an S_N2'-type attack of palladium(0) on the least hindered carbon of the olefin.



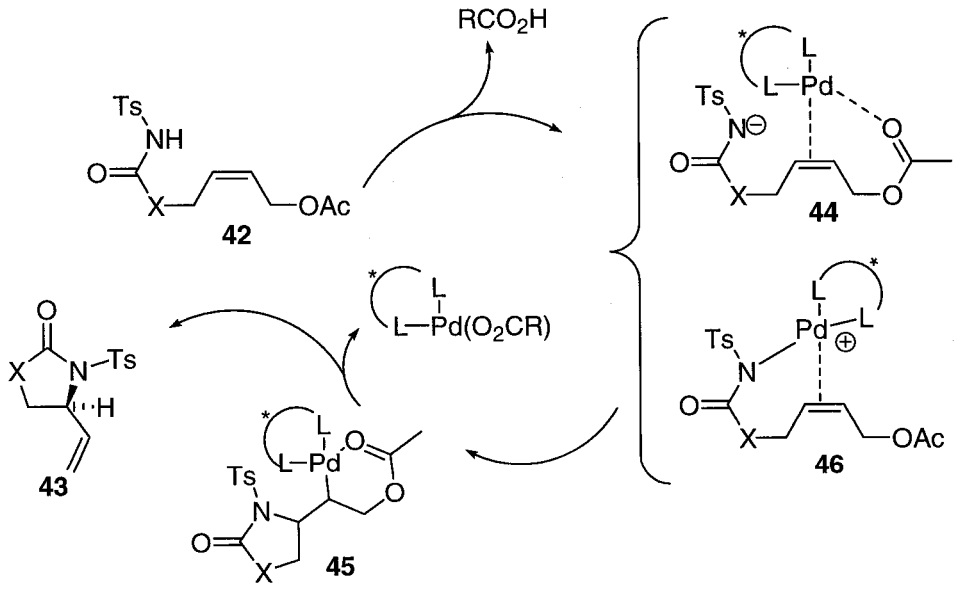
Scheme 3.21

Overman and co-workers have published a report on the catalytic asymmetric intramolecular aminopalladation of amides, carbamates, and ureas.[57] These intramolecular cyclizations were catalyzed by a Pd(II) source, ferrocenyloxazoline palladacycles (FOP catalysts) **41** (Scheme 3.22), to afford the asymmetric five-membered nitrogen heterocylces. The Pd(II)-catalyzed cyclization reactions were found to give the highest yield and enantioselectivity with the *N*-tosylcarbamate acetate **42** in a polar solvent comprised of a 1:1 mixture of CH_2Cl_2:$MeNO_2$ (> 95% yield, 91-93% e.e.) (Scheme 3.22).



Scheme 3.22

One drawback to this protocol was the lack of substrates that could be utilized. Overman and co-workers noted that a highly acidic nitrogen nucleophile was necessary for the conversion of **42** to **43**. Also, the *Z* configuration of the starting allylic *N*-arylsulfonylcarbamate **42** was required, since the *E* stereoisomer gave the desired product **43** at a very slow rate. Two general reaction mechanisms were proposed (Scheme 3.23). In the first mechanism, the C–N bond is formed through aminopalladation of the alkene resulting in the conversion of **44** to **45**. In the second mechanistic pathway, the alkene would insert into the Pd–N bond of **46** yielding **45** (Scheme 3.23).



Scheme 3.23

3.2 Results and Discussion

3.2.1 Introduction

At the outset of this research program, the goal was to develop new methodological approaches towards the synthesis of cyclic guanidines in the hope of applying this new protocol to the synthesis of guanidine natural products, such as anatoxin-a(s) **1** (Figure 3.8). There have been many general routes applied to the synthesis of cyclic guanidine natural products[1-3]; however, due to the structural diversity of these compounds new methods that could be applied towards their synthesis would be advantageous. Two methods for this methodological expansion were envisioned. The first method involved the use of iodocyclization reactions to obtain the desired guanidine compounds. The second method involved the application of the well-established transition metal catalyzed allylic cyclization reactions through the use of π-allyl chemistry. Although the use of π-allyl chemistry has not been utilized with guanidine nucleophiles, it was hoped that difficulties encountered could be overcome to lead to a new approach to the formation of cyclic guanidine compounds.

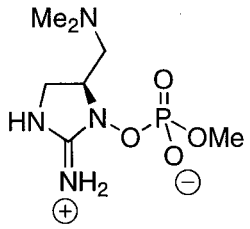
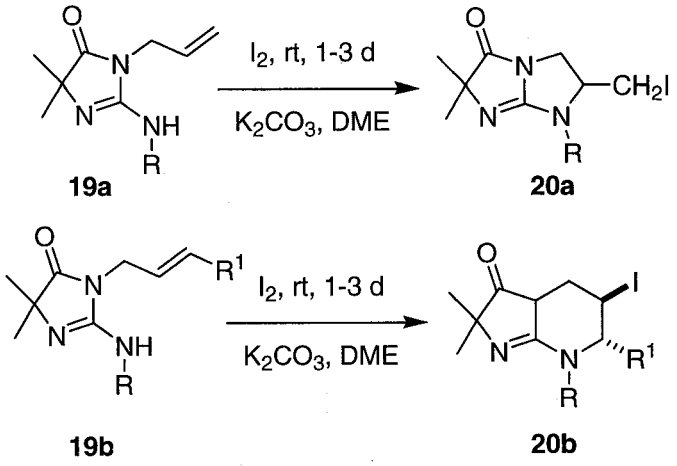


Figure 3.8 Structure of Anatoxin-a(s) (1)

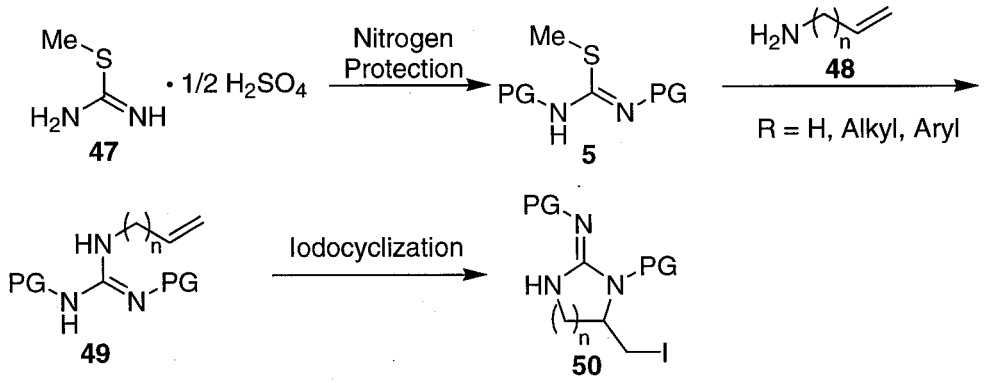
3.2.2 Cyclization Reactions Initiated by Iodine: Iodocyclization Reactions

Noguchi and co-workers have reported intramolecular cyclization reactions with imidazolinones **19a** and **19b** in the presence of iodine to give either the 5-*exo* **20a** or 6-*endo* **20b** product, depending on the substrate that was utilized (Scheme 3.24).[29]



Scheme 3.24

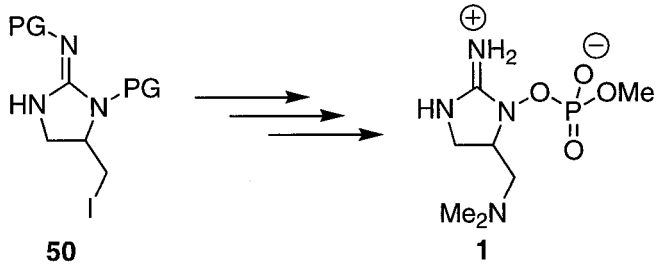
Given Noguchi's success with the synthesis of bicyclic guanidine compounds, it was hoped that a general procedure toward the synthesis of cyclic guanidine compounds could be developed, which would be initiated by iodine. The general strategy initially employed the use of the readily available guanidine precursor, *S*-methylisothiourea **47**, and was comprised of a 3 step sequence involving (1) protection of the *S*-methylisothiourea **47**, (2) conversion to the guanidine through a guanylation procedure with a suitable amine **48**, and (3) cyclization of the guanidine precursor **49** through an iodocyclization procedure (Scheme 3.25).



Scheme 3.25

This approach is advantageous since the obtained cyclic guanidine products **50** contain an iodine functionality, which can be used as a handle for further functionalization. It was anticipated that the olefin guanidine compounds **49** could be easily obtained and that iodocyclization procedures utilized by Noguchi and co-workers could be applied to this general

protocol.[29] It was hoped this protocol would lead to an efficient synthetic route to the synthesis of (±)-anatoxin-a(s) **1** (Scheme 3.26).



50 **1**

Scheme 3.26

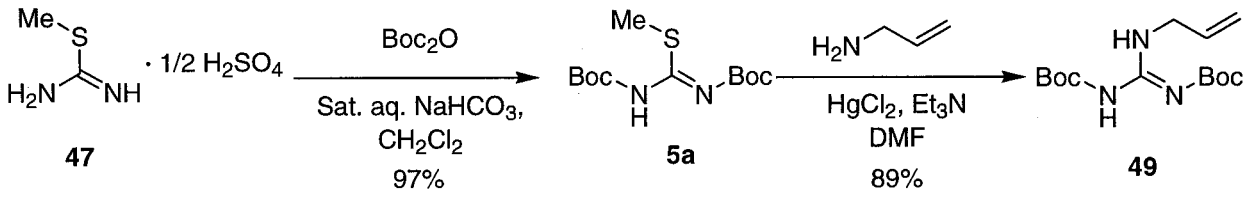
During the course of this research program, two general routes towards the synthesis of cyclic guanidine products using iodocyclization reactions were employed. These methods differ in the routes that were used to synthesize the iodocyclization precursors and are divided into two categories: cyclization precursors derived from guanylation of amino-alkene reagents and cyclization precursors derived from the Mitsunobu protocol. Both of these protocols will be discussed separately in the following sections.

3.2.2.1 Iodocyclization Reactions: Cyclization Precursors Derived from Guanylation of Amino-alkene Reagents

3.2.2.1.1 Preparation of Cyclization Precursors

The substrates employed in this iodocyclization procedure were readily synthesized from the *S*-methylisothiourea precursor **47** by first protecting the nitrogen functionalities as the Boc-carbamates **5a** (Scheme 3.27). Due to the high polarity and basicity, and corresponding water solubility, guanidine compounds are challenging functional groups often requiring non-standard techniques for their isolation and purification. Protection of one or more of the nitrogen functional groups as the carbamate or other electron-withdrawing substituents decreases the basicity of these compounds. Additionally, protection of the nitrogen functional groups as the carbamates, Boc for example, decreases the polarity of these molecules allowing for them to be purified using standard techniques, such as flash chromatography or crystallization, and also decreases the water solubility of the guanidine product. The olefin necessary for the iodocyclization reactions was installed by guanylation of allylamine to yield the desired

guanidine **49** (Scheme 3.27). Guanylation of allylamine was easily performed using the mercuric chloride promoted procedure, originally developed by Kim and co-workers.[58]

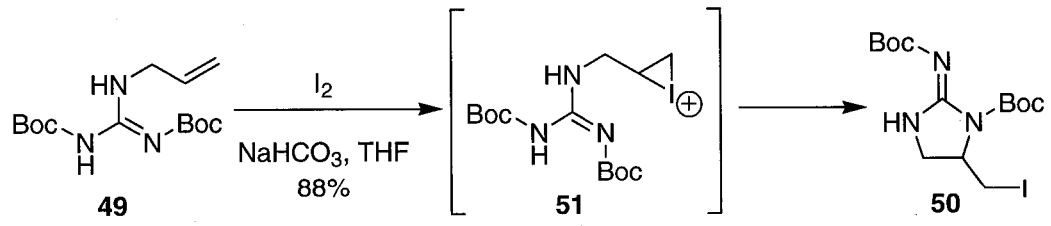


Scheme 3.27

3.2.2.1.2 Iodocyclization Reactions Using the Allylamine-Derived Guanidine

Having synthesized the required allylamine-derived guanidine **49** in excellent yields, this product was subjected to an iodocyclization procedure based on conditions similar to those employed by Noguchi and co-workers.[29] It was hoped that iodocyclization would occur through the iodonium ion complex **51**, giving rise the desired 5-*exo* product **50** (Scheme 3.28). Noguchi and co-workers have noted the 5-*exo* product is favoured over the 6-*endo* product when terminal olefins are utilized; therefore it was thought the same result could be obtained using the allylamine-derived guanidine **49**.[29]

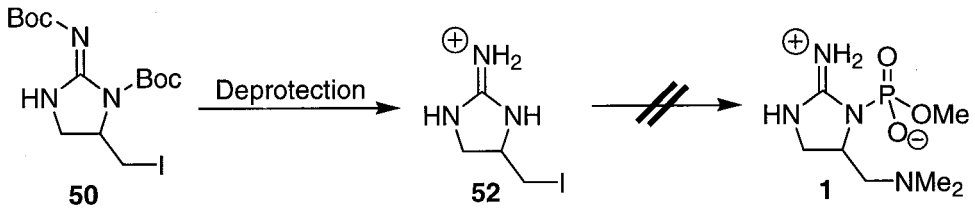
Allylamine-derived guanidine **49** was stirred with $NaHCO_3$ (2.2 equiv.) and iodine (2.0 equiv.) to yield the desired cyclic guanidine compound **50** in good yield (Scheme 3.28). The results from these initial experiments were encouraging and it was thought a general route towards the synthesis of cyclic guanidine compounds, such as anatoxin-a(s) **1** would be possible using this methodology.



Scheme 3.28

3.2.2.1.3 Analysis of the Iodocyclization Method Using Allylamine-Derived Guanidine

Although use of allylamine-derived guanidine **49** offered an expedient route to the synthesis of the 5-*exo* guanidine product **50**, there were significant disadvantages to this method making it a fairly undesirable general approach to cyclic guanidine products. This method, although it allows for further functionalization of the product through S_N2 displacement of the iodine functionality by a variety of nucleophiles, offers limited possibilities for further derivitization of the guanidine component. It is difficult to further functionalize unprotected nitrogens present in guanidine compounds making guanidine **50** difficult to derivatize through the available nitrogen. Deprotection of the guanidine by removal of the Boc groups would provide the free guanidine **52** which would be difficult to derivatize regioselectively (Scheme 3.29). For example, if this method were to be applied to the synthesis of (±)-anatoxin-a(s) **1** it would be extremely difficult to install the necessary phosphate ester regioselectively (Scheme 3.29).



Scheme 3.29

As a result of these complications and the lack of generality with this method based on allylamine-derived guanidine **49**, it was decided to abandon this route. A more general route toward the synthesis of cyclic guanidine products was developed.

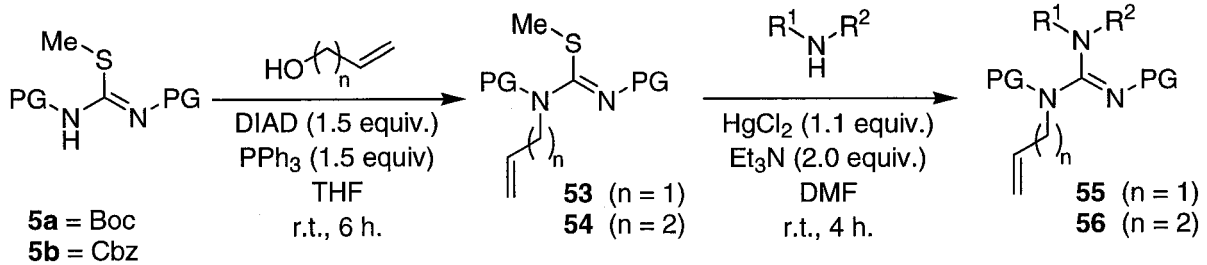
3.2.2.2 Iodocyclization Reactions: Cyclization Precursors Derived from the Mitsunobu Protocol

3.2.2.2.1 Preparation of Cyclization Precursors

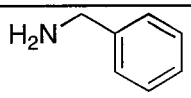
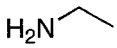
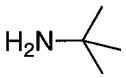
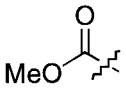
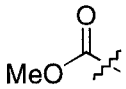
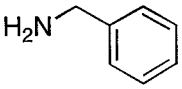
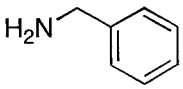
Based on the lack of generality with the allylamine-derived guanidine route, a more universal route was envisaged. One disadvantage with the previous route was with the use of allylamine. In this method, the olefin and the amine are installed through the guanylation procedure; however, this guanylation method is not very flexible since both of these components are installed simultaneously. A route where installation of the necessary olefin and guanylation of an amine occur in separate events would provide more diversity in the number of substrates that could be synthesized. By keeping these events separate, a variety of guanidines could be synthesized through guanylation of the desired amine. The synthetic strategy foreseen for such a procedure could be based on installation of the olefin from the corresponding alcohol-olefin reagent using the Mitsunobu reaction.

In a similar fashion to the preceding method, the bis-Boc-protected *S*-methylisothiourea **5a** was first synthesized. Additionally, the bis-Cbz and bis-methyl carbamate protected *S*-methylisothiourea compounds (**5b** and **5c**) were synthesised using modified procedures and were obtained in 95% and 52% yield, respectively. Installation of the olefin was accomplished by using the Mitsunobu protocol yielding the desired allylic- or 3-butene-derived *S*-methylisothiourea compounds **53** and **54**. Having installed the necessary olefin groups onto the *S*-methylisothiourea compounds, guanylation of a variety of amines was then performed using the mercuric chloride promoted method, originally developed by Kim and co-workers, yielding the desired guanidines **55** and **56** (Table 3.1).[58]

Table 3.1 Iodocyclization Precursors Synthesized Via the Mitsunobu Protocol



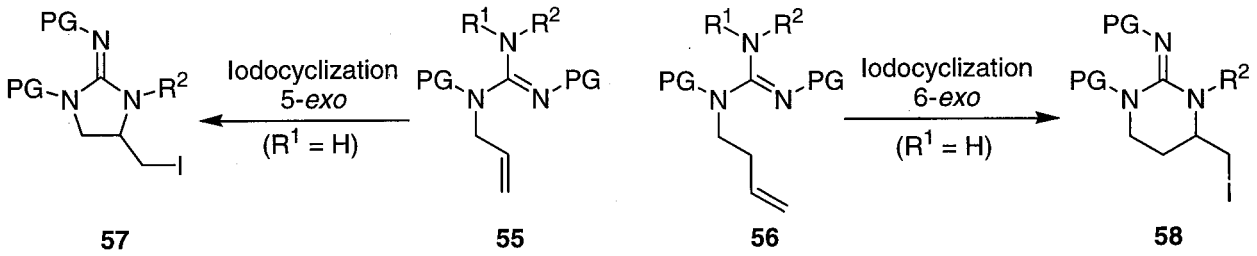
5a = Boc
5b = Cbz
5c = methyl carbamate

Entry	HO(CH2)nCH=CH2	PG	Compound	Yield 53, 54 (%)[a]	R1-NH-R2	Compound	Yield 55, 56 (%)[a]
1	n = 1	Boc	**53a**	98		**55a**	92
2	n = 1	Boc	**53a**	98		**55b**	53
3	n = 1	Boc	**53a**	98		**55c**	0[b]
4	n = 1	Cbz	**53b**	85	H_2N–Me	**55d**	57
5	n = 1		**53c**	96	H_2N–Me	**55e**	90
6	n = 1		**53c**	96		**55f**	30[c]
7	n = 2	Boc	**54a**	97		**56a**	90
8	n = 2	Cbz	**54b**	88	H_2N–Me	**56b**	60

[a] Yield of the purified product. [b] Only starting material was isolated. [c] The methyl carbamate-derived guanidine was very polar and difficulties with flash chromatography were encountered.

3.2.2.2.2 Iodocyclization Reactions Using Guanidines Derived From the Mitsunobu Protocol

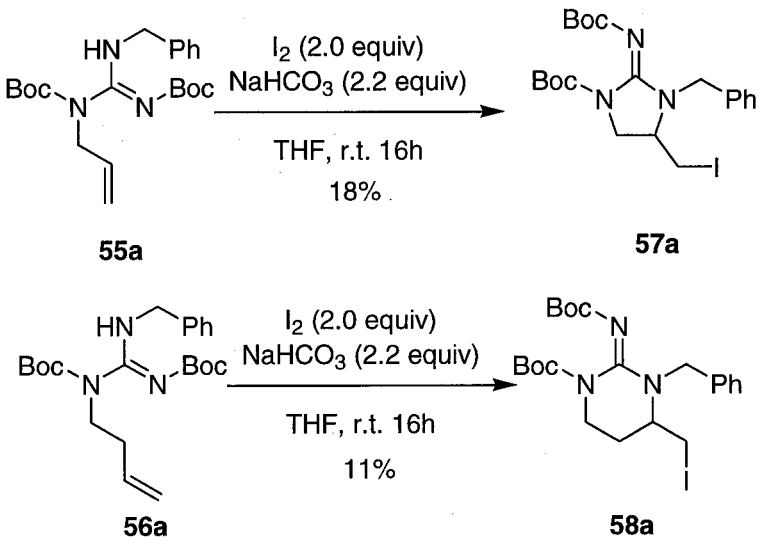
Having synthesized the required olefin-guanidine compounds using the versatile Mitsunobu protocol, iodocyclization reactions were then attempted. It was hoped this new approach would offer access to both the 5-*exo* **57** and 6-*exo* **58** products obtained from iodocyclization of either the allyl-derived guanidines **53** or from the 3-butene-derived guanidines **54** (Scheme 3.30). It was hoped the regioselectivity of the cyclization would occur via the more nucleophilic N^2-position over the electron-deficient carbamate-protected N^3-position. This would provide a general method towards the synthesis of a variety of 5- and 6-membered cyclic guanidine products.



Scheme 3.30

The N^1-allyl-N^2-benzyl-N^1,N^3-bis-Boc guanidine **55a** (Table 3.1, entry 1) was subjected to iodocyclization procedures similar to those reported by Noguchi and co-workers.[29] The guanidine **55a** was stirred with iodine (2.0 equiv.) and $NaHCO_3$ (2.2 equiv.) in anhydrous THF for 12 h. After isolation and purification, the desired cyclic 5-*exo* product **57a** was obtained, although the yield was low (18%) (Scheme 3.31). The results of these initial attempts were encouraging; however, all attempts to increase the yield for this iodocyclization procedure were unsuccessful. As a result, the N^1-but-3-enyl-N^2-benzyl-N^1,N^3-bis-Boc guanidine **56a** (Table 3.1, entry 7) was synthesized and subjected to the iodocyclization procedure. It was thought better results would be obtained in the synthesis of the corresponding 6-*exo* product **58a**. The *N*1-but-3-enyl-N^2-benzyl-N^1,N^3-bis-Boc guanidine **56a** (Table 3.1, entry 7) was combined with iodine (2.0 equiv.) and $NaHCO_3$ (2.2 equiv.) and the desired 6-*exo* product **58a** was obtained, although the yield for this transformation was again very low (11%) (Scheme 3.31). Extensive steps were taken in order to optimize the yield for this transformation; however, all attempts were again unsuccessful. The iodocyclization procedure was attempted with varying bases, such as

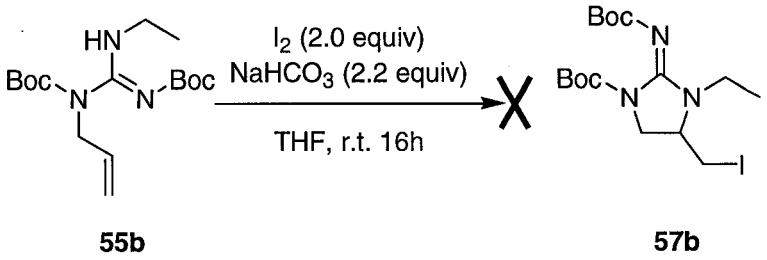
$NaHCO_3$, K_2CO_3, and Cs_2CO_3. In addition, the stoichiometry of the iodocyclization procedure was modified by changing the number of equivalents of iodine and base, as well as modifying the reaction time, temperature, and workup procedure. Unfortunately, all of these modifications did not lead to an increase in the yield of either the desired 5-*exo* **57a** or 6-*endo* **58a** products.



Scheme 3.31

3.2.2.2.3 Possible Steric Factors Inhibiting Iodocyclization

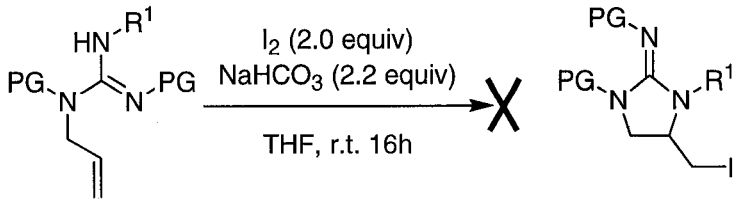
The presence of the N^1,N^3-bis-Boc carbamate groups on the iodocyclization precursors **55a** and **56a** was thought to inhibit cyclization to yield the desired guanidines based on steric factors. It was thought the N^2-benzyl substituent, which was the nucleophilic component, was too sterically hindered to perform the iodocyclization to give the desired cyclic guanidine in high yields. To probe this hypothesis, the N^1-allyl-N^2-ethyl-N^1,N^3-bis-Boc-guanidine **55b** (Table 3.1, entry 2) was synthesized and subjected to iodocyclization using the previously reported procedures (Scheme 3.32). Unfortunately, all attempts to obtain the desired 5-*exo* cyclic guanidine products **57b** were not successful; instead, a complex mixture of products was observed by ^{1}H NMR.



55b **57b**

Scheme 3.32

To further explore the hypothesis that steric factors were inhibiting iodocyclization with the substrates obtained via the Mitsunobu protocol, the less sterically bulky N^1,N^3-bis-Cbz-derived guanidines **55d** were synthesized. Subjecting N^1-allyl-N^1,N^3bis-Cbz-N^2-methyl guanidine **55d** (Table 3.1, entry 4) to iodocyclization again failed to yield the desired 5-*exo* guanidine **57d**, despite several attempts under differing reaction conditions and workup procedures (Scheme 3.33). Attempts to synthesize the 6-*exo* guanidine using the 3-butene-derived guanidine (Table 3.1, entry 8) were also unsuccessful. Finally, the sterically unhindered methyl carbamate derivatives were synthesized to again test the possibility that steric factors were inhibiting iodocyclization. Both N^1-allyl-N^1,N^3bis-methyl carbamate-N^2-methyl guanidine **55e** (Table 3.1, entry 5) and N^1-allyl-N^1,N^3bis-methyl carbamate-N^2-benzyl guanidine **55f** (Table 3.1, entry 6) were synthesized, although problems were encountered with purification of the benzyl-derived guanidine **55f** due to the high polarity of the methyl-carbamate protected guanidines. It was hoped that the nucleophilic benzyl-derived guanidine **55f** would undergo iodocyclization to give the 5-*exo* product **57f**; however, this process was unsuccessful despite repeated attempts. Iodocyclization attempts with the methyl-derived guanidine **55e** also failed to yield the desired product; instead, a complex mixture of products was obtained (Scheme 3.33).



55 **57**

55d PG = Cbz, R^1 = Me
55e PG = methyl carbamate, R^1 = Me
55f PG = methyl carbamate, R^1 = Bn

Scheme 3.33

3.2.2.2.4 Analysis of the Iodocyclization Reactions on Guanidines Derived from the Mitsunobu Protocol

Although the olefin substituted guanidine derivatives were readily synthesized in moderate (for the methyl carbamate-protected guanidines) to excellent yields (for the Boc and Cbz-protected guanidines), the iodocyclization reactions afforded either low yields of the desired cyclic guanidine products or a complex mixture of products. It was hoped this versatile method would provide a route toward the synthesis of cyclic guanidine natural products containing either a 5- or 6-membered core structure. Unfortunately, all attempts to synthesize the desired guanidine products failed. It was originally thought that steric factors associated with the bulky Boc-protecting groups were responsible for the low yields obtained in the iodocyclization reactions. However, iodocyclization reactions with bis-methyl carbamate-protected guanidines were unsuccessful, making steric factors unlikely in the reason for the low yields for this protocol.

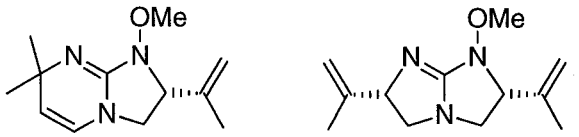
3.2.2.2.5 Iodocyclization Conclusions

Iodocyclization of allylamine-derived guanidine **49** was successful, yielding the desired 5-*exo* guanidine **50** in 88% yield. However, due to the lack of generality with this method, a more versatile route, which employed attachment of the olefin via a Mitsunobu reaction, followed by guanylation of an amine, was developed. Moderate to excellent yields of the cyclization precursors **55** and **56** were obtained; although iodocyclization with these substrates gave low yields of the desired products. The intriguing aspect with these iodocyclization results is with this protocol being successful for the guanidines derived from allylamine **49**, while being unsuccessful for those derived from the Mitsunobu reaction **55** and **56**.

3.2.3 Palladium-Catalyzed Allylic Cyclization Reactions

3.2.3.1 Introduction

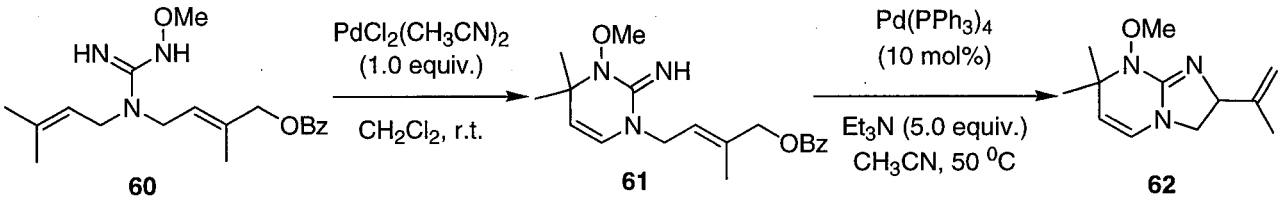
Büchi and co-workers, to the best of our knowledge, is the only group to have reported palladium-catalyzed π-allyl cyclization reactions involving guanidine substrates.[59] Interestingly, Büchi has utilized both Pd(0) and Pd(II) chemistry in two separate intramolecular cyclization reactions to yield the alkaloids alchorneine (**58**) and isoalchorneine (**59**) (Figure 3.9).



58 **59**

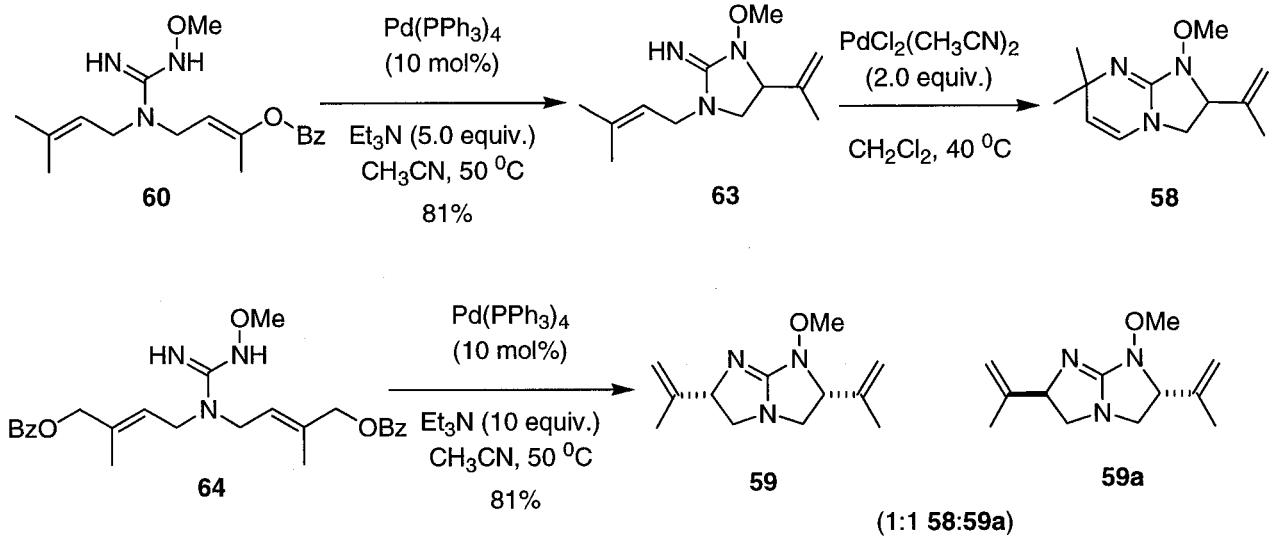
Figure 3.9 Structures of Alchorneine (58) and Isoalchorneine (59)

The methoxyguanidine compounds **60** were subjected to oxidative cyclization with $PdCl_2(CH_3CN)_2$ (1.0 equiv.) (Scheme 3.34). This gave the tetrahydropyrimidine **61** in 30% yield, which on treatment with $Pd(PPh_3)_4$ (10 mol%) and Et_3N at 50 °C gave the undesired compound **62**. Büchi notes the α-effect[60] as the cause of formation of the product since cyclization occurred first through the more nucleophilic methoxy-nitrogen. The α-effect is a phenomenon where the nucleophilicity of the attacking atom on the nucleophile is increased due to the presence of a lone pair of electrons on its adjacent atom. The precise reason for the increase in nucleophilicity has been the subject of some debate and the reasons for this phenomenon are not completely understood, although several explanations have been proposed.[60] The origin of the α-effect has been proposed to be the result of one or more of the following factors: (1) destabilization of the ground state of the α-nucleophile;[61] (2) stabilization of the transition state;[62] (3) stabilization of the products;[63] (4) reduced solvation of the α-nucleophile.[62]



Scheme 3.34

The α-effect was then utilized by Büchi to synthesize alchorneine (**58**). By simply reversing the previously discussed cyclization steps, the desired product was achieved. The methoxyguanidine **60** was heated with a catalytic amount of $Pd(PPh_3)_4$ to 50 °C, in the presence of Et_3N, yielding imidazolidine **63** in 81% yield (Scheme 3.35). Cyclization of **63** with $PdCl_2(CH_3CN)_2$ (2.0 equiv.) at 40 °C gave the desired alchorneine (**58**) in 46 % yield. Similarly, intramolecular cyclization of **64** was performed using $Pd(PPh)_3$ (20 mol%), Et_3N (10 equiv.), and heating to 50 °C. This resulted in the formation of a 1:1 mixture of isoalchorneine **59** and the *trans* epimer **59a**, which was separated using flash chromatography (Scheme 3.35).



Scheme 3.35

Although the scope of the palladium-catalyzed π-allyl cyclization reactions utilized by Büchi and co-workers was limited, this report shows that these cyclization are indeed possible

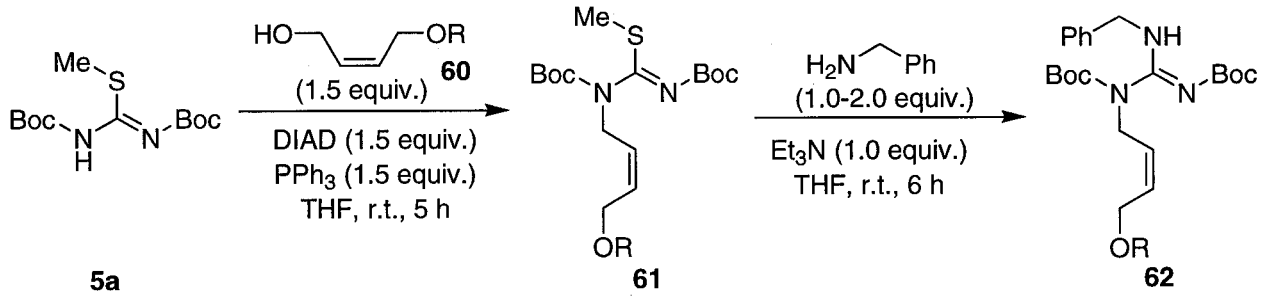
with guanidine nucleophiles. Based on their success, it was decided the scope of this reaction could be expanded by our research group to include a general method towards the synthesis of cyclic guanidine natural products.

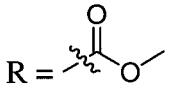
3.2.3.2 Intramolecular Palladium-Catalyzed π-Allyl Cyclization Methods

3.2.3.2.1 Preparation of the Cyclization Precursors

At the outset of this research program, a route enabling the synthesis of a wide range of guanidine-cyclization precursors was desired. Based on our previous experience with the iodocyclization protocol and the synthesis of those cyclization precursors, a similar strategy was adopted. The bis-Boc-*S*-methylisothiourea **5a**, synthesized from the *S*-methylisothiourea **47**, was treated with allylic alcohol derivatives **60a – 60c** using the Mitsunobu protocol (Table 3.2).

Table 3.2 Preparation of the Cyclization Precursors



Entry	HO—⟋⟍—OR	Compound	Yield (%)[a]	Compound	Yield (%)[a]
1	R = Ac	**61a**	96	**62a**	96
2	R = 	**61b**	96	**62b**	98
3	R = Troc	**61c**	99	**62c**	91[b]

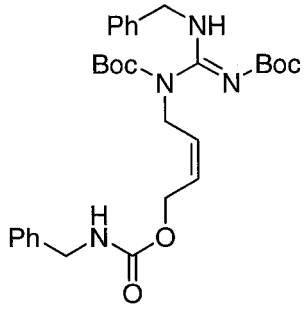
[a] Isolated yield after purification. [b] 1.0 equiv. of benzylamine added.

The allylic alcohol derivatives (**61a-61c**) were readily synthesized from (*Z*)-2-buten-1,4-diol to give the corresponding acetate **60a**, methyl carbamate **60b**, and Troc **60c** derived compounds in 41, 71, and 63% yields, respectively. The isolated yields for the synthesis of the allylic alcohol derivatives were low due to difficulties encountered with the reaction procedures,

since a considerable amount of the bis-functionalized products was always obtained and was removed through purification.

An alternate method to the Mitsunobu protocol was recently reported by our research group.[64] This method has been utilized for alkylation of the bis-Boc-*S*-methylisothiourea **5a** and is a more convenient method for the preparation of intermediates, such as **61a - 61c** (Table 3.2). The alkylation reactions using this biphasic protocol are clean, affording the product after purification through a small plug of silica gel, to remove the phase-transfer catalyst. Conversely, purification of intermediates obtained via the Mitsunobu protocol is more tedious since care must be taken to ensure the stoichiometric coupling reagents are removed with purification.

With the alkylated *S*-methylisothiourea derivatives synthesized in excellent yields, guanylation of benzylamine was then performed, which was chosen as a suitable amine due to its high nucleophilicity. It was hoped this highly nucleophilic benzylamine-guanidines **62a – 62c** would undergo cyclization preferentially over the *N*-carbamate nitrogen. This would offer regioselective control over the cyclization process, simplifying the number of intermediates synthesized. Guanylation of benzylamine with the isothiourea substrates **61a – 61c**, proceeds through an addition/elimination mechanism, since formation of the carbodiimide is not possible, and results in the formation of the desired guanidines in excellent yields. Care must be taken with the Troc-derived isothiourea **61c** and only 1.0 equivalent of benzylamine can be added. Addition of 2.0 equivalents results in formation of the guanidine; however, the Troc functional group is also displaced by the nucleophilic benzylamine, resulting in the formation of the benzylcarbamate-derived guanidine **63**.

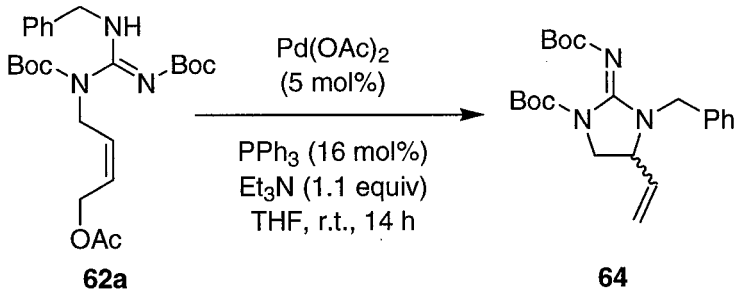


63

3.2.3.2.2 Palladium-Catalyzed Cyclization Attempts with Achiral Ligands

Having synthesized the required allylic substituted guanidines, attempts were made to perform palladium-catalyzed π-allyl cyclization with these substrates. Initially, $Pd(OAc)_2$ was

selected as the source of palladium. This palladium(II) source was reduced to palladium(0) by stirring with PPh_3 and after 1 h. of stirring under an atmosphere of nitrogen in a Schlenk flask, the guanidine substrates were then added via a syringe. The allylic acetate-derived guanidine **62a** provided the desired 5-*exo* cyclic guanidine **64** in 66% yield upon stirring with $Pd(OAc)_2$ (5 mol%) (Scheme 3.36); however, a minor isomeric product was also observed by ^1H NMR whose identity was not determined. This isomeric product, however, was not observed upon addition of Et_3N (1.1 equiv.) to the reaction mixture. It appears the product obtained was a result of cyclization through the benzylamine nitrogen. The regioisomer resulting from 5-*exo* cyclization through the N-Boc carbamate was not observed in this case.

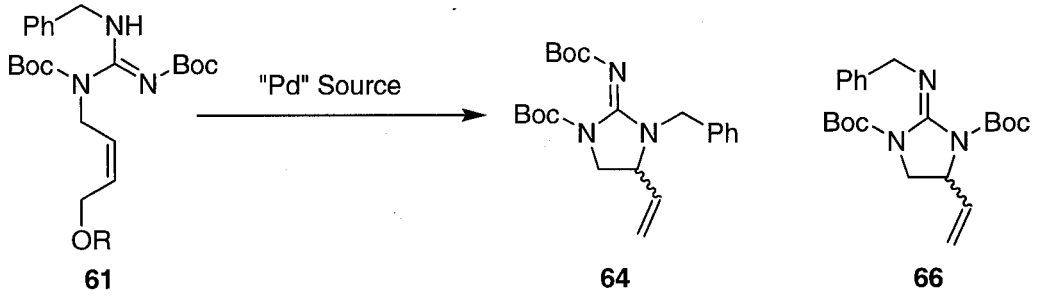


62a **64**

Scheme 3.36

The 2-D COSY spectrum of this cyclic guanidine **64** was obtained. This 2-D analysis shows the interesting chemical shift difference that occurs between the enantiotopic-benzylic protons of **64**. There was over 1 ppm chemical shift difference between the two benzylic protons, with one proton appearing as a doublet at δ 5.08 ppm and the other appearing as doublet at δ 3.93 ppm. Deprotection of this cyclic guanidine was performed by stirring with 1M HCl, affording the cyclic guanidine **65** as the HCl salt. Numerous attempts to increase the yield for this cyclization were attempted by varying the stoichiometric ratios of palladium to PPh_3, however, 66% yield was the maximum achieved using $Pd(OAc)_2$ as the palladium source.

The methyl carbonate **61b** and Troc **61c** derived guanidines were then subjected to palladium-catalyzed π-allyl cyclizations. However, widely varying results were obtained with these substrates. Depending on the reaction conditions, products resulting from either cyclization via the *N*-benzyl nucleophile **64** or via the *N*-Boc nucleophile **66** were obtained (Scheme 3.37).



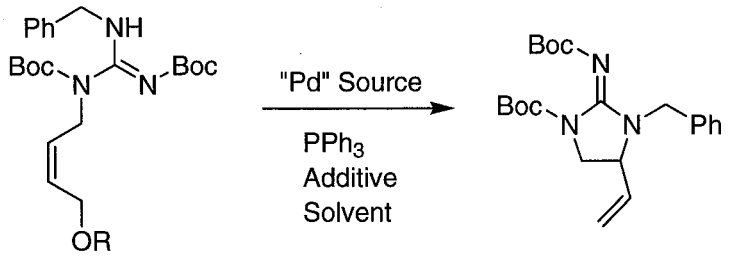
Scheme 3.37

Reactions in the following sections are grouped based on which regioisomeric product **64** and **66** was formed as the major compound.

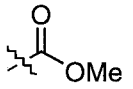
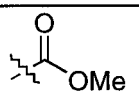
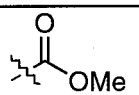
3.2.3.2.2.1 Cyclization Reactions Forming the N-Benzyl Cyclized Regioisomer (64)

When different guanidine substrates and reaction conditions were utilized, an interesting reversal in the regioselectivity for these cyclizations could be achieved. Shown below are the reaction conditions and substrates that gave the *N*-benzyl cyclized regioisomer **64** as the major product (Table 3.3).

Table 3.3 Cyclization Reactions Forming the *N*-Benzyl Cyclized Regioisomer (64)



61 64

Entry	R =	"Pd" Source (mol%)	Ligand (mol%)	Solvent (M)	Additive (equiv.)	Time, Temp. (°C)	Yield (%)[a]
1	Ac	$Pd(OAc)_2$ (5.0)	PPh_3 (16)	THF (0.1 M)	none	5 h, r.t.	66[b]
2	Ac	$Pd(OAc)_2$ (6.0)	PPh_3 (16)	THF (0.1 M)	Et_3N (1.1)	14 h, r.t.	59
3		$Pd(OAc)_2$ (10)	PPh_3 (30)	CH_2Cl_2 (0.17 M)	Et_3N (1.0)	16 h, r.t.	62[c]
4		$Pd(OAc)_2$ (100)	PPh_3 (300)	CH_2Cl_2 (0.05 M)	Et_3N (1.5)	16 h, r.t.	64
5		$Pd_2(dba)_3$ (5.0)	PPh_3 (7.2)	CH_2Cl_2 (0.10 M)	Et_3N (1.5)	3 h, 40 °C	92
6	Troc	$Pd(OAc)_2$ (100)	PPh_3 (300)	CH_2Cl_2 (0.05 M)	none	16 h, r.t.	47

[a] Isolated yield after purification [b] A minor isomer was also obtained [c] 29% yield of *N*-Boc cyclized product **66** was also isolated.

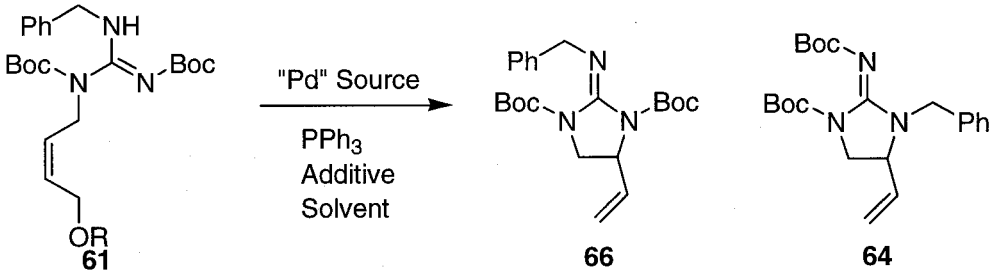
As mentioned earlier, reactions using the allylic acetate-derived guanidines (Table 3.3, entries 1-2) afforded the *N*-benzyl cyclized guanidine **64** in moderate yields. Subjecting the methyl carbonate-derived guanidines **61b** (Table 3.3, entry 3) to the reaction conditions using $Pd(OAc)_2$ as the palladium source, yielded *N*-benzyl cyclized guanidine **64** as the major compound (62%). A minor component whose ^1H NMR appeared to be very complicated was also isolated in 29% yield and this compound was initially thought to be some type of decomposition product; however, it was later determined this compound was in fact the *N*-Boc cyclized product **66**. The ^1H NMR for this compound was very complicated due to the presence of rotamers that caused extreme broadening of the proton signals. It was hypothesized that the turnover rate in the catalytic cycle was slow, due to the presence of the guanidine substrates,

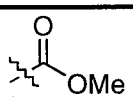
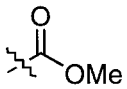
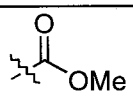
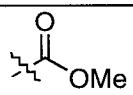
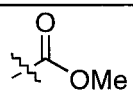
which can form complexes with the palladium source. Addition of 1.0 equivalent of $Pd(OAc)_2$ to the reaction mixture (Table 3.3, entry 4) resulted in the *N*-benzyl cyclized product being obtained in 64% yield. A dramatic increase in yield was obtained upon stirring guanidine substrate **61b** with $Pd_2(dba)_3$ at heating to 40 °C for 3 h, which gave the *N*-benzyl cyclized product **64** in 92% yield (Table 3.3, entry 5). The *N*-benzyl cyclized product **64** was also obtained as the major compound upon stirring the Troc-derived guanidine **61c** with 1.0 equivalent of $Pd(OAc)_2$ (Table 3.3, entry 6).

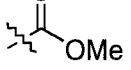
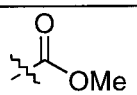
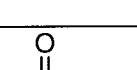
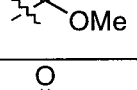
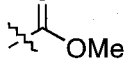
3.2.3.2.2.2 Cyclization Reactions Forming the N-Boc Cyclized Regioisomer (66)

The palladium-catalyzed π-allyl cyclization reactions that yielded the *N*-Boc cyclized product **66** as the major or exclusive regioisomer are shown below (Table 3.4).

Table 3.4 Cyclization Reactions Forming the *N*-Boc Cyclized Regioisomers 66 and 64



Entry	R =	"Pd" Source (mol%)	Ligand (mol%)	Solvent (M)	Additive (equiv.)	Time, Temp. (°C)	Yield (%)[a]
1		$Pd_2(dba)_3$ (4.7)[b]	PPh_3 (14)	CH_2Cl_2 (0.21 M)	none	16 h, r.t.	83 (**66**)
2		$Pd_2(dba)_3$ (20)[b]	PPh_3 (61)	CH_2Cl_2 (0.10 M)	none	16 h, r.t.	98 (**66**)
3		$Pd_2(dba)_3$ (5)[b]	PPh_3 (7.3)	CH_2Cl_2 (0.05 M)	Hünig's Base (1.6)	10 h, r.t.	60 (**66**) 8 (**64**)
4		$Pd_2(dba)_3$ (5)[b]	PPh_3 (7.3)	CH_2Cl_2 (0.05 M)	Cs_2CO_3 (1.5)	10 h at r.t, then 6 h at 40 °C.	65 (**66**) 18 (**64**)
5		$Pd_2(dba)_3$ (4.4)[b]	PPh_3 (13)	CH_2Cl_2 (0.10 M)	Et_3N (2.0)	16 h, r.t.	62 (**66**) 16 (**64**)

6		$[(C_3H_5)PdCl]_2$ (20)[b]	PPh_3 (59)	CH_2Cl_2 (0.10 M)	Et_3N (1.0)	16 h, r.t.	77 (**66**)
7		$[(C_3H_5)PdCl]_2$ (20)[b]	PPh_3 (56)	CH_2Cl_2 (0.10 M)	none	16 h, -78 °C	75 (**66**)
8		$[(C_3H_5)PdCl]_2$ (20)[b]	PPh_3 (56)	CH_2Cl_2 (0.10 M)	Bu_4NCl (1.0)	16 h, r.t.	72 (**66**) 21 (**64**)
9		$[(C_3H_5)PdCl]_2$ (20)[b]	PPh_3 (60)	CH_2Cl_2 (0.10 M)	none	16 h, r.t.	79 (**66**)
10		$Pd(OAc)_2$ (2.5)	PPh_3 (63)	CH_2Cl_2 (0.10 M)	Bu_4NCl (10)	16 h, r.t.	70 (**66**) 20 (**64**)
11	Troc	$Pd_2(dba)_3$ (5.0)[b]	PPh_3 (15)	CH_2Cl_2 (0.05 M)	none	16 h, r.t.	88 (**66**)
12	Troc	$Pd_2(dba)_3$ (5.0)[b]	PPh_3 (15)	CH_2Cl_2 (0.04 M)	Et_3N (1.5)	3 h, 40 °C	84 (**66**)
13	Troc	$Pd_2(dba)_3$ (4.8)[b]	PPh_3 (14)	CH_2Cl_2 (0.05 M)	Et_3N (1.4)	16 h, r.t.	80 (**66**)

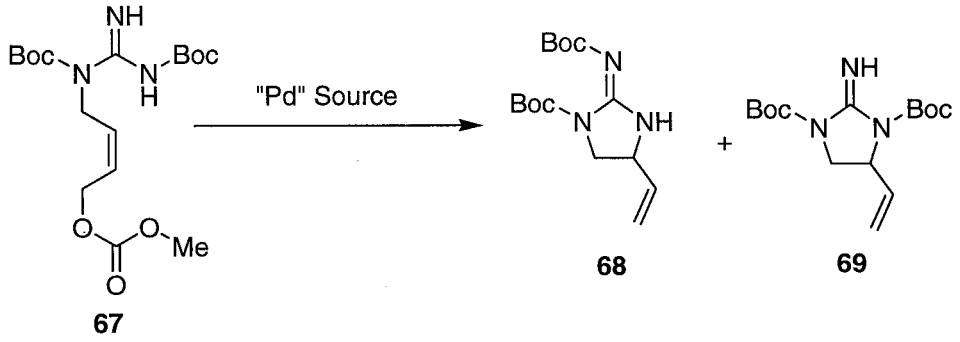
[a] Isolated yield after purification [b] Represents the total mol% of palladium

When the methyl carbonate-derived guanidine was stirred with $Pd_2(dba)_3$ the *N*-Boc cyclized product was obtained in either 83% yield of 98% yield when 4.7 mol% or 20 mol% of palladium was used, respectively (Table 3.4, entries 1-2). The ^1H NMR for this cyclic compound appeared initially to be a complex mixture of products; therefore, many attempts were made to rectify this apparent problem. These attempts included adding a variety of bases to observe any change in the obtained spectra. Hunig's base, Et_3N, and Cs_2CO_3 (Table 3.4, entries 3-5) were used as bases and these produced small amounts of the N-benzyl cyclized product **66** (Scheme 3.37), with major compound being the complex mixture previously observed. However, it was later determined that this apparent complex mixture was in fact the *N*-Boc cyclized regioisomer **66** and was experiencing extreme peak broadening in the ^1H NMR spectra due to the formation of rotamers.

The source of palladium was then changed to the palladium-allyl chloride dimer (Table 3.4, entries 6-9) with the methyl carbonate-derived guanidine substrates. In all cases, the *N*-Boc cyclized product **66** was formed as the major product. The cyclization reaction conditions were varied by stirring the mixture at –78 °C for 16 h. and this gave *N*-Boc cyclized regioisomer **66** as

the only compound that could be isolated. Many research groups have found that addition of a catalytic or stoichiometric amount of chloride ions can dramatically affect these palladium-catalyzed reactions.[44-46] Chloride ions present in the reaction mixture can increase the rate of apparent allyl exchange (Scheme 3.18). Chloride ions were therefore added to the reaction mixture by using Bu_4NCl (1.0 equiv.), however, no difference in the obtained product was observed with the palladium-allyl chloride dimer as the palladium source (Table 3.4, entry 8). However, an interesting reversal in regioselectivity was observed when using the chloride-free source of palladium, $Pd(OAc)_2$, with Bu_4NCl (1.0 equiv.) as an additive. In the previous examples, the use of $Pd(OAc)_2$ as the palladium source with the methyl carbonate-derived guanidines (Table 3.3, entry 3) gave the *N*-benzyl cyclic guanidine **64** as the major regioisomer. Upon addition of Bu_4NCl, however, *N*-Boc cyclized regioisomer **66** was formed as the major regioisomer, with only a minor amount of the *N*-benzyl cyclized regioisomer **64** obtained (20%) (Table 3.4, entry 10). The palladium-catalyzed cyclization reactions with the Troc-derived guanidines, using Pd_2dba_3 gave the *N*-Boc cyclized regioisomer in all cases (Table 3.4, entries 11-13).

The palladium-catalyzed π-allyl intermolecular cyclization reactions were attempted with other guanidine substrates. The cyclization protocol was attempted with the N^1,N^3-bis-Boc-guanidine **67**, however, all attempts to yield the cyclized guanidine product **68** and **69** were unsuccessful (Scheme 3.38). Instead, a complex mixture of products was obtained in all cases.



Scheme 3.38

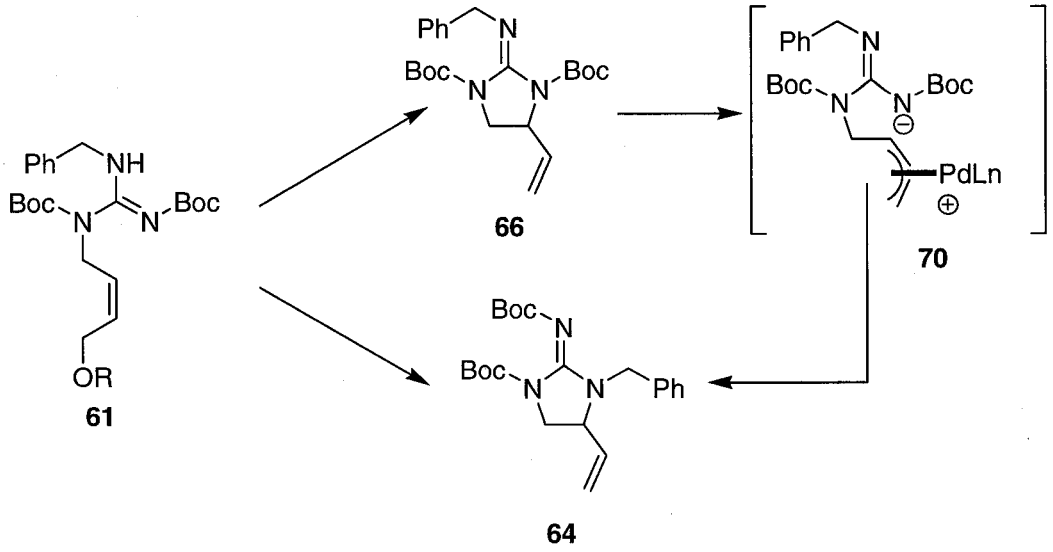
3.2.3.2.3 Analysis of the Cyclization Reactions with Achiral Ligands

Interesting differences in the regioselectivities for the palladium-catalyzed intramolecular cyclization reactions were obtained. It is still not apparent why the reversals in regioselectivites are occurring depending on which substrate, palladium source, and reaction conditions are used; however, some general trends have emerged. Several hypotheses as to why certain regioisomers are observed with certain reaction conditions will also be given below. It is important to note that these hypotheses are simply speculated reasons as to why different regioisomeric products were obtained.

3.2.3.2.3.1 The Observed Affect of the Acetate Counterions

When sources of acetate counterions were used in the intramolecular palladium-catalyzed cyclization reactions, the *N*-benzyl cyclized regioisomer **64** was formed. For example, with the allylic acetate-derived guanidine substrates **61a**, cyclization with $Pd(OAc)_2$ afforded regioisomer **64** (Table 3.3, entries 1-2). Additionally, when the methyl carbonate- or Troc-derived guanidines were subjected to the reaction conditions with $Pd(OAc)_2$ as the palladium source, regioisomer **64** was also obtained (Table 3.3, entries 3-5). The only deviation that occurred with the use of $Pd(OAc)_2$ was when Bu_4NCl (1.0 equiv.) was added to the reaction mixture, which afforded the *N*-Boc cyclized regioisomer **66** as the major product (Table 3.4, entry 10).

The *N*-benzyl cyclized regioisomer **64** was also formed in the absence of acetate counterions in solution. When the methyl carbonate-derived guanidine **61b** was heated to 40 °C with $Pd_2(dba)_3$, regioisomer **64** was obtained in 92% yield. It is not clear why this regioisomer **64** was obtained with heating (Table 3.3, entry 5), while the opposite regioisomer was obtained under similar reaction conditions, but at room temperature (Table 3.4, entry 1). A possible hypothesis is that the *N*-benzyl cyclized regioisomer **64** is the thermodynamic product. The *N*-Boc cyclized regioisomer **66** could be the kinetic product; however, its formation could be reversible. As shown in **70** (Scheme 3.39), regioisomer **66** contains a carbamate functional group at the allylic position and carbamates are good leaving groups in the formation of π-allyl intermediates. Therefore, upon heating, regioisomer **66** could undergo ring opening to form the π-allyl intermediate, which undergoes intramolecular cyclization to yield the other regioisomer **64** (Scheme 3.39).



Scheme 3.39

3.2.3.2.4 Cyclization Attempts with Chiral Ligands

This palladium-catalyzed π-allyl cyclization protocol was hoped to yield the desired cyclic guanidine products in high yield. Additionally, this method could be used for the enantioselective formation of the desired guanidine products by utilizing the large number of chiral ligands that have been developed. Since excellent yields could be obtained in some of the previous cyclization attempts with achiral ligands, chiral ligands were next utilized. The ligands used (Figure 3.10) for these enantioselctive cyclization reactions and the results attempts are shown below (Table 3.5).

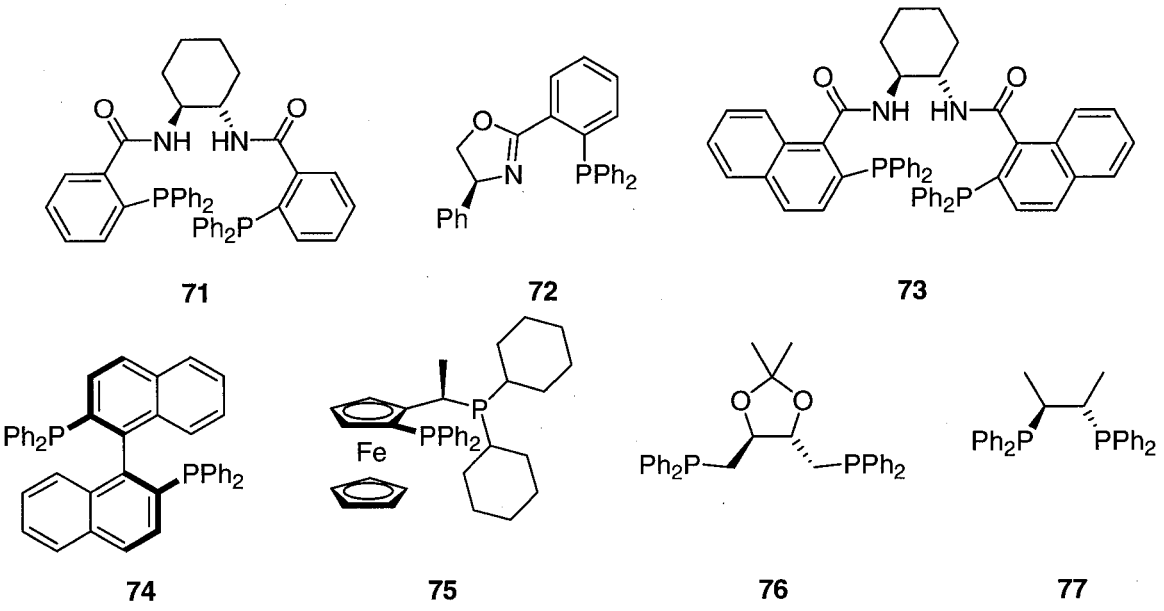
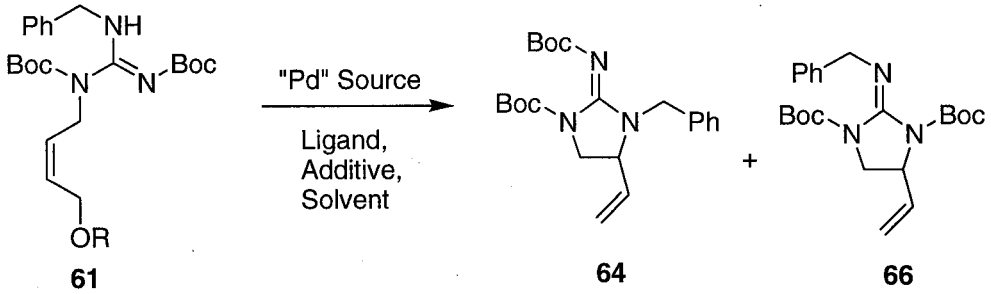
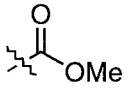
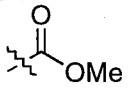
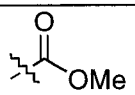
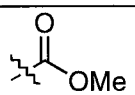


Figure 3.10 Chiral Ligands Used for Intramolecular Cyclization Reactions

Table 3.5 Intramolecular Cyclization Reactions with Chiral Ligands



Entry	R =	"Pd" Source (mol%)	Ligand (mol%)	Solvent (M)	Additive (equiv.)	Time, Temp. (°C)	Yield (%)[a]
1	Ac	$Pd(OAc)_2$ (5)	**72** (16)	THF (0.1)	Et_3N (1.1)	16 h, r.t.	42 (**64**) (24% e.e.)
2	Ac	$Pd(OAc)_2$ (10)	**71** (16)	THF (0.30)	Et_3N (1.2)	12 h, r.t.	0[b]
3	Ac	$Pd(OAc)_2$ (9)	**74** (13)	THF (0.30)	Et_3N (1.2)	16 h, r.t.	32 (**64**) (42% e.e.)
4	Ac	$Pd(OAc)_2$ (9)	**76** (13)	THF (0.25)	Et_3N (2.0)	24 h, r.t.	37 (**64**) (4% e.e.)
5	Ac	$Pd(OAc)_2$ (8)	**71** (13)	THF (0.26)	Et_3N (2.0)	16 h, reflux	13 (**64**) (7% e.e.)
6	Ac	$Pd(OAc)_2$ (20)	**71** (32)	THF (0.22)	Et_3N (2.0)	12 h, reflux	20 (**64**) (21% e.e.)
7	Ac	$Pd(OAc)_2$	**77**	THF	Et_3N	16 h,	30 (**64**)

		(10)	(15)	(0.11)	(2.0)	50 °C	(0% e.e.)
8	Ac	$Pd(OAc)_2$ (10)	**74** (14)	THF (0.11)	Et_3N (2.0)	16 h, 50 °C	37 (**64**) (28% e.e.)
9	Ac	$Pd(OAc)_2$ (9)	**75** (14)	THF (0.11)	Et_3N (3.1)	10 h, 50 °C	49 (**64**) (19% e.e.)
10	Ac	$Pd_2(dba)_3$ (10)[c]	**74** (15)	THF (0.11)	Et_3N (2.0)	20 h, 50 °C	51 (**64**) (46% e.e.)
11	Ac	$Pd(OAc)_2$ (10)	**73** (14)	THF (0.12)	Et_3N (3.7)	24 h, 50 °C	21 (**64**) (10% e.e.)
12	Ac	$Pd(OAc)_2$ (9)	**75** (14)	THF (0.11)	Et_3N (3.1)	10 h, 50 °C	49 (**64**) (19% e.e.)
13	Ac	$PdCl_2(COD)$ (10)	**74** (16)	THF (0.12)	Et_3N (3.0)	16 h, r.t.	49 (**64**) (44% e.e.)
14	Ac	$Pd_2(dba)_3$ (10)[c]	**72** (16)	THF (0.12)	Et_3N (3.0)	16 h, r.t.	66 (**64**) (8% e.e.)
15		$Pd_2(dba)_3$ (2.5)[c]	**71** (7.4)	CH_2Cl_2 (0.05)	Et_3N (1.4)	5 h, 40 °C	74 (**64**) (15% e.e.)
16		$Pd_2(dba)_3$ (2.5)[c]	**74** (15)	CH_2Cl_2 (0.05)	Et_3N (1.5)	10 h, 40 °C	30 (**64**) (40% e.e.)
17		$Pd_2(dba)_3$ (2.5)[c]	**72** (10)	CH_2Cl_2 (0.05)	Et_3N (1.5)	10 h, 40 °C	96 (**64**) (10% e.e.)
18		$Pd_2(dba)_3$ (2.5)[c]	**77** (7.1)	CH_2Cl_2 (0.05)	Et_3N (1.5)	10 h, 40 °C	98 (**64**) (<1% e.e.)

[a] Isolated yield after purification [b] Starting material was isolated. [c] Represents the total mol% of palladium

3.2.3.2.5 Analysis of the Cyclization Reactions with Chiral Ligands

Initial attempts were made with a variety of chiral ligands in hopes of attaining good enantioselectivites for the cyclization reactions. All asymmetric reactions performed with the bidentate chiral ligands were more sluggish, compared to the use of PPh_3. At this stage it is unclear as to why the slow rates of reaction were observed; however, interesting results were obtained in some cases. For example, the highest enantioselectivites were obtained using (*R*)-BINAP **74** (Table 3.5, entries 3, 10, 13, and 16), however, only moderate yields were obtained with this chiral ligand. Interestingly, the highest yields for these reactions were obtained using Pflatz' ligand (**72**) (Table 3.5, entries 14 and 17).

3.2.3.3 Conclusions

The intermolecular palladium-catalyzed cyclization reactions have initially given encouraging results. Initially, it was thought that the *N*-benzyl cyclized regioisomer **64** was the only product that was obtained with this protocol, since the by-product gave a ^{1}H NMR that appeared to be a complex mixture of products. It was later determined that the by-product of the reaction was in fact the *N*-Boc cyclized regioisomer **66**. Difficulties were encountered with the purification of the *N*-Boc cyclized regioisomer **66**, since this product was not UV active and did not stain under TLC conditions with a variety of staining agents. As a result of these difficulties, it is possible that the low yields for some of *N*-benzyl cyclization reactions are due to formation of the *N*-Boc regioisomer. However, since it was originally thought that the *N*-Boc regioisomer **66** was a decomposition product, an accurate yield of this product was not obtained in some examples, but a more thorough analysis will be carried out in the future.

It has been shown these intramolecular reactions with palladium catalysts are indeed possible with guanidine substrates and in some cases give excellent yields of the desired cyclic guanidine products. Perhaps the most beneficial results were the regioselective control attained over the intramolecular cyclization reactions, depending on the palladium source and leaving group that was chosen on the cyclization precursor. This regioselective control is extremely beneficial and was an unforseen advantage to this protocol. Control over which regioisomer could be obtained, depending on which nitrogen cyclized, is a powerful feature that can be used in the synthesis of cyclic guanidine natural products. Additionally, it has been shown that these palladium-catalyzed cyclization reactions can occur asymmetrically, although much fine-tuning is still required to obtain high enantioselectivities. With the success encountered with this protocol, we are confident this method will represent a new route towards the synthesis of cyclic guanidine products, both natural and synthetic.

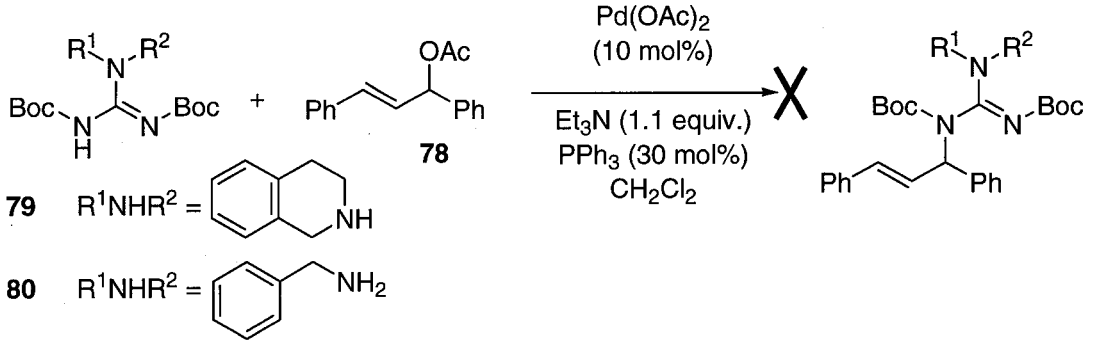
3.2.3.4 Future Work

3.2.3.4.1 Intramolecular Cyclization Reactions

This palladium-catalyzed cyclization protocol, given its initial success, will continue to be explored as a general method to synthesize guanidine compounds both racemically and asymmetrically. The beneficial regioselective control that was observed will continue to be explored and applied towards the synthesis of cyclic guanidine natural products, such as anatoxin-a(s) **1** (Figure 3.8). However, given the inherent difficulties in controlling the regioselectivity with these reactions, the cyclic guanidine precursors will be simplified so that cyclization via either nitrogen will result in formation of the same compound.

3.2.3.4.2 Intermolecular Cyclization Reactions

The palladium-catalyzed intermolecular π-allyl reactions have been attempted with guanidine substrates, although no success with these reactions has yet been achieved. As an example, 3-acetoxy-1,3-diphenylpropene **78** was synthesized in a series of reactions and attempts were made to react this substrate with a variety of guanidine compounds (Scheme 3.40). The tetrahydroisoquinoline-derived guanidine **79** and then benzylamine-derived guanidine **80** were stirred with the allylic substrate **78**, however, only starting material was isolated. These intermolecular π-allyl reactions will continue to be developed.


Pd(OAc)2
(10 mol%)
Et3N (1.1 equiv.)
PPh3 (30 mol%)
CH2Cl2
Boc
Boc
OAc
Ph
Ph
78
79 R1NHR2 =
NH
80 R1NHR2 =
NH2

Scheme 3.40

3.3 Experimental Section

3.3.1 Chemical Characterization

Melting points were determined using a Fisher-Johns melting point apparatus. Infrared spectra were obtained from a Perkin-Elmer Spectrum 1000 series FTIR as KBr disks for solid samples and neat for liquid samples using KBr plates. Nuclear magnetic resonance spectra were obtained using either a 300 MHz Varian Mercury or 400 MHz Varian Unity spectrometer (^{1}H NMR) and a 400 MHz Varian Unity spectrometer operating at 100 MHz (^{13}C NMR) and all signals are reported in ppm (δ). All ^{1}H NMR spectra were referenced to an internal standard (TMS) when using deuteriochloroform as the solvent. The ^{13}C-NMR spectra were obtained using deuteriochloroform and residual solvent signals were referenced to δ 77.0 ppm. ^{1}H NMR spectra are listed in the experimental section as follows: chemical shift (ppm), (number of protons, multiplicity, coupling constants). Line broadening is apparent in some NMR spectra and is due to rotamers around the carbamate nitrogen. Low-resolution mass spectral data were obtained from Dr. Alex Young at the University of Toronto using a Bell and Howell 21-490 spectrometer. High-resolution mass spectral data were also obtained from Dr. Alex Young at the University of Toronto using a AEI MS3074 spectrometer.

3.3.2 General Procedures

All reagents, unless otherwise stated, were used as received from commercial suppliers. THF was distilled from sodium metal/benzophenone ketyl under an atmosphere of argon. Dichloromethane was distilled from calcium hydride under an atmosphere of argon prior to use. DMF was distilled from 4 Å molecular sieves under reduced pressure. Where appropriate, reactions were conducted under an inert atmosphere in flame dried or oven-dried glassware. Reactions were monitored by TLC using 1.5 cm x 5 cm aluminum plates precoated with silica gel 60, 0.2 mm thick (F_{254}, E. Merck). The TLC plates were viewed under a U.V. lamp (254nm/366nm). Flash chromatography was performed using silica gel 60 (0.040-0.063 nm, 230-400 mesh A.S.T.M.) with reagent grade solvents.

3.3.3 Experimental Procedures

3.3.3.1 Iodocyclization General Procedures

General Procedure A – The Mercury-Promoted Guanylation Reaction:

In a typical reaction, a solution of anhydrous DMF (10 mL) was added the bis-Boc-*S*-methylisothiourea (1.9 mmol) and Et_3N (1.9 mmol, 1.0 equiv.). The amine (2.9 mmol, 2.0 equiv.) was then added, followed by $HgCl_2$ (2.1 mmol, 1.1 equiv.) and the mixture was stirred at r.t. for 16 h. The solution was diluted with Et_2O (50 mL) and filtered through a plug of celite. The filtrate was washed with H_2O (2 x 30 mL) and brine (2 x 30 mL) and was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes: EtOAc) gave the product.

General Procedure B - The Mitsunobu Reaction:

In a typical reaction, a solution of the bis-Boc-*S*-methyl isothiourea (1.75 mmol) in anhydrous THF (9 mL) was stirred with PPh_3 (2.63 mmol) and the alcohol (2.79 mmol). The mixture was stirred at rt under an atmosphere of N_2 and then diisopropyl azodicarboxylate (2.60 mmol) was slowly added. The orange mixture was stirred for 13 h, diluted with H_2O (30 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (silica gel, hexanes: EtOAc).

General Procedure C – The Guanylation Reaction in the Absence of a Metal:

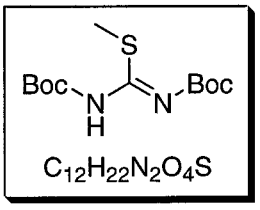
In a typical reaction, a solution of anhydrous CH_3CN (10 mL) was added the *N*-substituted bis-Boc-*S*-methylisothiourea (1.9 mmol) and Et_3N (1.9 mmol, 1.0 equiv.). The amine (2.9 mmol, 2.0 equiv.) was then added and the mixture was stirred at r.t. for 16 h. The mixture was concentrated *in vacuo* and was the residue was taken up in CH_2Cl_2 (30 mL), washed with H_2O (2 x 30 mL) and brine (2 x 30 mL) and was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes: EtOAc) gave the product.

General Procedure D – The Iodocyclization Reaction:

To a solution of the guanidine (0.676 mmol) in anhydrous THF (10 mL) was added iodine (1.35 mmol) and $NaHCO_3$ (1.48 mmol). The mixture was stirred at r.t. until all of the starting material had disappeared by TLC (~ 6 h.). The reaction mixture was treated with saturated aqueous sodium sulfite to reduce the excess of iodine after which it was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexanes: EtOAc) gave the product.

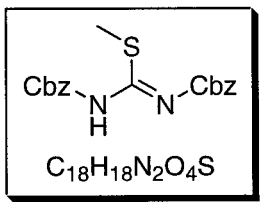
3.3.3.2 Iodocyclization Experimental Procedures

N^1,N^2-Bis-(*tert*-butoxycarbonyl)-*S*-methylisothiourea (5a):



Di-*tert*-butyl dicarbonate (25.9 g, 119 mmol) and *S*-methylisothiourea· ½ H_2SO_4 (15.0 g, 108 mmol) were vigorously stirred in a biphasic mixture of CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (100 mL) for 24 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). After washing with H_2O (2 x 100 mL) the mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (80% $CHCl_3$: 20% hexanes) gave the desired product as a white solid (11.7 g, 80%). R_f = 0.31 (80% $CHCl_3$: 20% hexanes); mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (1H, br s), 2.40 (3H, s), 1.52 (9H, s), 1.50 (9H, s). This compound has been previously characterized, see: Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1987**, *52*, 1700-1703.

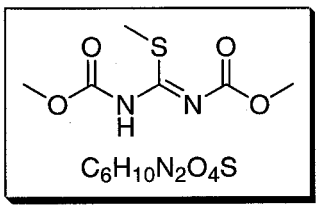
N^1,N^2-Bis-(benzyloxycarbonyl)-*S*-methylisothiourea (5b):



To a solution of the *S*-methylisothiourea· ½ H_2SO_4 (5.88 g, 21.1 mmol) in a biphasic mixture of CH_2Cl_2 (45 mL) and water (45 mL) was added NaOH (3.40 g, 85.0 mmol) and benzyl chloroformate (5.73 mL, 40.1 mmol). The mixture was vigorously stirred for 24 h. and the layers were separated. The organic layers were washed with brine (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (80% hexanes: 20% EtOAc) gave the product as a clear oil, which became a white solid upon standing for 2 days (6.82 g, 95%). R_f = 0.38 (80% hexanes: 20% EtOAc); mp

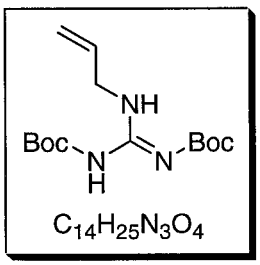
34-34.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (1H, br s), 7.49-7.23 (10H, m), 5.20 (2H, s), 5.18 (2H, s), 2.42 (3H, s); MS (EI) *m/e* (relative intensity) 358 (M^+, 1), 311 (8), 203 (40), 177 (14), 161 (12), 143 (15), 107 (40), 91 (100); HRMS (EI) (M^+) calcd. 358.0987, found 358.0993. This compound has been previously characterized, see: Tian, Z.; Edwards, P.; Roeske, R. W. *Int. J. Peptide Protein Res.* **1992**, *40*, 119-126.

N^1,N^2-Bis-(methoxycarbonyl)-*S*-methylisothiourea (5c):



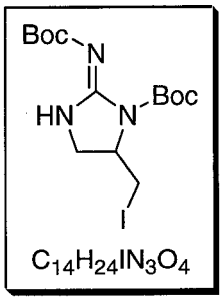
To a mixture of the *S*-methyl isothiourea (4.81 g, 17.3 mmol) in H_2O (90 mL) was added methyl chloroformate (5.34 mL, 69.1 mmol). The mixture was cooled in an ice-water bath and was stirred vigorously. A solution of NaOH (5.53 g in 90 mL of H_2O) was then slowly added to the mixture over a 2 h period. The mixture was stirred for a further 4 h and the product was extracted with CH_2Cl_2 (2 x 200 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was recrystallized from MeOH (~60 mL) to yield the product as a white solid (1.86 g, 52%). R_f = 0.37 (80% hexanes: 20% EtOAc); mp 34-34.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (1H, br s), 3.82 (3H, s), 3.79 (3H, s), 2.42 (3H, s). This compound has been previously reported, see: Weinhardt, K.; Beard, C. C.; Dvorak, C.; Marx, M.; Patterson, J.; Roszkowski, A.; Schuler, M.; Unger, S. H.; Wagner, P. J.; Wallach, M. B. *J. Med. Chem.* **1984**, *27*, 616-627.

N^2-Allyl-N^1,N^3-bis(*tert*-butoxylcarbonyl)guanidine (49):



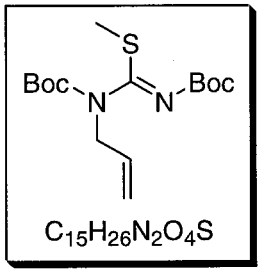
The product was synthesized using General Procedure A and was purified by flash chromatography (90% hexanes: 10% EtOAc) to give the product as a white solid (89%). R_f= 0.57 (80% hexanes: 20% EtOAc); mp 87-89 °C; IR (KBr) ν 3338, 3133,2985, 1725, 1641, 1613, 1570, 1412, 1363, 1324, 1257, 1229, 1131, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (1H, br s), 8.35 (1H, br s), 5.82 (1H, dddd, *J* = 16.0, 10.0, 5.5, 5.5 Hz), 5.10 (1H, d, *J* = 6.0 Hz), 5.08 (1H, d, *J* = 10.0 Hz), 4.01 (2H, m), 1.43 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 155.9, 153.2, 133.2, 116.6, 83.0, 79.2, 43.1, 28.2, 28.0; MS (EI) *m/e* (relative intensity) 300, (MH^+, 23), 244 (30), 226, (11), 187 (29), 170 (65), 152 (20), 143 (31), 128 (31), 99 (15), 84 (14), 57 (100); HRMS (EI) (MH^+) calcd 300.1923, found 300.1938.

N^1,N^2-Bis(*tert*-butoxycarbonyl)-5-iodomethyl-imidazolidine (50):



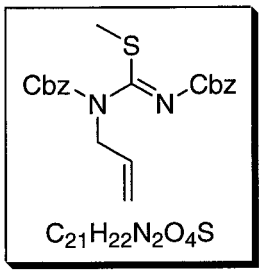
The product was synthesized using General Procedure D and was purified by flash chromatography (90% hexanes: 10% EtOAc with 1% Et_3N) to give the product as a yellow oil (88%). R_f = 0.52 (80% hexanes: 20% EtOAc); IR (neat) ν 3386, 2969, 2921, 1643, 1622, 1507, 1334, 1306, 1272, 1242, 1160, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09-3.96 (1H, br m), 3.72-3.68 (1H, m) 3.38 (1H, dd, J = 13.0, 3.5 Hz), 3.18-3.08 (2H, m), 1.33 (9H, s), 1.27 (9H, s) (one NH signal not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 83.3, 80.3, 56.0, 27.6, 27.5, 7.90 (one quaternary carbon not observed); MS (EI) *m/e* (relative intensity) 425 (M^+, 2), 370 (3), 325 (6), 314 (20), 296 (8), 269 (28), 252 (6), 128 (18), 110 (11), 98 (21), 84 (34), 57 (100); HRMS (EI) (M^+) calcd 425.0812, found 425.0820.

N^1-Allyl-N^1,N^2-bis-(*tert*-butoxycarbonyl)-*S*-methylisothiourea (53a):



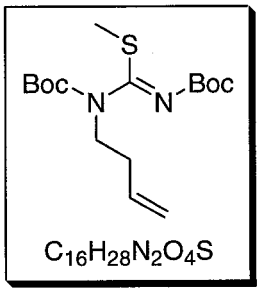
The product was synthesized using General Procedure B and was purified by flash chromatography (90% hexanes: 10% EtOAc) to give the product as a light yellow oil (98%). R_f = 0.14 (90% hexanes: 10% EtOAc); IR (neat) ν 2978, 1721, 1619, 1368, 1249, 1143, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, m), 5.25 (1H, d, J = 17.0 Hz), 5.19 (1H, d, J = 10.5 Hz), 4.14 (2H, m), 2.38 (3H, s), 1.52 (9H, s), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 157.8, 151.6, 133.0, 117.8, 82.4, 81.7, 51.2, 28.0, 15.5; MS (EI) *m/e* (relative intensity) 330 (M^+, 1), 277 (73), 218 (15), 201 (25), 185 (8), 174 (11), 152 (7), 115 (6), 77 (13), 57 (100); HRMS (EI) (M^+) calcd 330.1613, found 330.1609.

N^1-Allyl-N^1,N^2-bis-(benzyloxycarbonyl)-*S*-methylisothiourea (53b):



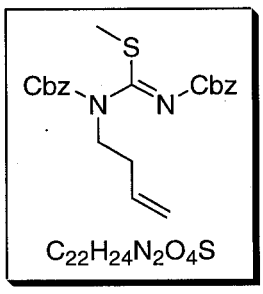
The product was synthesized using General Procedure B and was purified by flash chromatography (90% hexanes: 10% EtOAc) to give the product as a colourless oil (85%). R_f = 0.18 (90% hexanes: 10% EtOAc); IR (neat) ν 2955, 1728, 1613, 1384, 1344, 1252, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (10H, m), 5.90-5.77 (1H, m), 5.23 (1H, d, J = 17.5 Hz), 5.16 (1H, d, J = 10.5 Hz), 5.09 (2H, s), 5.06 (2H, s), 4.21 (2H, d, J = 6.0 Hz), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 158.4, 152.6, 135.4, 135.2, 132.2, 128.6, 128.4, 128.3 (2 signals), 128.2 (2 signals), 128.0, 118.3, 68.3, 51.4, 15.4; MS (EI) *m/e* (relative intensity) 398 (M^+, 1), 307 (3), 263 (3), 219 (3), 91 (100), 77 (8), 65 (17); HRMS (EI) (M^+) calcd 398.1300, found 398.1287.

N^1-But-3-enyl-N^1,N^2-bis-(*tert*-butoxycarbonyl)-*S*-methylisothiourea (54a):



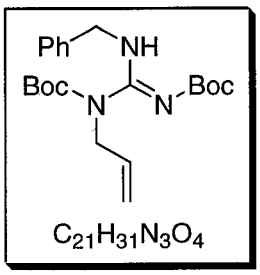
The product was synthesized using General Procedure B and was purified by flash chromatography (90% hexanes: 10% EtOAc) to give the product as a light yellow oil (97%). R_f = 0.35 (80% hexanes: 20% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, dddd, J = 17.0, 10.5, 7.0, 7.0 Hz), 5.11 (1H, d, J = 17.0 Hz), 5.04 (1H, d, J = 10.5 Hz), 3.60-3.56 (2H, m), 2.46-2.40 (2H, m), 2.39 (3H, s), 1.51 (9H, s), 1.49 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 157.8, 151.7, 134.6, 116.9, 82.2, 81.7, 48.2, 33.1, 27.9, 15.5.

N^1-But-3-enyl-N^1,N^2-bis-(benzyloxycarbonyl)-*S*-methylisothiourea (54b):



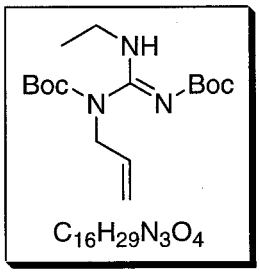
The product was synthesized using General Procedure B and was purified by flash chromatography (90% hexanes: 10% EtOAc) to give the product as a light yellow oil (88%). R_f = 0.32 (80% hexanes: 20% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (10H, m), 5.76-5.44 (1H, m), 5.09 (2H, s), 5.06 (2H, s), 5.09-4.98 (2H, m) 3.68-3.62 (2H, m), 2.42-2.32 (2H, m), 2.37 (3H, s); MS (EI) *m/e* (relative intensity) 412 (M^+, 1), 397 (3), 365 (4), 277 (4), 91 (100), 77 (7), 65 (17); HRMS (EI) (M^+) calcd 412.1458, found 412.1436.

N^1-Allyl-N^2-benzyl-N^1,N^2-bis(*tert*-butoxycarbonyl)guanidine (55a):



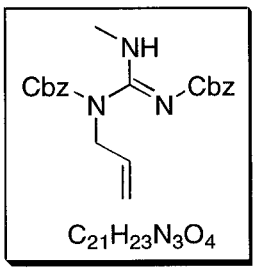
The product was synthesized using General Procedure C and was purified by flash chromatography (75% hexanes: 25% EtOAc with 1% Et_3N) to give the product as a light yellow oil (92%). R_f = 0.33 (75% hexanes: 25% EtOAc with 1% Et_3N); IR (neat) ν 3253, 2977, 1720, 1614, 1367, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.23 (5H, m), 5.82 (1H, dddd, *J* = 16.5, 10.0, 6.5, 6.5 Hz), 5.22 (1H, d, *J* = 17.0 Hz), 5.12 (1H, d, *J* = 10.0 Hz), 4.43 (2H, s), 4.27 (2H, d, *J* = 6.5 Hz), 1.49 (9H, s), 1.48 (9H, s) (one NH proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 128.9, 128.0, 127.8, 118.0, 50.1, 47.9, 28.2, 28.1 (4 quaternary carbons not observed); MS (EI) *m/e* (relative intensity) 390 (MH^+, 5), 334 (5), 277 (20), 260 (28), 233 (26), 214 (12), 174 (15), 124 (16), 106 (23), 91 (66), 57 (100); HRMS (EI) (MH^+) calcd 390.2393, found 390.2382.

N^1-Allyl-N^2-ethyl-N^1,N^2-bis(*tert*-butoxycarbonyl)guanidine (55b):



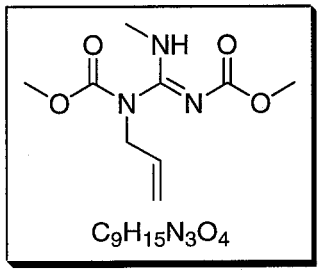
The product was synthesized using General Procedure C and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to give the product was a colourless oil (53%). R_f = 0.30 (80% hexanes: 20% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (1H, dddd, *J* = 17.0, 10.5, 6.5, 6.5 Hz), 5.20 (1H, d, *J* = 17.0 Hz), 5.13 (1H, d, *J* = 10.5 Hz), 4.25 (2H, d, *J* = 6.0 Hz), 3.29 (2H, q, *J* = 7.5 Hz), 1.50 (9H, s), 1.47 (9H, s), 1.23 (3H, t, *J* = 7.5 Hz) (one NH proton not observed).

N^1-Allyl-N^1,N^3-bis(benzyloxycarbonyl)-N^2-methylguanidine (55d):



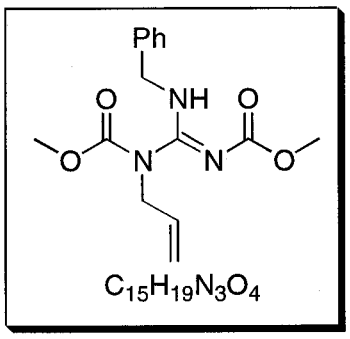
The product was synthesized using General Procedure C and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to give the product as a clear, colourless oil (57%). R_f= 0.24 (80% hexanes: 20% EtOAc); IR (neat) ν 3296, 2941, 1717, 1616, 1452, 1395, 1344, 1249, 1147, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.21 (10H, m), 5.84 (1H, dddd, *J* = 17.0, 10.5, 7.0, 7.0 Hz), 5.22-5.15 (2H, m), 5.19 (2H, s), 5.14 (2H, s), 4.35 (2H, br d, *J* = 5.5 Hz), 2.81 (3H, s) (one NH proton not observed); MS (EI) *m/e* (relative intensity) 381 (1, M^+), 298 (3), 232 (4), 165 (7), 128 (43), 108 (59), 91 (100); HRMS (EI) (M^+) calcd 381.1689, found 381.1691.

N^1-Allyl-N^2-methyl-N^1,N^3-bis-(methoxycarbonyl)-S-methylisothiourea (55e):



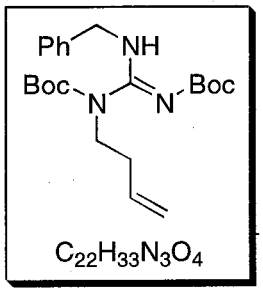
The product was synthesized using General Procedure C and was purified by flash chromatography (100% EtOAc with 1% Et_3N) to give the product was an amorphous solid (90%). R_f = 0.10 (100% EtOAc); IR (neat) ν 3303, 2976, 1728, 1619, 1439, 1266, 1150, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93-5.80 (1H, m), 5.30-5.11 (2H, m), 4.36 (2H, br s), 3.79 (3H, s), 3.72 (3H, s), 2.92 (3H, s); MS (EI) *m/z* (relative intensity) 230 (M^+, 84), 217 (37), 198 (44), 170 (66), 154 (34), 128 (60), 115 (39), 90 (27), 83 (39), 71 (51), 56 (100); HRMS (EI) (M^+) calcd. 229.1063, found 229.1065.

N^1-Allyl-N^2-benzyl-N^1,N^2-bis-(methyloxycarbonyl)guanidine (55f):



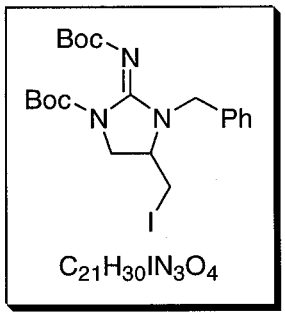
The product was synthesized using General Procedure C and was purified by flash chromatography (50% hexanes: 50% EtOAc with 1% Et_3N) to give the product as a clear, colourless oil (30%). R_f = 0.20 (50% hexanes: 50% EtOAc); IR (neat) ν 3317, 2955, 1717, 1612, 1537, 1439, 1249, 1157; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.18 (5H, m), 5.85-5.73 (1H, m), 5.25 (1H, d, *J* = 18.0 Hz), 5.18 (1H, d, *J* = 10.0 Hz), 4.43 (2H, s), 4.34-4.31 (2H, m), 3.76 (3H, s), 3.72 (3H, s) (one NH proton not observed).

N^2-Benzyl-N^1-but-3-enyl-N^1,N^3-bis-(*tert*-butoxycarbonyl)guanidine (56a):



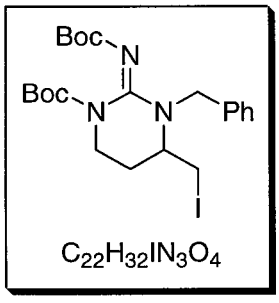
The product was synthesized using General Procedure C and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to give the product was a light yellow oil (90%). R_f = 0.29 (80% hexanes: 20% EtOAc); IR (neat) ν 3269, 2976, 2928, 1714, 1609, 1541, 1452, 1364, 1279, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (5H, m), 5.76 (1H, dddd, *J* = 17.0, 10.5, 6.5, 6.5 Hz), 5.09-4.99 (2H, m), 4.44 (2H, s), 3.78 (2H, t, *J* = 7.0 Hz), 2.32 (2H, dt, *J* = 7.5, 7.0 Hz), 1.49 (9H, s), 1.48 (9H, s) (one NH signal not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 135.3, 128.9, 127.9, 127.7, 116.8, 82.4, 79.4, 47.9, 47.0, 33.5, 28.2 (3 quaternary carbons not observed); MS (EI) *m/e* (relative intensity) 404 (24, MH^+), 403 (17, M^+), 303 (11), 291 (17), 273 (47), 247 (34), 106 (44), 91 (83), 57 (100); HRMS (EI) *m/e* (MH^+) calcd 404.2549, found, 404.2547.

3-Benzyl-2-*tert*-butoxycarbonylimino-4-iodomethyl-imidazolidine-1-carboxylic acid *tert*-butyl ester (57):



The product was synthesized using General Procedure D and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to give the product as a clear oil (18%). R_f = 0.29 (50% hexanes: 50% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (5H, m), 4.96 (1H, d, *J* = 15.5 Hz), 4.19 (1H, d, *J* = 15.5 Hz), 3.91 (1H, dd, *J* = 9.0, 9.0 Hz), 3.67 (1H, dd, *J* = 11.0 Hz, 4.0 Hz), 3.56-3.48 (1H, m), 3.17-3.10 (1H, m), 3.05-2.96 (1H, m), 1.53 (9H, s), 1.51 (9H, s).

3-Benzyl-2-*tert*-butoxylcarbonylimino-4-iodomethyl-tetrahydro-pyrimidine-1-carboxylic acid *tert*-butyl ester (58):



The product was synthesized using General Procedure D and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to give the product as a clear oil (11%). R_f = 0.40 (50% hexanes: 50% EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (5H, m), 5.44 (1H, d, *J* = 15.0 Hz), 4.13 (1H, d, *J* = 15.0 Hz), 4.00 (1H, dt, *J* = 13.0, 7.0 Hz), 3.56-3.43 (1H, m), 3.46-3.32 (1H, m), 3.23-3.15 (1H, m), 3.14-3.07 (1H, m), 2.11-1.98 (2H, m), 1.52 (9H, s), 1.50 (9H, s).

3.3.3.3 Palladium-Catalyzed π-Allyl General Procedures

General Procedure E - The Mitsunobu Reaction:

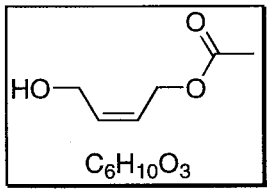
In a typical reaction, a solution of the bis-Boc-*S*-methyl isothiourea (1.75 mmol) in anhydrous THF (9 mL) was stirred with PPh_3 (2.63 mmol) and the alcohol (2.79 mmol) The mixture was stirred at r.t. under an atmosphere of N_2 and then diisopropyl azodicarboxylate (2.60 mmol) was slowly added. The orange mixture was stirred for 13 h, diluted with H_2O (30 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (silica gel, hexanes: EtOAc).

General Procedure F – The Guanylation Reaction in the Absence of a Metal:

In a typical reaction, a solution of anhydrous CH_3CN (10 mL) was added the *N*-substituted bis-Boc-*S*-methylisothiourea (1.9 mmol) and Et_3N (1.9 mmol, 1.0 equiv.). The amine (2.9 mmol, 2.0 equiv.) was then added and the mixture was stirred at r.t. for 16 h. The mixture was concentrated *in vacuo* and was the residue was taken up in CH_2Cl_2 (30 mL), washed with H_2O (2 x 30 mL) and brine (2 x 30 mL) and was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes: EtOAc) gave the product.

3.3.3.4 Palladium-Catalyzed π-Allyl Experimental Procedures

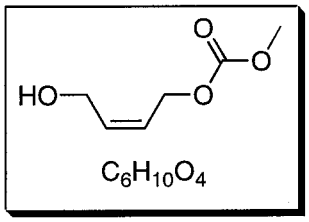
(*Z*)-1-Acetoxy-2-buten-4-ol (60a):



To a solution of the (*E*)-2-buten-1,4-diol (2.00 mL, 28.0 mmol) in anhydrous CH_2Cl_2 (140 mL) was added pyridine (3.41 mL, 42.1 mmol) and the mixture was cooled to 0 °C. Acetic anhydride (2.66 mL, 28.1 mmol) was then added and the mixture was stirred at 0 °C under an atmosphere of N_2. After 3 h, the solution was warmed to rt and was stirred for 16 h. The mixture was washed with 10 % NH_4Cl (1 x 40 mL) and the organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (50% hexanes: 50% EtOAc) gave the product as a colourless oil (1.51 g, 41%). R_f = 0.34 (50% hexanes: 50% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.89-5.79 (1H, m), 5.67-5.57 (1H, m), 4.67 (2H, d, J = 7.0 Hz), 4.26 (2H, d, J = 6.5 Hz), 2.55-2.29 (1H, br s), 2.07 (3H, s). This

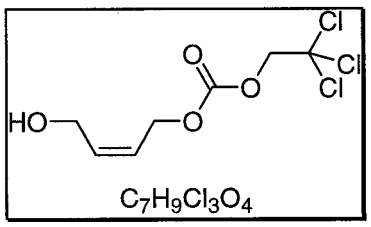
compounds has been previously characterized, see: Genet, J.-P.; Balabane, M.; Legras, Y. *Tetrahedron Lett.* **1982**, *23*, 331-334.

(Z)-Carbonic acid 4-hydroxy-but-2-enyl ester methyl ester (60b):



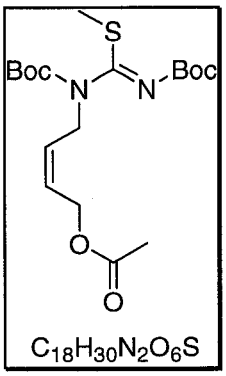
To a solution of the diol (17.1 g, 194 mmol) in anhydrous THF (400 mL) was added DMAP (2.37 g, 19.4 mmol) and Et_3N (27.1 mL, 194 mmol). The mixture was cooled to -78 °C and a solution of methyl chloroformate (15.0 mL, 194 mmol) in anhydrous THF (100 mL) was added dropwise using an addition syringe at a rate of 1 mL/min. The mixture was warmed to rt and stirred for 6 h. and was then concentrated *in vacuo*. The product was then distilled (bp 95 °C @ 1.0 mmHg) to the desired compound as a clear oil (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98-5.82 (1H, m), 5.72-5.60 (1H, m), 4.74 (2H, br d, J = 7.0 Hz), 4.27 (2H, br t, J = 6.0 Hz), 3.79 (3H, s) 2.20 (1H, br s); MS (EI) *m/e* (relative intensity) 128 (10, M^+), 116 (9), 84 (24), 77 (100); HRMS (EI) (M^+) calcd 128.0473, found 128.0473. This compound has been previously characterized, see: Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta.* **1993**, *76*, 23229-2337.

(Z)-Carbonic acid 4-hydroxy-but-2-enyl ester 2,2,2-trichloro-ethyl ester (60c):



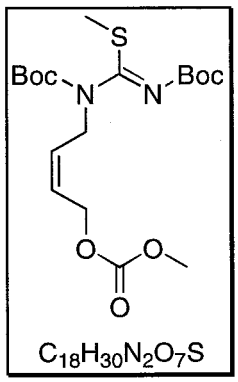
To a solution of (*E*)-2-buten-1,4-diol (1.00 g, 11.4 mmol) in anhydrous THF (60.0 mL) was added pyridine (1.38 mL, 17.0 mmol). The solution was stirred under an atmosphere of N_2 at -10 °C using an ice: salt water bath. To this solution was added 2,2,2-trichloroethyl chloroformate (1.56 mL, 11.3 mmol) and the mixture was allowed to warm to r.t. over a 3 h period. After 16 h of stirring at r.t., the mixture was diluted with 1M HCl (50 mL) and was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (60% hexanes: 40% EtOAc) gave the product as a clear oil (1.90 g, 63%). R_f = 0.19 (60% hexanes: 40% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97-5.91 (1H, m), 5.75-5.63 (1H, m), 4.84 (2H, d, J = 7.0 Hz), 4.77 (2H, s), 4.29 (2H, dd, J = 6.5, 6.0 Hz) (O-H proton not observed).

N^1,N^2-Bis-(*tert*-butoxycarbonyl)-N^1-but-2-enyl-4-acetoxy-*S*-methylisothiourea (61a):



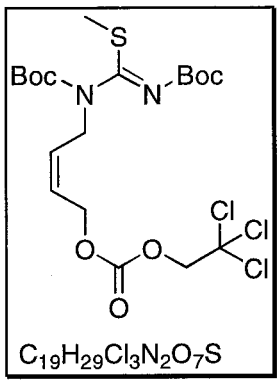
The product was synthesised using General Procedure E and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to give the product as a colourless oil (96%). R_f = 0.10 (80% hexanes: 20% EtOAc); IR (neat) ν 2978, 2933, 1721, 1621, 1455, 1368, 1246, 1142, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84-5.63 (2H, m), 4.68 (2H, d, J = 6.0 Hz), 4.25 (2H, d, J = 6.0 Hz), 2.39 (3H, s), 2.06 (3H, s), 1.51 (9H, s), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 162.6, 157.9, 151.7, 129.6, 126.7, 82.7, 81.8, 60.2, 45.9, 28.2 (2 signals), 21.0, 15.7; MS (EI) *m/z* (relative intensity) 402 (M^+, 1), 344 (2), 343 (5), 287 (5), 229 (6), 187 (22), 169 (3), 143 (6), 113 (10), 57 (100); HRMS (EI) (M^+) calcd 402.1825, found 402.1814.

N^1,N^2-Bis-(*tert*-butoxycarbonyl)-N^1-but-2-enyl-4-methylcarbonate-*S*-methylisothiourea (61b):



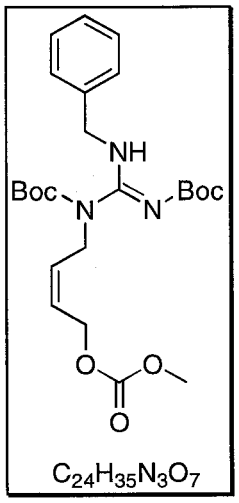
The product was synthesised using General Procedure E and was purified by flash chromatography (80% hexanes: 20% EtOAc) to give the product as a clear-colourless oil (96%). R_f = 0.28 (80% hexanes: 20% EtOAc); IR (neat) ν 2980, 2939, 1750, 1619, 1451,1366, 1282, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82-5.71 (2H, m), 4.76 (2H, d, J = 6.0 Hz), 4.26 (2H, d, J = 6.0 Hz), 3.79 (3H, s), 2.39 (3H, s), 1.52 (9H, s), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 157.7, 155.6, 151.5, 130.0, 126.0, 82.8, 81.9, 63.3, 54.8, 46.7, 28.0 (2 signals), 15.5; MS (EI) *m/z* (relative intensity) 418 (M^+, 24), 362 (37), 287 (5), 245 (10), 187 (34), 169 (5), 129 (7), 95 (6), 68 (7), 57 (100); HRMS (EI) (M^+) calcd 418.1774, found 418.1779.

N^1,N^2-Bis-(*tert*-butoxycarbonyl)-N^1-but-2-enyl-4-2,2,2-trichloroethyl ester-*S*-methylisothiourea (61c):



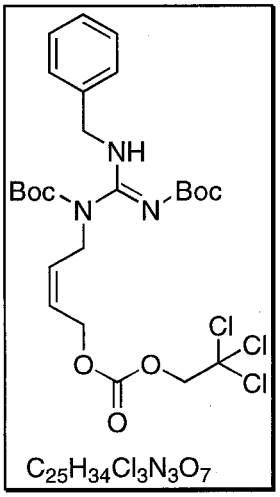
The product was synthesised using General Procedure E and was purified by flash chromatography (90% hexanes: 10% EtOAc) to give the product as a clear, colourless oil (99%). R_f = 0.29 (85% hexanes: 15% EtOAc); IR (neat) ν 2972, 2932, 1760, 1724, 1619, 1366, 1255, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86-5.70 (2H, m), 4.83 (2H, d, *J* = 6.0 Hz), 4.75 (2H, s), 4.25 (2H, d, *J*= 6.0 Hz), 2.38 (3H, s), 1.51 (9H, s), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 153.6, 130.7, 125.3, 82.9, 76.8, 64.3, 45.6, 28.2 (2 signals), 15.6 (one quaternary carbon not observed); MS (EI) *m/z* (relative intensity) 535 (M^+, 1), 480 (2), 381 (5), 363 (6), 343 (6), 287 (9), 231 (13), 187 (49), 143 (16), 91 (20), 57 (100); HRMS (EI) (M^+) calcd. 535.0839, found 535.0832.

N^2-Benzyl-N^1,N^3-Bis-(*tert*-butoxycarbonyl)-N^1-but-2-enyl-4-methylcarbonate-guanidine (62b):



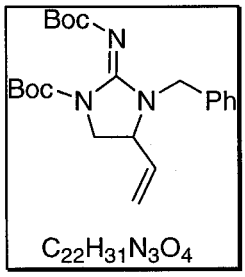
The product was synthesized using General Procedure F and was purified by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) to give the product as a colourless, highly viscous oil (98%). R_f = 0.16 (80% hexanes: 20% EtOAc); IR (neat) ν 3284, 2979, 1750, 1717, 1616, 1447, 1366, 1262, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80-9.60 (1H, br s), 7.34-7.24 (5H, m), 5.71-5.56 (2H, m), 4.76 (2H, d, *J* = 6.0 Hz), 4.40 (2H, s), 4.34 (2H, d, *J* = 6.0 Hz), 3.75 (3H, s), 1.48 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 152.8, 136.5, 129.7, 128.9, 127.9, 127.7, 126.6, 83.0, 79.3, 63.4, 54.7, 47.9, 44.3, 28.1; MS (EI) *m/e* (relative intensity) 478 (MH^+, 1), 421 (5), 402 (8), 365 (6), 346 (22), 290 (52), 272 (83), 246 (66), 228 (21), 202 (15), 91 (83), 57 (100); HRMS (EI) (MH^+) calcd 478.2553, found 478.2547.

N^2-Benzyl-N^1,N^3-Bis-(*tert*-butoxycarbonyl)-N^1-but-2-enyl-4-2,2,2-trichloroethyl ester-guanidine (62c):



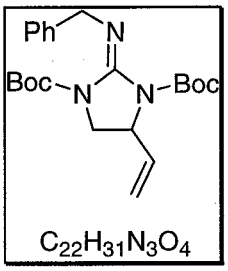
The product was synthesized using General Procedure F and was purified by flash chromatography (90% hexanes: 10% EtOAc with 1% Et_3N) to give the product as a clear viscous oil (91%). R_f = 0.33 (70% hexanes: 30% EtOAc); IR (neat) ν 3277, 2972, 1760, 1710, 1612, 1538, 1451, 1370, 1238, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, br s), 7.37-7.24 (5H, m), 5.74-5.59 (2H, m), 4.86 (2H, d, *J* = 6.0 Hz), 4.73 (2H, s), 4.40 (2H, s), 4.35 (2H, d, *J* = 6.0 Hz), 1.48 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.8, 136.5, 130.3, 128.9, 128.0, 127.7, 126.0, 94.4, 83.1, 79.4, 76.8, 64.5, 47.9, 44.3, 28.1 (2 quaternary carbons were not observed); MS (EI) *m/e* (relative intensity) 594 (MH^+, 1), 464 (2), 420 (5), 346 (5), 290 (15), 272 (31), 246 (17), 228 (13), 202 (6), 184 (8), 136 (12), 106 (13), 91 (100) 57 (45); HRMS (EI) (MH^+) calcd 594.1541, found 594.1549.

3-Benzyl-2-tert-butoxycarbonylimino-4-vinyl-imidazolidine-1-carboxylic acid tert-butyl ester (64):



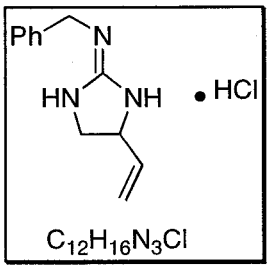
A flame-dried Schlenk flask was cooled under a steady stream of N_2 and was charged with a Pd source, as indicated on Table 3.3, PPh_3 (Ligand:Pd = 3:1), anhydrous THF, and Et_3N (1.1 equiv). The mixture was stirred at r.t. for 1 h and then a solution of the guanidine (0.120 mmol, 1.0 equiv) in anhydrous THF was added via a syringe. The mixture was stirred for 16 h. and was then concentrated *in vacuo*. Purification by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) gave the product as a clear oil (Table 3.3). R_f = 0.24 (80% hexanes: 20% EtOAc); IR (neat) ν 2969, 1751, 1677, 1619, 1361, 1252, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (5H, m), 5.64 (1H, ddd, *J* = 17.0, 10.0, 8.5 Hz), 5.28 (1H, d, *J* = 10.0 Hz), 5.17 (1H, d, *J* = 17.0 Hz), 5.08 (1H, d, *J* = 15.0 Hz), 3.93 (1H, m), 3.93 (1H, d, *J* = 15.0 Hz), 3.92-3.81 (1H, m), 3.56 (1H, dd, *J* = 10.5, 5.5 Hz), 1.54 (9H, s), 1.49 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 151.4, 149.9, 135.8, 134.5, 128.5, 128.4, 127.5, 120.5, 82.5, 78.8, 56.3, 49.7, 45.9, 28.2, 28.0.

2-Benzylimino-4-vinyl-imidazolidine-1,3-dicarboxylic acid di-*tert*-butyl ester (66):



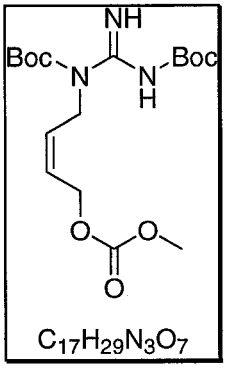
A flame-dried Schlenk flask was cooled under a steady stream of N_2 and was charged with a Pd source, as indicated on Table 3.4, PPh_3 (Ligand:Pd = 3:1), anhydrous THF, and Et_3N (1.1 equiv). The mixture was stirred at r.t. for 1 h and then a solution of the guanidine (0.120 mmol, 1.0 equiv) in anhydrous THF was added via a syringe. The mixture was stirred for 16 h. and was then concentrated *in vacuo*. Purification by flash chromatography (80% hexanes: 20% EtOAc with 1% Et_3N) gave the product as a clear oil (Table 3.4). R_f = 0.35 (80% hexanes: 20% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 7.49-7.18 (5H, m), 5.92-5.70 (1H, m), 5.38-5.09 (2H, m), 4.84 (1H, dd, *J* = 26.0, 16.5 Hz), 4.71-4.49 (1H, m), 4.37 (1H, dd, *J* = 26.0, 16.5 Hz), 3.95-3.77 (1H, m), 3.71-3.52 (1H, m), 1.50 (18H, s); MS (EI) *m/e* (relative intensity) 401 (M^+, 1), 345 (10), 289 (100), 244 (83), 200 (51), 131 (10), 106 (16), 91 (28), 57 (63); HRMS (EI) (M^+) calcd. 401.2315, found 401.2309.

2-Benzyl-5-vinyl-imidazolidin-2-ylideneamine Hydrochloride (66a):



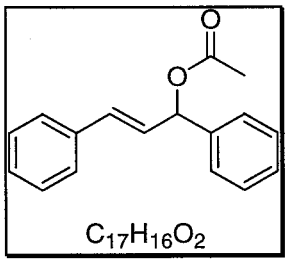
To an aqueous solution of 1M HCl (5 mL) was added the di-Boc protected guanidine (0.109 g, 0.271 mmol) along with DME (1mL). The light brown mixture was stirred vigorously at rt for 16 h and was then concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 and silica gel was added. The slurry was concentrate *in vacuo* to give a free flowing silica gel-product mixture which was loaded onto a pre-packed column and was purified by flash chromatography (silca gel, 90 % CH_2Cl_2: 10 % MeOH) to give the product as a light brown amorphous solid (0.049 g, 76 %). R_f = 0.12 (90 % CH_2Cl_2: 10 % MeOH); IR (KBr) ν 3380, 3169, 1669, 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83-8.50 (1H, br s), 8.60-8.38 (1H, br s), 8.00-7.65 (1H, br s), 7.34-7.24 (5H, m), 5.76-5.65 (1H, m), 5.23 (1H, d, *J* = 17.5 Hz), 5.17 (1H, d, *J* = 10.5 Hz), 4.52 (2H, s), 4.42-4.21 (1H, br s), 3.68 (1H, dd, *J* = 9.5, 8.5 Hz), 3.26 (1H, dd, *J*= 7.5, 7.5 Hz), 2.09 (broad H_2O signal); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 136.0, 135.1, 128.7, 127.9, 127.6, 118.4, 57.5, 48.6, 46.7; MS (EI) *m/e* (relative intensity) 202 (MH^+, 100), 201 (M^+, 68), 200 (49), 174 (9), 124 (8), 110 (6), 106 (27), 96 (10), 91 (54), 81 (20), 56 (23); HRMS (EI) (M^+) calcd 201.1266, found 201.1263.

N^1,N^3-Bis-(*tert*-butoxycarbonyl)-N^1-but-2-enyl-4-methylcarbonate-guanidine (67):



The product was synthesised using General Procedure E and was purified by flash chromatography (85% hexanes: 15% EtOAc with 1% Et_3N) to give the product as a light orange-viscous oil (99 %). R_f = 0.53 (70 % hexanes: 30 % EtOAc); IR (neat) ν 3394, 3281, 2954, 1753, 1715, 1648, 1616, 1511, 1440, 1370, 1268, 1148, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.26 (1H, br s), 9.13 (1H, br s), 5.71-5.58 (2H, m), 4.88 (2H, d, *J* = 5.0 Hz), 4.58 (2H, d, *J* = 5.5 Hz), 3.78 (3H, s), 1.51 (9H, s), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 160.0, 155.7, 154.7, 130.1, 125.4, 84.2, 78.7, 64.0, 54.7, 42.1, 28.4, 28.0; MS (EI) *m/e* 388 (MH^+, 3), 331 (6), 275 (32), 256 (16), 230 (9), 214 (19), 200 (100); HRMS (EI) (MH^+) calcd 388.2084, found 388.2092.

(Z)-Acetic acid 1,3-diphenyl-allyl ester (78):



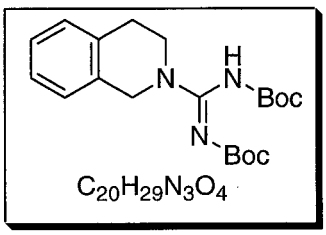
A solution of bromobenzene (5.3 mL, 50 mmol) in anhydrous Et_2O (50 mL) was placed in a dropping funnel and 1/3 of this solution was added to a round-bottom flask containing Mg turnings (1.2 g, 50 mmol). The round-bottom flask was fitted with a condenser and the dropping funnel was placed on top of the condenser. The reaction mixture was heated using a heating mantle until the solution became cloudy and refluxed. The heating mantle was removed and the bromobenzene solution was added dropwise over 30 min. to maintain reflux. Once all of the bromobenzene was added, the mixture was refluxed for 15 min. using a heating mantle.

To the freshly made Grignard reagent was added cinnamaldehyde (6.3 mL, 50 mmol) in dry Et_2O (10 mL) over a 15 min. period. This mixture was stirred at rt for 1 h and was then quenched with sat. aq. NH_4Cl (30 mL) and was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (1 x 50 mL) and were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. No purification of the resulting alcohol was performed.

To a solution of the alcohol (8.87 g, 42.2 mmol) was added pyridine (20 mL) and acetic anhydride (4.40 mL, 46.6 mmol). After stirring for 18 h at rt under an atmosphere of N_2, the mixture was concentrated *in vacuo*. The residue was diluted with H_2O (20 mL) and was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with H_2O (1 x 20

mL) and brine (3 x 20 mL) and were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was distilled at 165-171 °C (1.5 mmHg) to yield the desired acetate as a light yellow oil (7.97 g, 63 % over 3 steps). R_f = 0.49 (90 % hexanes: 10 % EtOAc); bp 165-171 °C (1.5 mmHg, oil bath); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.22 (10H, m), 6.63 (1H, d, *J* = 16.0 Hz), 6.44 (1H, d, *J* = 7.0 Hz), 6.35 (1H, dd, *J* = 16.0, 7.0 Hz), 2.14 (3H, s). Experimental reference: Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2044.

N^1,N^2-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine (79):



The product was synthesised using General Procedure A and was purified by flash chromatography (80% hexanes:20% EtOAc) to yield a clear oil (86%). R_f = 0.28 (80% hexanes:20% EtOAc); IR (neat) ν 3104, 2978, 1747, 1614, 1415, 1366, 1299, 1146, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (1H, bs), 7.19-7.09 (4H, m), 4.71 (2H, bs), 3.77 (2H, bs), 2.97 (2H, t, *J* = 6.0 Hz), 1.51 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 134.6, 132.7, 128.3, 126.7, 126.3, 126.2, 82.2, 79.4, 48.8, 45.0, 28.6, 28.2, 28.1 (2 quaternary carbons not observed); MS (EI) *m/e* 375 (6, M^+), 319 (19), 263 (61), 246 (32), 219 (40), 174 (27), 132 (87), 131 (29), 59 (30), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{20}H_{29}N_3O_4$) 375.2158, found 375.2141.

3.4 References

(1) Berlinck R. G. S. *Nat. Prod. Rep.* **2002**, *19*, 617-649.

(2) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339-365.

(3) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377-409.

(4) Hemscheidt, T.; Burgoyne, D. L.; Moore, R. E. *Chem. Commun.* **1995**, 205-206.

(5) Moore, B. S.; Ohtani, I.; De Koning, C. B.; Moore, R. E.; Carmichael, W. W. *Tetrahedron Lett.* **1992**, *33*, 6595-6598.

(6) Mahmood, N. A.; Carmichael, W. W. *Toxicon* **1987**, *25*, 1221-1227.

(7) Matsunaga, S.; Moore, R. E.; Niemczura, W. P.; Carmichael, W. W. *J. Am. Chem. Soc.* **1989**, *111*, 8021-8023.

(8) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brosse, C. D.; Mai, S.; Truneh, A.; Carte, B.; et al. *J. Org. Chem.* **1995**, *60*, 1182-1188.

(9) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814-1819.

(10) DeMong, D. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 3529-3532.

(11) Snider, B. B.; Xie, C. *Tetrahedron Lett.* **1998**, *39*, 7021-7024.

(12) McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849-1853.

(13) Heintzelman, G. R.; Parvez, M.; Weinreb, S. M. *Synlett* **1993**, 551-552.

(14) Looper, R. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 769-771.

(15) Xie, C.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017-5024.

(16) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330-7335.

(17) Agami, A.; Couty, F.; Venier, O. *Synlett* **1995**, 1027-1028.

(18) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *J. Org. Chem.* **1997**, *62*, 2106-2112.

(19) Friesen, R. W.; Giroux, A. *Can. J. Chem.* **1994**, *72*, 1857-1865.

(20) Friesen, R. W. *Tetrahedron Lett.* **1990**, *31*, 4249-4252.

(21) Friesen, R. W.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 4888-4895.

(22) Friesen, R. W.; Giroux, A.; Cook, K. L. *Tetrahedron Lett.* **1993**, *34*, 5983-5986.

(23) Friesen, R. W.; Blouin, M. *J. Org. Chem.* **1993**, *58*, 1653-1654.

(24) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1991**, *32*, 6359-6362.

(25) Kimura, M.; Saeki, N.; Uchida, S.; Harayama, H.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7611-7614.

(26) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752-3757.

(27) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571.

(28) Watanabe, M.; Okada, H.; Teshima, T.; Noguchi, M.; Kakehi, A. *Tetrahedron* **1996**, *52*, 2827-2838.

(29) Noguchi, M.; Okada, H.; Watanabe, M.; Okuda, K.; Nakamura, O. *Tetrahedron* **1996**, *52*, 6581-6590.

(30) Okawa, T.; Eguichi, S.; Kakehi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 247-254.

(31) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615-2649.

(32) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-393.

(33) Trost, B. M. *Pure Appl. Chem.* **1981**, *53*, 2357-2370.

(34) Trost, B. M. *Chemtracts: Organic Chemistry* **1988**, *1*, 415-435.

(35) Trost, B. M. *Angew. Chem. Int. Ed.* **1989**, *28*, 1173-####.

(36) Trost, B. M. *ACS Adv. Chem.* **1992**, *230*, 463-478.

(37) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: New York, 1980.

(38) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197-206.

(39) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361-4401.

(40) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.

(41) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975-1015.

(42) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033-2046.

(43) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046-2054.

(44) Andersson, P. G.; Harden, A.; Tanner, D.; Norrby, P.-O. *Chem. Eur. J.* **1995**, *1*, 12-16.

(45) Gogoll, A.; Oernebro, J.; Grennberg, H.; Baeckvall, J.-E. *J. Am. Chem. Soc.* **1994**, *116*, 3631-3632.

(46) Fagnou, K.; Lautens, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 26-47.

(47) Hansson, S.; Norrby, P. O.; Soegren, M. P. T.; Aakermark, B.; Cucciolito, M. E.; Giordano, F.; Vitagliano, A. *Organometallics* **1993**, *12*, 4940-4948.

(48) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; 2 ed.; University Science Books: Sausalito, California, 1999.

(49) Larsson, A. L. E.; Gatti, R. G. P.; Backvall, J.-E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2873-2877.

(50) Aggarwal, V. K.; Monteiro, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2531-2537.

(51) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143-10144.

(52) Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36*, 8737-8740.

(53) Tietze, L. F.; Schirok, H. *Angew. Chem. Int. Ed.* **1997**, *36*, 1124-1125.

(54) Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881-6882.

(55) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689-1708.

(56) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1987**, *28*, 4837-4840.

(57) Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12-13.

(58) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7667-7680.

(59) Buchi, G.; Rodriguez, A. D.; Yakushijin, K. *J. Org. Chem.* **1989**, *54*, 4494-4496.

(60) March, J. *Advanced Organic Chemistry*; 4 ed.; John Wiley & Sons: New York, 1992.

(61) Buncel, E.; Hoz, S. *Tetrahedron Lett.* **1983**, *24*, 4777-4780.

(62) Laloi-Diard, M.; Verchere, J. F.; Gosselin, P.; Terrier, F. *Tetrahedron Lett.* **1984**, *25*, 1267-1268.

(63) Wolfe, S.; Mitchell, D. J.; Schlegel, H. B.; Minot, C.; Eisenstein, O. *Tetrahedron Lett.* **1982**, *23*, 615-618.

(64) Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.*, in press.