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

David A. Powell, Philip D. Ramsden, and Robert A. Batey*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

rbatey@chem.utoronto.ca

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An operationally straightforward and efficient method for the alkylation of carbamate-protected guanidines with various alkyl halides and mesylates is described. This protocol proceeds via deprotonation of the acidic *N*-carbamate hydrogen of the guanidine under biphasic conditions using a catalytic amount of a tetrabutylammonium salt as a phase-transfer catalyst. In this manner, highly functionalized guanidines can be obtained. The reaction is tolerant of a wide range of functional groups on both the alkyl halide and guanidine component. In addition, the reaction is sufficiently mild such that simple aqueous workup and filtration through a short silica gel column yields the substituted guanidines in high purity. In conjunction with the EDCI-mediated guanylation of disubstituted thioureas with amines, phase-transfer catalyzed alkylation of guanidines via a one-pot, three-component synthesis of substituted guanidines was achieved.

A growing number of biologically and pharmaceutically relevant compounds incorporate guanidine functionality. Guanidine secondary metabolites, for example,[1] occur in a variety of species and display a correspondingly diverse range of structures, substitution patterns, and biological behavior.[2] Moreover, guanidines are also present in pharmaceuticals,[3] such as the synthetically derived influenza inhibitor zanamivir.[4] Substituted guanidines, whether of natural or unnatural origin, pose significant challenges as synthetic targets. Multiple substitution patterns are possible for guanidines, including alkyl and aryl substituents, present at varying oxidation states. Furthermore, the high basicity and polarity, and consequent water solubility of many guanidines, also cause considerable practical difficulties. These considerations place stringent limitations on the synthetic planning for complex guanidines, both strategically and tactically. New methods for guanidine synthesis are required to address their increasing importance as natural product and pharmaceutical targets.

Guanylation and Guanidinylation Methods. In this paper, we refer to the conversion of an amine to a guanidine, where the amine nitrogen is incorporated into the newly formed guanidine functional group, as a *guanylation*,[5] since this reaction formally involves the attachment of a $-C(=NH)NH_2$ group (or substituted derivative), traditionally referred to as a *guanyl* group.[6] Most guanylating methods involve the reaction of a primary or secondary amine **1** with guanylating reagents of general structure **2**. Improvements to this process have focused on the use of more electrophilic amidine species and better leaving groups that can be displaced under milder conditions (Scheme 1).[7−12] Significant advances in guanidine synthesis were achieved with the introduction

* To whom correspondence should be addressed. Tel/Fax: (416) 978-5059.

(1) (a) *Guanidines: Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds*; Mori, A.; Cohen, B. D.; Lowenthal, A. Eds.; Plenum Press: New York, 1985. (b) *Guanidines 2: Further Explorations of the Biological and Clinical Significance of Guanidino Compounds*; Mori, A., Cohen, B. D., Koide, H., Eds.; Plenum Press: New York, 1987.

(2) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339−365 and references therein.

(3) Greenhill, J. L.; Lue, P. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science: New York, 1993; Vol. 30, Chapter 5.

(4) (a) von Itzstein, M.; Wu, W.-Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan, T. V.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418−423. (b) Howes, P. D.; Smith, P. W. *Tetrahedron Lett.* **1996**, 37, 6595−6598. (c) Staschke, K. A.; Colacino, J. M.; Baxter, A. J.; Air, G. M.; Bansal, A.; Hornback, W. J.; Munroe, J. E.; Laver, W. G. *Virology* **1995**, *214*, 642−646.

(5) There is little consensus in the literature over the use of the terms *guanylation* and *guanidinylation*. For a thorough discussion of guanidine terminology as used in the scientific community, see: Jones, J. H. *J. Peptide Sci.* **2002**, *8*, 285−287.

(6) The term *guanyl* has officially been superseded by the term *carbamimidoyl*, and this conversion should technically be referred to as a *carbamimidoylation*; however, this is a rather laborious term and is rarely used in the literature.

(7) For guanylations with reagent **2a**, see: Hg promoted: (a) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 3138−3141. (b) Zhang, J.; Shi, Y.; Stein, P.; Atwal, K.; Li, C. *Tetrahedron Lett.* **2002**, *43*, 57−59. (c) Cunha, S.; Costa, M. B.; Napolitano, H. B.; Lariucci, C.; Vencato, I. *Tetrahedron* **2001**, *57*, 1671−1675. (d) Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron*, **1997**, *53*, 5291−5304. (e) Jirgensons, A.; Kums, I.; Kauss, V.; Kalvins, I. *Synth. Comm.* **1997**, *27*, 315−322. (f) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *48*, 7677−7680. EDCI promoted: (g) Manimala, J. C.; Anslyn, E. V. *Tetrahedron Lett.* **2002**, *43*, 565−567. (h) Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566−1568. (i) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933−5936. Other promoters: (j) Guisado, O.; Martínez, S.; Pastor, J. *Tetrahedron Lett.* **2002**, *43*, 7105−7109.

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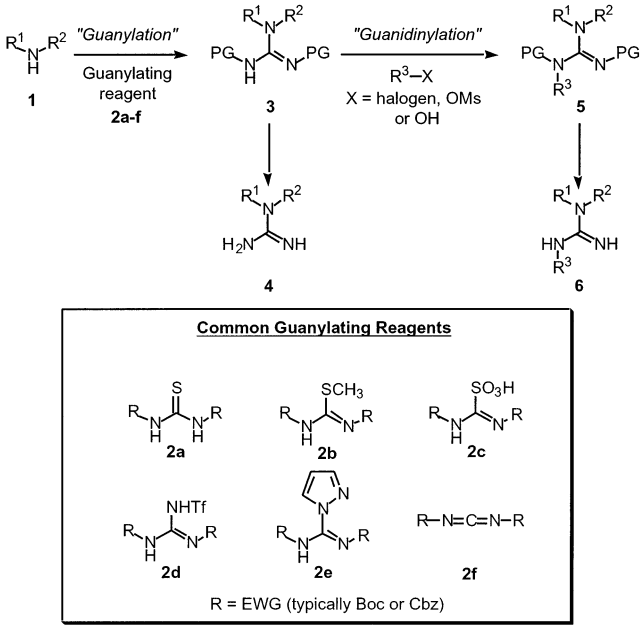
SCHEME 1



of more activated carbamate-protected (typically Boc or Cbz) guanylating reagents **2** that allow for the direct synthesis of protected guanidines. Unlike free guanidines, protected guanidines are less polar and basic and can be easily purified by chromatography and utilized in subsequent reactions. Though much progress has been made in the range of primary or secondary amines which can be guanylated to give **3** (Scheme 1), this transformation remains fundamentally restricted to the synthesis (following deprotection) of mono- or N^1,N^1-disubstituted guanidines **4**.[13] Entry into more highly and differentially substituted guanidines is often required. Consequently, methods wherein guanidines of general type **3** could, by virtue of their fairly acidic N−H protons, be further functionalized with a variety of electrophiles are of clear value. Such methods would also expand the range of substrates that could be converted into guanidine products, as currently amines serve as the most common entry point into guanidine-containing compounds. This type of reaction, in which an electrophile is reacted with a nucleophilic guanidine **3**, to give a more highly substituted guanidine **5**, we refer to as a *guanidinylation*[14] (Scheme 1), as here a *guanidino* moiety −NH(C=NH)-NH_2 is introduced onto the alkyl halide/alcohol.[15] Thus, we propose a clear distinction between the terms *guanylation* and *guanidinylation*, which are often confusingly used in an interchangeable manner. [16]

In contrast to the significant number of guanylation methods available for the synthesis of guanidines, to the best of our knowledge, there are only two methods that are commonly used for the further functionalization of protected guanidines of general structure **3**.[17−20] The first involves deprotonation of guanidine **3** (PG = Boc) with NaH followed by reaction with an alkyl halide to give the functionalized guanidine **5** (Scheme 1).[21] Although the reaction works for certain alkyl halides including methyl iodide and benzyl bromide, less reactive substrates such as 2-iodopropane and *n*-butyl bromide give lower yields of product (50% and 45%, respectively). In

(8) For guanylations with reagent **2b**, see: (a) Moroni, M.; Koksch, B.; Osipov, S. N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K. *J. Org. Chem.* **2001**, *66*, 130−133. (b) Guo, Z.-X.; Cammidge, A. N.; Horwell, D. C. *Synth. Comm.* **2000**, *30*, 2933−2943. (c) Miel, H.; Rault, S. *Tetrahedron Lett.* **1998**, *39*, 1565−1568. (d) Elliott, A. J.; Morris, P. E., Jr.; Petty, S. L.; Williams, C. H. *J. Org. Chem.* **1997**, *62*, 8071−8075. (e) Chandrakumar, N. S. *Synth. Comm.* **1996**, *26*, 2613−2616. (f) Yuan, C.; Williams, R. M. *Tetrahedron Lett.* **1996**, *37*, 1945−1948. Silver promoted: (g) Chen, B.-C.; Shiu, S.; Yang, D.-Y. *J. Chin. Chem. Soc.* **1998**, *45*, 549−553. (h) Feldman, P. L. *Tetrahedron Lett.* **1991**, *32*, 875−878.

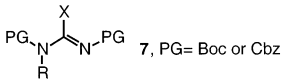
(9) For guanylations with reagent **2c,** see: (a) Miller, A. E.; Bischoff, J. J. *Synthesis* **1986**, 777−779. For examples where R = H, see: (b) Jursic, B. S.; Neumann, D.; McPherson, A. *Synthesis* **2000**, 1656−1658. (c) Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882−1884.

(10) For guanylations with reagent **2d**, see: (a) Goodman, M.; Zapf, C.; Rew, Y. *Biopolymers* **2001**, 60, 229−245. (b) Zapf, C. W.; Creighton. C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133−1136. (c) Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1038−1042. (d) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804−3805.

(11) For guanylations with reagent **2e**, see: (a) Ghosh, A. K.; Hol, W. G. J.; Fan, E. *J. Org. Chem.* **2001**, *66*, 2161−2164. (b) Drake, B.; Patek, M.; Lebl, M. *Synthesis* **1994**, 579−582. (c) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389−3392.

(12) For guanylations with other reagents, see: (a) Wu, Y.-Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. *J. Org. Chem.* **2002**, *67*, 7553−7556 (b) Musiol, H.-J.; Moroder, L. *Org. Lett.* **2001**, *3*, 3859−3861. (c) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080−8082. (d) Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770−7773. (e) Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7779−7785. (f) Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7774−7778. (g) Kent, D. R.; Cody, W. L.; Doherty, A. M. *Tetrahedron Lett.* **1996**, *37*, 8711−8714.

(13) There have been some reports on the synthesis and reaction of guanylating reagents of general structure **7** (where X = SCH_3 or pyrazole) with primary or secondary amines, although the yields for this type of reaction are generally low and require forcing conditions; see: (a) Pátek, M.; Smrcina, M.; Nakanishi, E.; Izawa, H. *J. Comb. Chem.* **2000**, *2*, 370−377. (b) Kim, H.-O.; Mathew, F.; Ogbu, C. *Synlett* **1999**, 193−194.



7, PG= Boc or Cbz

(14) The terms guanidinylation and guanylation have previously been used interchangeably to describe the same conversion (an amine to a guanidine), despite the strictly incorrect use of the word guanidinylation for this reaction (guanidinylation of an amine would imply the conversion $-NH_2$ to $-NH-NH(C=NH)NH_2$). The terminology outlined in this paper avoids such confusions.

(15) Of course, this transformation can also formally be classified as an alkylation of a guanidine (i.e., for the case where R^3 = alkyl, Scheme 1). For intermolecular reactions, the usage of these descriptions will depend on the degree of complexity associated with the guanidine and the alkylating group. In the case where the alkylating group R^3-X is the more complex component, the reaction can be described as a guanidinylation of R^3-X.

(16) This terminology is different from that proposed by Jones, who does not distinguish between the two reaction types and favors the use of guanidinylation to describe the conversion of an amine to a guanidine (see ref 5).

(17) Unprotected guanidines, which are considerably more nucleophilic than their carbamate-protected counterparts, can be further functionalized under a variety of conditions, including conjugate addition, addition to aldehydes/ketones, and nucleophilic displacement. For some representative examples, see refs 18−20.

(18) Conjugate additions: (a) Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547−6554 (b) Louwrier, S.; Tuynman, A.; Hiemstra, H. *Tetrahedron* **1996**, *52*, 2629−2646. (c) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828−3839.

(19) Addition of unprotected guanidines to aldehydes/ketones and nucleophilic displacements: (a) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Org. Lett.* **2002**, *4*, 2679−2682. (b) Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. *Org. Lett.* **2002**, *4*, 177−180. (c) Franklin, A. S.; Gilbert, S. K. L.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512−1519. (d) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697−5700. (e) Xie, C.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017−5024.

addition, the strongly basic conditions employed are not tolerated by base-sensitive functional groups such as esters. The second method involves the reaction of guanidine **3** with a primary or secondary alcohol under Mitsunobu conditions.[22] This method is more general and works well for a wide variety of alcohols; however, it requires expensive stoichiometric coupling reagents, which often complicate the purification procedure.

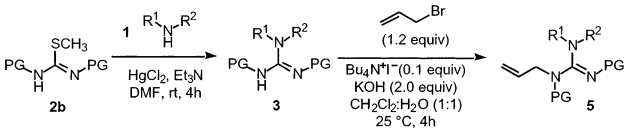
Herein, we describe a relatively mild and efficient protocol for the guanidinylation of various alkyl halides in a biphasic medium containing an aqueous solution of KOH, an organic solvent, and a catalytic amount of a phase-transfer catalyst (PTC). This procedure is scaleable to multigram quantities, yielding highly functionalized and protected guanidines **5** that are readily purified.

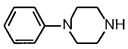
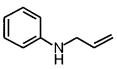
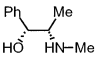
Synthesis. Guanidines **3** were prepared, using a known procedure,[8b,e] in good to excellent yields by reaction of amines **1** with N^1,N^2-bis-(Boc or Cbz)-*S*-methylisothiourea **2b**[23] in the presence of a mercury(II) salt promoter (Table 1). The protected guanidines were then alkylated with 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 4 h, simple aqueous workup and purification through a short silica gel column, to remove the PTC, yielded the corresponding substituted guanidines **5**. Both the Boc- and Cbz-protected pyrrolidine-derived guanidines were readily allylated under the reaction conditions in excellent yields (Table 1, entries 1 and 2). The N^1,N^2-bis-Boc-guanidine (Table 1, entry 3) was regioselectively allylated at one of the carbamate nitrogens. Alkylation of this substrate under phase-transfer conditions provides an alternative method for the synthesis of monosubstituted guanidines from alkyl bromides under milder conditions than previously reported.[21] Furthermore, alkylation occurs only once even in the presence of a large excess of allyl bromide (5 equiv), with extended reaction times (24 h) or with heating (50 °C). Other N^1,N^2-bis-Boc-N^3,N^3-disubstituted guanidines were similarly allylated in high yield (Table 1, entries 4−11). The reaction is tolerant to a wide range of functional groups on the guanidine including esters, amines, ketones, alcohols, and alkenes. Competitive hydrolysis of the ethyl ester in substrate **3e** was minimized by reducing the reaction time. (−)-Ephedrine-derived guanidine **3k** was allylated in 78% yield to give protected guanidine **5k**.[24] Deprotection of the Boc groups using 1 M aqueous HCl gave the optically active trisubstituted guanidine **6k** as an HCl salt in 64% yield (Table 1, entry 11).

The procedure is readily adapted to larger scales, as exemplified by the allylation of the tetrahydroisoquinoline-derived guanidine **3g**, which was conducted on a 12.0 g (31.2 mmol) scale (Table 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, using aqueous 1 M HCl, to yield the trisubstituted guanidine **6g** as the HCl salt in 90% yield.

Unfortunately, reaction of primary amine derived guanidines **3**, where R^2 = H, with alkyl halides under the biphasic conditions proved to be problematic as these classes of compounds contain two possible alkylation sites. For example, reaction of N^1,N^2-bis-Boc-N^3-phe-

TABLE 1. Phase-Transfer Catalyzed Alkylation of Guanidines 3 with Allyl Bromide



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	Boc	**3c**	99[b]	**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] (90)[g]
8		Boc	**3h**	89	**5h**	96
9		Boc	**3i**	78	**5i**	91
10		Boc	**3j**	69	**5j**	91
11		Boc	**3k**	87	**5k**	78 (64)[g]

[a] Isolated yield. [b] Guanylation carried out in the absence of $HgCl_2$. [c] Reaction carried out for 2 h. [d] Reaction conducted on a 31 mmol scale. [e] Yield with Bu_4NBr as the PTC. [f] Yield with Bu_4NCl as the PTC. [g] Yield of the corresponding HCl salt after deprotection of both Boc groups.

(20) Other reactions of unprotected guanidines: (a) Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2001**, *66*, 3167−3175. (b) Coffey, D. S.; Overman, L. E. Stappenbeck, F. *J. Am. Chem. Soc.* **2000**, *122*, 4904−4914. (c) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893−4903. (d) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520−1528.

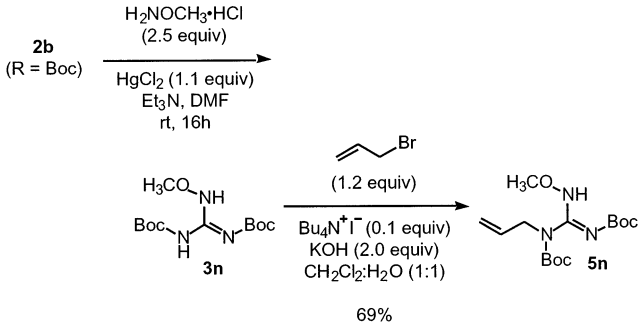
(21) (a) Ko, S. Y.; Lerpiniere, J.; Christofi, A. M. *Synlett* **1995**, 815−816. (b) Vaidyanathan, G.; Zalutsky, M. R. *J. Org. Chem.* **1997**, *62*, 4867−4869.

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

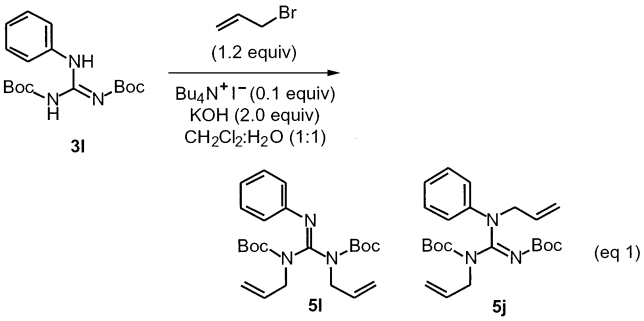
(23) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1987**, *52*, 1700−1703.

(24) Characterization of compound **5k** was problematic due to rotamers, and it was therefore deprotected to give **6k** which was fully characterized.

SCHEME 2



nylguanidine **3l** with allyl bromide gave a separable mixture of diallylated compounds **5l** and **5j** in a 7:3 ratio, in addition to the guanidine starting material **3l** (eq 1). Treatment of N^1,N^2-bis-Boc-N^3-benzylguanidine **3m** with 5 equiv of allyl bromide also gave a mixture of diallylated compounds in a similar ratio, although these compounds could not be separated. These results are similar to previous studies where reaction of primary amine-derived guanidines **3** with allyl alcohols under Mitsunobu conditions gave mixtures of diallylated compounds.[25]



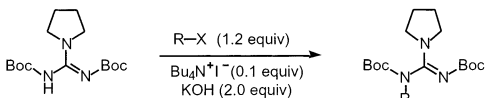
(eq 1)

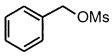
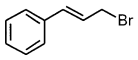
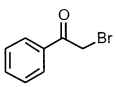
5l:5j = 7:3 (99% yield, based on allybromide)

However, it is possible to achieve selective monoallylation of primary amine-derived guanidines **3** (R^2 = H) for those substrates where the nucleophilicity of the nitrogen attached to R^1 is very low. As described above, N^1,N^2-bis-Boc-guanidine **3c** could be monoallylated regioselectively at the carbamate nitrogen (Table 1, entry 3). In addition, N^1,N^2-bis-Boc-N^3-methoxyguanidine **3n** gave the corresponding monoallylated guanidine **5n** in 69% yield, with the other regioisomeric *N*-methoxyallylated and bis-allylated guanidines being formed in less than 5% yield (Scheme 2).

Having demonstrated functional group tolerance in the guanidine component, the effect of variation of the electrophilic component was required. Specifically, guanidinylation of a range of electrophiles using the bis-Boc-protected model substrate **3a** was examined (Table 2). Saturated alkyl halides such as iodomethane (Table 2, entry 1) and bromopropane (Table 2, entry 3) were cleanly displaced by the guanidine nucleophile, although in the latter case, the reaction needed to be heated to 50 °C for 12 h. Secondary alkyl bromides could also be guanidinylated regioselectively to provide the isopropyl and cyclohexenyl guanidines in moderate yield (Table 2, entries 5 and 11). In contrast, secondary alkyl bromides underwent elimination using the sodium hydride/DMF methodology, rather than alkylation.[21] For larger scale syntheses, the use of alkyl chlorides over the more costly alkyl bromides is highly desirable. It was gratifying to observe that the biphasic alkylation of **3a** with reactive alkyl halides such as benzyl chloride ($2.27/mol) proceeded under similar conditions and yield (Table 2, entry 4) as with the more expensive benzyl bromide ($39.80/mol)[26] (Table 2, entries 6 and 7). However, the guanidi-

TABLE 2. Phase-Transfer-Catalyzed Alkylation of N^1,N^2-Bis-Boc-N^3-pyrrolidine-1-carboxamidine 3a with Various Electrophiles

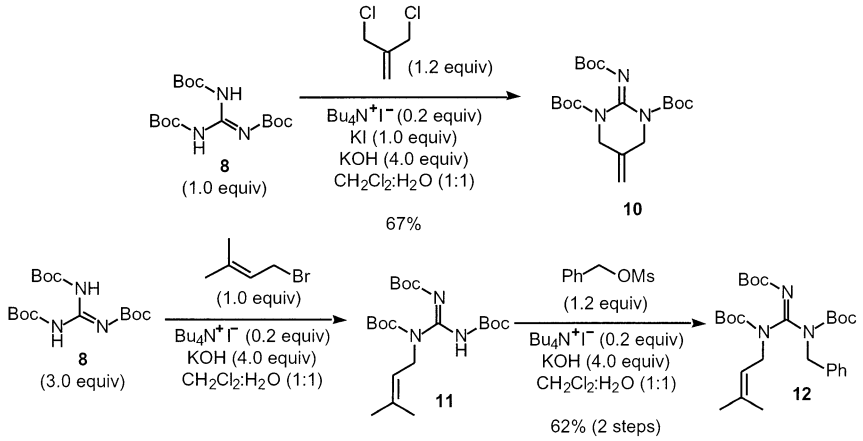


Entry	R—X	Time (h)	Temp (°C)	Compound 5	Yield (%)[a]
1	CH_3I	5	25	**5o**	95[b]
2		12	50	**5p**	77[b]
3		12	50	**5p**	81[b]
4		48	50	**5p**	0[b,c]
5		48	50	**5q**	60[b]
6		4	25	**5r**	95
7		12 (10)[d]	25 (50)[d]	**5r**	88 (89)[d]
8		16	25	**5r**	92[e]
9		4	25	**5s**	92
10		4	25	**5t**	99
11		25	25	**5u**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

(25) Tomioka, M. *Book of Abstracts*. 219th National Meeting of the American Chemical Society, San Francisco, CA, March 26−31, 2000; American Chemical Society: Washington, DC, 2000; MEDI-230.

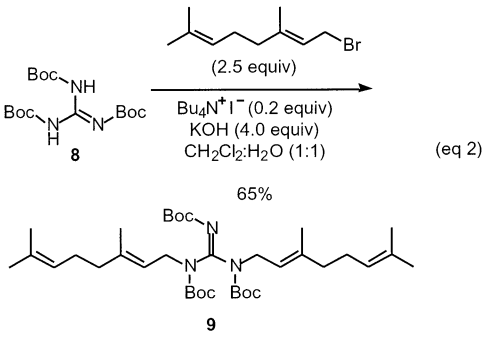
SCHEME 3



nylation of unreactive alkyl chlorides, such as 1-chloropropane, was not successful (Table 2, entry 4). Since nonchlorinated solvents, such as toluene, are often preferred industrially, the use of toluene as a cosolvent in the biphasic protocol was examined. Heating of guanidine substrate **3a** with benzyl chloride in a biphasic mixture of toluene and water at 50 °C for 10 h in the presence of the PTC and KOH gave the benzylated product **5r** in 89% yield (Table 2, entry 7). The scope of the guanidinylation procedure was also extended to the use of mesylates (Table 2, entry 8) which are readily accessible from the corresponding alcohols. Clean alkylation of the guanidine was observed with propargyl bromide (Table 2, entry 9) and 4-bromo-2-methyl-2-butene (Table 2, entry 10). Reaction at the secondary carbon of 3-bromocyclohexene (Table 2, entry 11), as with 2-bromopropane, was slower than displacement at a primary carbon, and consequently, longer reaction times were required. This difference in reactivity at primary and secondary sites may also be responsible for the regioselective alkylation of cinnamyl bromide (Table 2, entry 12) which undergoes guanidinylation at the S_N2 site rather than the S_N2' site.

Other phase-transfer catalysts, such as Bu_4NBr and Bu_4NCl, afforded products in yields similar to those obtained with Bu_4NI. Treatment of tetrahydroisoquinoline-derived guanidine **3g** with allyl bromide, using either Bu_4NCl or Bu_4NBr as the PTC, afforded **5g** in similar yields compared to the Bu_4NI catalyst (Table 1, entry 7). Phase-transfer catalysis conditions have been used to prepare alkyl iodides via a Finkelstein reaction,[27] and we investigated whether such a process was occurring under our reaction protocol. Reaction of guanidine **3a** and 1-chloropropane did not occur under refluxing biphasic conditions, with either Bu_4NCl or Bu_4NI, even after 24 h (Table 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, entry 2). Since alkylation of **3a** using Bu_4NI phase-transfer catalyst failed with 1-chloropropane, but was successful using 1-iodopropane, an in situ Finkelstein reaction does not occur under the reaction conditions.

Recently, Goodman and co-workers have demonstrated the use of N^1,N^2,N^3-tri-Boc-guanidine **8** as a nucleophile for the guanidinylation of alcohols under Mitsunobu conditions.[28] This substrate 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 **8** was dialkylated in the presence of 2.5 equivalents of geranyl bromide to give the substituted guanidine **9** in 65% yield (eq 2).



(eq 2)

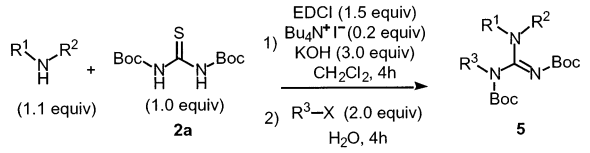
The tri-Boc-guanidine **8** could also be treated with 1 equiv of 3-chloro-2-chloromethyl-1-propene in the presence of 1 equiv of KI to give the cyclic guanidine **10**, resulting from tandem-intermolecular and intramolecular alkylation (Scheme 3). Alkylation of tri-Boc-guanidine **8** with two separate electrophiles is possible using a two-step procedure. Thus, reaction of 3 equiv of the tri-Boc-guanidine **8** with 1 equiv of prenyl bromide gave the alkylated guanidine **11**. After purification to remove excess tri-Boc-guanidine **8**, reaction of **11** with 1 equiv of benzyl mesylate gave the differentially dialkylated guanidine **12** in 62% yield over the two-step procedure (Scheme 3).

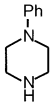
Three-Component Coupling. The PTC guanidinylation method was successfully applied to a one-pot, three-component synthesis of highly substituted guanidines. Reaction of the N^1,N^2-bis-Boc-thiourea **2a** guanylating reagent[7] with a secondary amine in the presence of EDCI, a phase-transfer catalyst, and a base afforded N^1,N^2-bis-Boc-N^3,N^3-disubstituted guanidine intermediate **3**. Direct treatment of **3** in the same reaction vessel with an alkylating reagent in the presence of a small amount of water afforded the substituted guanidine **5** (Table 3). This protocol represents one of the few ex-

(26) Listed prices available from the Aldrich Chemical Co., 2002.
(27) *Phase-Transfer Catalysis: Principles and Techniques*; Starks, C. M., Liotta, C., Eds.; Academic Press: New York, 1978; pp 112−125

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

TABLE 3. One-Pot, Three-Component Guanidine Synthesis



Entry	R^1-NH-R^2	R^3–X	Compound	Yield
			5	(%)[a]
1			**5a**	67
2			**5x**	58
3			**5y**	64

[a] Isolated yield.

amples of a sequential multicomponent guanidine synthesis,[7b,h] a process which we anticipate will be increasingly demanded given the importance of the guanidine functionality in biologically significant molecules.

Conclusion. An efficient method for the alkylation of *N*-dicarbamate-protected guanidines using a variety of alkyl halides has been 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 functionalized guanidines. This protocol provides an alternate method for the alkylation of protected guanidines from those currently utilized. 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 byproducts are generated and at the end of the reaction, simple aqueous workup followed by filtration through a short plug of silica gel (to remove the PTC) gives high yields of the desired products. Furthermore, less expensive benzyl chlorides serve as effective electrophiles. Replacement of dichloromethane with toluene as the organic solvent gives comparable results and is ideal for larger-scale preparation of substituted guanidines. A convenient protocol for sequential three-component coupling, was achieved by combination of the guanidinylation methodology with an initial guanylation reaction. Finally, we propose a differentiation in the terminology for two distinct classes of reactions, guanylations and guanidinylations.

Experimental Section

General Methods. All reagents, unless otherwise stated, were used as received from commercial suppliers. Toluene was distilled from sodium metal/benzophenone ketyl under argon. CH_2Cl_2 was distilled from CaH_2 under argon. 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. NMR spectra were recorded at either 300 or 400 MHz (^{1}H NMR) and 75 or 100 MHz (^{13}C NMR), referenced to an internal standard (TMS) or residual solvent protons and signals are reported in ppm (δ). Line broadening is apparent in some NMR spectra and is due to rotamers around the carbamate nitrogen. Flash chromatography was performed using silica gel (60 Å, 230−400 mesh) with reagent-grade solvents.

General Procedure for the Synthesis of Guanidines 3.[8b,c] To a solution of amine **1** (3.00 mmol), N^1,N^2-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea **2b** (3.30 mmol, 960 mg), and triethylamine (9.00 mmol, 1.25 mL) in dry DMF (10 mL) was added $HgCl_2$ (3.30 mmol, 891 mg). The suspension was stirred at room temperature 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), and 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 for the Biphasic, Phase-Transfer-Catalyzed Synthesis of Guanidines 5. A biphasic solution of guanidine **3** (0.50 mmol), tetrabutylammonium iodide (0.05 mmol, 18 mg), and KOH (1.0 mmol, 56 mg) 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). The reaction was stirred at 25−50 °C (depending on electrophile, see Table 2) for 2−4 h, and then the reaction mixture was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 × 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 for the Deprotection of N^1,N^2-Bis(*tert*-butoxycarbonyl)guanidines 5. A solution of the guanidine **5** (0.25 mmol) in 1 M aqueous HCl (2 mL) was stirred at room temperature 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 silica gel chromatography to give the unprotected guanidine as an HCl salt.

General Procedure for the One-Pot, Three-Component Synthesis of Guanidines 5. A solution of N^1,N^2-bis(*tert*-butoxycarbonyl)thiourea **2a** (0.910 mmol, 250 mg), EDCI (1.20 mmol, 237 mg), tetrabutylammonium iodide (0.170 mmol, 61.0 mg), and finely ground KOH (2.50 mmol, 140 mg) in CH_2Cl_2 (5 mL) was treated with amine **1** (0.82 mmol). The reaction was stirred vigorously for 4 h, at which point TLC indicated the complete consumption of thiourea **2a**. Water (5 mL) and the alkyl halide (1.60 mmol) were added, and the biphasic reaction mixture was stirred for 4−16 h. The mixture was poured into saturated aqueous NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography to yield the guanidine product **5**.

***N*^{1},*N*^{2}-Bis(benzyloxycarbonyl)pyrrolidine-1-carboxamidine (3b).** Obtained as a clear oil in 80% yield: R_f = 0.10 (80% hexanes/20% EtOAc); IR (neat) ν 3033, 2972, 2888, 1752, 1614, 1492, 1271, 1214, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (1H, bs), 7.38−7.29 (10H, m), 5.13 (4H, s), 3.57 (4H, bs), 2.02−1.85 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 128.3, 128.0, 67.4, 49.1, 24.9 (4 carbons not observed); MS (EI) *m*/*e* 274 (34), 166 (100), 139 (56), 91 (74); HRMS (EI) *m*/*e* (M^+) calcd (for $C_{21}H_{23}N_3O_4$) 381.1689, found 381.1678.

***N*^{1},*N*^{2}-Bis(*tert*-butoxycarbonyl)-*N*^{3}-methylguanidino-*N*^{3}-acetic Acid Ethyl Ester (3e).** Obtained as a white solid in 87% yield: R_f = 0.18 (80% hexanes/20% EtOAc); mp 72−73 °C; IR (KBr) ν 3175, 2980, 1750, 1613, 1393, 1143, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (1H, bs), 4.22 (2H, q, J = 7.0 Hz), 4.16 (2H, bs), 3.11 (3H, s), 1.48 (18H, s), 1.29 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 162.1, 156.1, 61.1, 52.1, 38.3, 28.0, 14.0 (2 equivalent carbons not

observed); MS (EI) *m/e* 230 (37), 212 (35), 203 (24), 186 (20), 156 (27), 116 (35), 112 (28), 59 (40), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{16}H_{29}N_3O_6$) 359.2056, found 359.2040.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)phenylpiperazine-1-carboxamidine (3f).** Obtained as a white foam in 86% yield: R_f = 0.19 (80% hexanes/20% EtOAc); IR (neat) ν 2976, 1747, 1603, 1491, 1366, 1230, 1133, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.29 (1H, bs), 7.30 (2H, t, J = 7.5 Hz), 6.94 (2H, d, J = 8.5 Hz), 6.92 (1H, t, J = 7.5 Hz), 3.78 (4H, bs), 3.28 (4H, t, J = 5.0 Hz), 1.54 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 150.7, 129.0, 120.2, 116.4, 48.9, 46.7, 28.0 (2 equivalent quaternary carbons not observed); MS (EI) *m/e* 285 (13), 231 (14), 230 (15), 229 (13), 187 (16), 160 (40), 145 (41), 132 (100), 120 (32), 104 (44), 59 (37); HRMS (EI) *m/e* (M^+) calcd (for $C_{21}H_{32}N_4O_4$) 404.2424, found 404.2439.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine (3g).** Obtained as 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}; ^1H 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.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-quinoline-1-carboxamidine (3h).** Obtained as a white powder in 89% yield: R_f = 0.38 (80% hexanes/20% EtOAc); mp 159−161 °C; IR (KBr) ν 3211, 2951, 2246, 1750, 1634, 1574, 1602, 1493, 1391, 1303, 1243, 1162, 1131 cm^{-1}; ^1H 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 (for $C_{20}H_{29}N_3O_4$) 375.2158, found 375.2156.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-4-oxopiperidine-1-carboxamidine (3i).** Obtained as a white solid in 78% yield: R_f = 0.13 (70% hexanes/30% EtOAc); mp 123−124 °C; IR (KBr) ν 3184, 2979, 2932, 1747, 1614, 1486, 1367, 1297, 1231, 1150, 1079, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.26 (1H, bs), 3.82 (4H, s), 2.58−2.56 (4H, m), 1.48 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 155.3, 45.5, 40.4, 28.0 (2 quaternary carbons not observed); MS (EI) *m/e* 341 (7, M^+), 285 (26), 229 (83), 212 (69), 129 (36), 98 (47), 84 (46), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{16}H_{27}N_3O_5$) 341.1951, found 341.1956.

***N*¹-Allyl-*N*²,*N*³-bis(*tert*-butoxycarbonyl)-*N*¹-phenylguanidine (3j).** Obtained as a clear oil in 69% yield: R_f = 0.27 (80% hexanes/20% EtOAc); IR (neat) ν 3199, 2983, 1755, 1632, 1450, 1368, 1251, 1152, 1079, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (1H, s), 7.32 (2H, t, J = 7.5 Hz), 7.21 (2H, d, J = 7.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 5.96 (1H, ddt, J = 17.0, 10.5, 5.5 Hz), 5.18 (1H, dd, J = 17.0, 1.0 Hz), 5.11 (1H, d, J = 10.5 Hz), 4.53 (2H, d, J = 5.5 Hz), 1.52 (9H, s), 1.20 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 153.7, 149.0, 132.9, 128.7, 126.2, 125.9, 117.6, 81.5, 79.4, 54.5, 28.1, 27.5; MS (EI) *m/e* 264 (22), 247 (32), 220 (67), 200 (29), 160 (35), 132 (36), 93 (27), 59 (47), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{20}H_{29}N_3O_4$) 375.2159, found 375.2154.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*³-[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*³-methylguanidine (3k).** Obtained as white foam in 87% yield: R_f = 0.10 (80% hexanes/20% EtOAc); IR (neat) ν 3289, 2979, 1750, 1600, 1495, 1453, 1392, 1367, 1298, 1243, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.18 (1H, bs), 7.39 (2H, d, J = 8.0 Hz), 7.33 (2H, t, J = 8.0 Hz), 7.27 (1H, t, J = 8.0 Hz), 4.90 (1H, s), 4.28−4.26 (1H, m), 2.59 (3H, s), 1.50 (9H, s), 1.47 (9H, s), 1.28 (3H, d, J = 7.5 Hz);); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 156.8, 150.1, 141.6, 128.1, 127.4, 126.4, 82.2, 79.5, 62.5, 57.6, 36.1, 28.2, 28.0, 12.8; MS (EI) *m/e* 244 (41), 235 (35), 217 (37), 189 (40), 188 (199), 170 (41), 144 (100), 118 (32), 100 (34), 59 (47), 58 (56), 57 (100); HRMS (EI) *m/e* (MH^+) calcd (for $C_{21}H_{34}N_3O_5$) 408.2498, found 408.2492; $[\alpha]^{20}_D$ = −13.8 (*c* 0.10, MeOH).

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*³-methoxyguanidine (3n).** Obtained as a white foam in 61% yield: R_f = 0.17 (80% hexanes/20% EtOAc); IR (neat) ν 3421, 3310, 2979, 1760, 1660, 1454, 1394, 1369, 1246, 1151, 1055, 893 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.11 (1H, bs), 7.76 (1H, bs), 3.86 (3H, s), 1.50 (9H, s), 1.49 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 149.4, 141.0, 83.0, 81.1, 61.6, 27.9, 27.8; MS (EI) *m/e* 160 (12), 133 (58), 89 (29), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{12}H_{23}N_3O_5$) 289.1638, found 289.1652.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)pyrrolidine-1-carboxamidine (5a).** Obtained as 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 (for $C_{18}H_{31}N_3O_4$) 353.2315, found 353.2306.

***N*¹-Allyl-*N*¹,*N*²-bis(benzyloxycarbonyl)pyrrolidine-1-carboxamidine (5b).** Obtained as a clear oil in 87% yield: R_f = 0.55 (50% hexanes/50% EtOAc); IR (neat) ν 2975, 2880, 1725, 1590, 1456, 1392, 1235, 1150, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (10H, m), 5.81 (1H, ddt, J = 17.0, 10.0, 4.5 Hz), 5.19−5.04 (6H, m), 4.21 (1H, m), 3.72−3.38 (5H, m), 1.80 (4H, bs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 153.6, 153.0, 136.6, 135.7, 131.9, 128.4, 128.3, 128.1, 128.0, 127.7, 127.7, 119.5, 67.6, 67.0, 50.2, 48.2, 47.7, 24.9, 24.5; MS (EI) *m/e* 351 (17), 286 (17), 242 (12), 91 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{24}H_{27}N_3O_4$) 421.2002, found 421.2000.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)guanidine (5c).** Obtained as a clear oil in 94% yield: R_f = 0.52 (80% hexanes/20% EtOAc); IR (neat) ν 3386, 2979, 1715, 1611, 1509, 1368, 1295, 1246, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (1H, bs), 9.28 (1H, bs), 5.84 (1H, ddt, J = 16.5, 10.0, 5.0 Hz), 5.15−5.09 (2H, m), 4.56 (2H, d, J = 5.5 Hz), 1.49 (18H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 160.5, 154.9, 134.0, 115.9, 83.7, 78.8, 46.7, 28.3, 27.9; MS (EI) *m/e* 300 (6, MH^+), 244 (13), 187 (72), 170 (27), 143 (24), 128 (43), 98 (25); HRMS (EI) *m/e* (MH^+) calcd (for $C_{14}H_{26}N_3O_4$) 300.1923, found 300.1928. Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 56.17; H, 8.42; N, 14.04. Found: C, 56.47; H, 8.42; N, 14.01.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)-*N*³-diethylguanidine (5d).** Obtained as a light yellow oil in 90% yield: R_f = 0.39 (80% hexanes/20% EtOAc); IR (neat) ν 2977, 2934, 1720, 1594, 1457, 1366, 1251, 1164, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, ddt, J = 17.0, 10.0, 7.0 Hz), 5.17 (1H, dd, J = 17.0, 1.0 Hz), 5.09 (1H, dd, J = 10.0, 1.0 Hz), 4.19 (1H, bs), 3.72 (1H, bs), 3.56 (1H, bs), 3.22 (3H, m), 1.43 (9H, s), 1.42 (9H, s), 1.09 (6H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 153.7, 152.5, 132.8, 118.9, 81.4, 78.6, 50.3, 41.7, 28.1, 28.0, 13.6, 11.5; MS (EI) *m/e* 355 (8, M^+), 255 (19), 226 (25), 199 (49), 182 (20), 170 (24), 126 (22), 99 (22), 74 (22), 72 (55), 57 (100); HRMS (EI) *m/e* (M^+), calcd (for $C_{18}H_{33}N_3O_4$) 355.2471, found 355.2478.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)-*N*³-methylguanidino-*N*³-acetic Acid Ethyl Ester (5e).** Obtained as a clear oil in 78% yield: R_f = 0.08 (80% hexanes/20% EtOAc); IR (neat) ν 2979, 1720, 1603, 1456, 1368, 1252, 1146, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92−5.88 (1H, m), 5.27−5.16 (2H, m), 4.20 (2H, q, J = 7.0 Hz), 4.14−3.77 (4H, m), 3.04 (3H, bs), 1.48 (18H, s), 1.28 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 159.0, 154.5, 152.2, 132.5, 119.2, 81.8, 79.5, 61.2, 51.5, 50.6, 37.0, 28.2, 28.1, 14.1; MS (EI) *m/e* 199 (18),

152 (34), 112 (17), 69 (100), 57 (48); HRMS (EI) *m/e* (M^+) calcd (for $C_{19}H_{33}N_3O_6$) 399.2369, found 399.2372.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)phenylpiperazine-1-carboxamidine (5f).** Obtained as a clear oil in 87% yield: R_f = 0.28 (50% hexanes/50% Et_2O); IR (neat) ν 2977, 1715, 1600, 1446, 1367, 1140, 1088, 1017, 935, 858, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, t, J = 8.0 Hz), 6.93 (2H, d, J = 8.0 Hz), 6.91 (1H, t, J = 8.0 Hz), 5.87 (1H, ddt, J = 17.0, 10.0, 4.5 Hz), 5.26 (2H, d, J = 17.0 Hz), 5.19 (2H, d, J = 10.0 Hz), 4.32−3.64 (6H, m), 3.28−3.09 (4H, m), 1.50 (9H, s), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.6, 152.1, 150.6, 132.3, 129.1, 120.5, 119.6, 116.5, 81.7, 79.3, 50.1, 49.2, 45.5, 28.2, 28.0; MS (EI) *m/e* 445 (12, MH^+), 315 (13), 271 (28), 243 (16), 213 (27), 200 (55), 169 (23), 161 (21), 156 (31), 145 (86), 132 (82), 112 (35), 105 (30), 104 (38), 83 (27), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{24}H_{36}N_4O_4$) 444.2737, found 444.2747.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine (5g).** Obtained as 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 (for $C_{23}H_{33}N_3O_4$) 415.2471, found 415.2480.

***N*¹-Allyl-*N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-quinoline-1-carboxamidine (5h).** Obtained as a clear, colorless 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 (for $C_{23}H_{33}N_3O_4$) 415.2471, found 415.2465.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)-4-oxopiperidine-1-carboxamidine (5i).** Obtained as a yellow oil in 91% yield: R_f = 0.10 (50% hexanes/50% EtOAc); IR (neat) ν 2977, 1719, 1597, 1453, 1367, 1284, 1248, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, ddt, J = 17.0, 10.0, 4.5 Hz), 5.20 (1H, d, J = 17.0 Hz), 5.13 (1H, d, J = 10.0 Hz), 3.81−3.69 (4H, m), 2.49−2.43 (4H, m), 1.43 (9H, s), 1.41 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 159.0, 153.2, 152.1, 132.2, 119.6, 82.0, 79.6, 50.3, 44.3, 40.2, 28.0, 27.9; MS (EI) *m/e* 381 (6, M^+), 325 (17), 269 (37), 252 (50), 225 (72), 181 (20); HRMS (EI) *m/e* (M^+) calcd (for $C_{19}H_{31}N_3O_5$) 381.2264, found 381.2270.

***N*¹,*N*³-Bisallyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)-*N*³-phenylguanidine (5j).** Obtained as a clear oil in 91% yield: R_f = 0.05 (90% hexanes/10% Et_2O); IR (neat) ν 2978, 1719, 1617, 1584, 1496, 1367, 1252, 1223, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.17 (5H, m), 5.95 (1H, ddt, J = 17.0, 10.5, 6.0 Hz), 5.52 (1H, ddt, J = 17.0,10.0, 6.5 Hz), 5.13−5.07 (2H, m), 5.00−4.95 (2H, m), 4.35 (2H, bs), 3.67−3.60 (2H, m), 1.45 (9H, s), 1.40 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 152.4, 142.3, 133.4, 132.8, 128.9, 127.0, 126.6, 118.0, 117.4, 81.8, 79.7, 55.0, 51.0, 28.1; MS (EI) *m/e* 416 (5, MH^+), 342 (1), 314 (12), 286 (37), 257 (61), 258 (63), 214 (42), 132 (40), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{23}H_{33}N_3O_4$) 415.2471, found 415.2471.

***N*¹,*N*²-Bisallyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)-*N*³-phenylguanidine (5l).** Obtained as a clear oil in 69% yield (based on allyl bromide): R_f = 0.23 (90% hexanes/10% Et_2O); IR (neat) ν 3081, 2979, 1728, 1640, 1596, 1478, 1451, 1368, 1227, 1146, 982, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, t, J = 8.0 Hz), 7.02 (1H, t, J = 7.5 Hz), 6.84 (2H, d, J = 7.5 Hz), 6.01 (1H, ddt, J = 17.0, 10.0, 5.5 Hz), 5.53−5.39 (1H, m), 5.24 (1H, d, J = 17.0 Hz), 5.15 (1H, d, J = 10.0 Hz), 5.01−4.96 (2H, m), 4.37 (2H, d, J = 5.5 Hz), 3.74 (2H,d, J = 6.5 Hz), 1.49 (9H, s), 1.34 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 147.1, 145.9, 133.8, 133.0, 128.8, 123.7, 121.1, 117.9, 117.2, 82.1, 81.5, 50.9, 28.2, 28.1; MS (EI) *m/e* 415 (6, M^+), 259 (23), 214 (28), 174 (27), 159 (27), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{23}H_{33}N_3O_4$) 415.2471, found 415.2469.

***N*¹-Allyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)-*N*³-methoxyguanidine (5n).** Obtained as a clear oil in 69% yield: R_f = 0.55 (80% hexanes/20% EtOAc); IR (neat) ν 3424, 2979, 1752, 1645, 1457, 1369, 1250, 1146, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, bs), 5.93 (1H, ddt, J = 17.0, 10.0, 4.5 Hz), 5.22 (1H, dd, J = 17.0, 1.0 Hz), 5.13 (1H, d, J = 10.0 Hz), 4.06 (2H, d, J = 6.0 Hz), 3.84 (3H, s), 1.47 (9H, s), 1.45 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 148.9, 142.6, 133.5, 117.5, 81.4, 81.2, 61.8, 51.3, 28.0, 27.9; MS (EI) *m/e* 330 (13, MH^+), 218 (24), 173 (36), 128 (32), 98 (27), 57 (100); HRMS (EI) *m/e* (MH^+) calcd (for $C_{15}H_{28}N_3O_5$) 330.2029, found 330.2031.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)pyrrolidine-*N*¹-methyl-1-carboxamidine (5o).** Obtained as 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 (for $C_{16}H_{29}N_3O_4$) 327.2158, found 327.2149.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(1-propyl)pyrrolidine-1-carboxamidine (5p).** Obtained as 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 (for $C_{18}H_{33}N_3O_4$) 355.2471, found 355.2474.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(2-propyl)pyrrolidine-1-carboxamidine (5q).** Obtained as a clear oil in 60% yield: R_f = 0.23 (50% hexanes/50% Et_2O); IR (neat) ν 2974, 1712, 1588, 1455, 1264, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00−3.96 (1H, m), 3.44 (4H, bs), 1.89 (4H, bs), 1.46 (9H, s), 1.44 (9H, s), 1.23 (6H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.1, 151.5, 80.6, 78.8, 49.3, 48.1, 48.0, 28.3, 28.2, 25.3, 25.0, 20.9; MS (EI) *m/e* 355 (M^+, 19), 254 (20), 226 (27), 198 (44), 154 (42), 142 (32), 98 (38), 70 (75), 58 (59), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{18}H_{33}N_3O_4$) 355.2471, found 355.2471.

***N*¹-Benzyl-*N*¹,*N*²-bis(*tert*-butoxycarbonyl)pyrrolidine-1-carboxamidine (5r).** Obtained as 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 (for $C_{22}H_{33}N_3O_4$) 403.2471, found 403.2462.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(propargyl)pyrrolidine-1-carboxamidine (5s).** Obtained as a yellow oil in 92% yield: R_f = 0.23 (50% hexanes/50% Et_2O); IR (neat) ν 3252, 2975, 1722, 1592, 1455, 1367, 1243, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (1H, bs), 3.83−3.45 (5H, m), 2.21 (1H, t, J = 2.5 Hz), 1.88 (4H, bs), 1.44 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.5, 151.6, 81.9, 78.8, 77.3, 72.1, 48.0, 47.8, 36.1, 28.2, 28.1, 24.5, 24.3; MS (EI) *m/e* 278 (17), 251 (19), 239

(17), 222 (63), 196 (28), 195 (82), 194 (30), 178 (37), 151 (94), 150 (47), 123 (21), 97 (23), 70 (39), 57 (100); HRMS (EI) *m/e* (MH^+) calcd (for $C_{18}H_{30}N_3O_4$) 352.2236, found 352.2243.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(2-methylbut-2-enyl)-pyrrolidine-1-carboxamidine (5t).** Obtained as a yellow oil in 99% yield: $R_f = 0.13$ (80% hexanes/20% EtOAc); IR (neat) ν 2975, 2879, 1720, 1594, 1455, 1366, 1242, 1137 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (1H, t, $J = 7.0$ Hz), 4.18 (1H, bs), 3.68 (1H, bs), 3.52−3.38 (4H, m), 1.84 (4H, bs), 1.65 (3H, s), 1.61 (3H, s), 1.44 (9H, s), 1.42 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 153.2, 152.2, 136.4, 119.0, 80.9, 78.6, 47.8, 47.5, 44.6, 28.2, 28.0, 25.6, 25.2, 24.8, 17.6; MS (EI) *m/e* 382 (MH^+, 17), 381 (M^+, 12), 281 (34), 225 (100), 184 (47), 180 (43), 166 (29), 97 (41), 84 (50), 72 (54), 70 (51), 57 (92); HRMS (EI) *m/e* (M^+) calcd (for $C_{20}H_{35}N_3O_4$) 381.2628, found 381.2611.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(2-cyclohex-2-enyl)-pyrrolidine-1-carboxamidine (5u).** Obtained as a yellow oil in 78% yield: $R_f = 0.21$ (50% hexanes/50% Et_2O); IR (neat) ν 2975, 1716, 1589, 1455, 1366, 1330, 1270, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 5.76−5.72 (2H, m), 4.36 (1H, bs), 3.52−3.44 (4H, m), 1.98−1.78 (9H, m), 1.63−1.60 (1H, m), 1.47 (9H, s), 1.46 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 159.2, 152.0, 129.2, 80.9, 78.6, 54.4, 48.1, 28.3, 28.2, 27.1, 25.3, 24.9, 24.5, 21.6 (2 carbons not observed); MS (EI) *m/e* 393 (9, M^+), 293 (18), 237 (58), 193 (25), 184 (24), 158 (23), 151 (21), 96 (46), 72 (42), 70 (37), 57 (100), 55 (26); HRMS (EI) *m/e* (M^+) calcd (for $C_{21}H_{35}N_3O_4$) 393.2628, found 393.2635.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(3-phenylallyl)pyrrolidine-1-carboxamidine (5v).** Obtained as a yellow oil in 95% yield: $R_f = 0.18$ (50% hexanes/50% Et_2O); IR (neat) ν 2976, 2878, 1715, 1593, 1454, 1367, 1271, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (5H, m), 6.56 (1H, d, $J = 16.0$ Hz), 6.25 (1H, dt, $J = 16.0$, 7.5 Hz), 4.44 (1H, bs), 3.82 (1H, bs), 3.54−3.44 (4H, m), 1.86 (4H, bs), 1.50 (9H, s), 1.49 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.0, 152.1, 136.4, 133.8, 128.5, 127.7, 126.4, 124.0, 81.3, 78.8, 49.2, 48.0, 47.7, 28.2, 28.1, 25.2, 24.8; MS (EI) *m/e* 273 (73), 228 (19), 132 (31), 117 (49), 115 (22), 97 (29), 91 (21), 72 (22), 70 (31), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{24}H_{35}N_3O_4$) 429.2628, found 429.2632. Anal. Calcd for $C_{24}H_{35}N_3O_4$: C, 67.11; H, 8.21; N, 9.78. Found: C, 67.00; H, 8.18; N, 9.71.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(2-oxo-2-phenylethyl)pyrrolidine-1-carboxamidine (5w).** Obtained as 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 (for $C_{23}H_{33}N_3O_5$) 431.2420, found 431.2427.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)morpholine-4-carboxamidine (5x).** Obtained as a clear oil in 58% yield: $R_f = 0.38$ (80% hexanes/20% EtOAc); IR (neat) ν 2976, 2926, 2858, 1720, 1598, 1455, 1367, 1285, 1253, 1146, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 5.82 (1H, ddt, $J = 17.0$, 10.0, 4.5 Hz), 5.22 (1H, dd, $J = 17.0$, 1.0 Hz), 5.16 (1H, dd, $J = 10.0$, 0.5 Hz), 4.25−4.05 (1H, m), 3.70−3.48 (9H, m), 1.47 (9H, s), 1.46 (9H,s); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ 159.3, 153.7, 152.1, 132.2, 132.0, 119.7, 119.2, 81.8, 79.4, 66.3, 66.2, 50.2, 47.9, 46.0, 36.0, 28.2, 29.0; MS (EI) *m/e* 369 (5, M^+), 313 (7), 269 (16), 257 (14), 240 (33), 213 (100), 196 (19), 169 (19), 113 (17), 86 (20), 57 (69); HRMS (EI) *m/e* (M^+) calcd (for $C_{18}H_{31}N_3O_5$) 369.2264, found 369.2269.

***N*¹,*N*²-Bis(*tert*-butoxycarbonyl)-*N*¹-(2-oxo-2-phenylethyl)phenylpiperazine-1-carboxamidine (5y).** Obtained as an off-white foam in 64% yield: $R_f = 0.15$ (80% hexanes/20% EtOAc); IR (neat) ν 2977, 2930, 1702, 1597, 1496, 1450, 1367, 1295, 1227, 1147, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, $J = 7.5$ Hz), 7.59 (1H, t, $J = 7.5$ Hz), 7.47 (2H, t, $J = 7.5$ Hz), 7.28 (2H, t, $J = 8.0$ Hz), 6.94 (2H, d, $J = 8.0$ Hz), 6.90 (1H, t, $J = 7.5$ Hz), 5.29−5.07 (1H, m), 4.40−4.06 (3H, m), 3.78−3.42 (4H, m), 3.18−3.13 (2H, m), 1.54 (9H, s), 1.48−1.45 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 159.1, 154.8, 152.0, 150.8, 134.9, 133.7, 129.2, 128.8, 127.8, 120.4, 116.5, 82.6, 79.3, 53.9, 48.8, 46.3, 28.2; MS (EI) *m/e* 522 (7, M^+), 403 (24), 247 (28), 234 (27), 162 (67), 161 (58), 146 (66), 145 (100), 132 (33), 105 (25), 91 (43), 57 (45); HRMS (EI) *m/e* (M^+) calcd (for $C_{29}H_{38}N_4O_5$) 522.2842, found 522.2856.

***N*¹-Allyl-*N*²-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine Hydrochloride (6g).** Obtained as a white powder in 90% yield as the HCl salt: $R_f = 0.30$ (90% CH_2Cl_2/10% MeOH); mp 163−164 °C; 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 (for $C_{13}H_{17}N_3$) 215.1422, found 215.1419.

***N*¹-Allyl-*N*²-[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*²-methylguanidine Hydrochloride (6k).** Obtained as a yellow oil in 50% yield (two steps): IR (neat) ν 3332, 2401, 1708, 1590, 1455, 1423, 1045 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.45−7.31 (5H, m), 5.80 (1H, ddt, $J = 17.0$, 10.5, 5.0 Hz), 5.17 (1H, dd, $J = 10.5$, 1.0 Hz), 5.09 (1H, d, $J = 17.0$ Hz), 4.92 (4H, bs), 4.71 (1H, d, $J = 8.0$ Hz), 4.18 (1H, dt, $J = 12.5$, 6.5 Hz), 3.81−3.79 (2H, m), 2.61 (3H, s), 1.39 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 158.28, 141.95, 133.61, 129.32, 129.10, 127.67, 116.91, 76.87, 61.20, 45.41, 32.54, 15.16; MS (EI) *m/e* 229 (31), 175 (27), 146 (31), 132 (27), 118 (100), 117 (51), 91 (38), 58 (57), 57 (44); HRMS (EI) *m/e* (MH^+, free guanidine) calcd (for $C_{14}H_{22}N_3O$) 248.1763, found 248.1768; $[\alpha]^{20}_D = -7.0$ (*c* 0.08, MeOH).

***N*¹,*N*²-Bis(3,7-dimethylocta-2,6-dienyl)-*N*¹,*N*²,*N*³-tris(*tert*-butoxycarbonyl)guanidine (9).** Obtained as a yellow oil in 65% yield: $R_f = 0.54$ (80% hexanes/20% EtOAc); IR (neat) ν 2978, 2931, 1739, 1648, 1454, 1367, 1249, 1228, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (2H, t, $J = 6.5$ Hz), 5.07 (2H, t, $J = 6.5$ Hz), 4.14 (4H, d, $J = 6.5$ Hz), 2.05−1.98 (8H, m), 1.67 (6H, s), 1.65 (6H, s), 1.59 (6H, s), 1.49 (9H, s), 1.46 (18H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 151.7, 149.0, 138.1, 131.2, 123.8, 119.5, 81.9, 80.7, 46.3, 39.7, 28.2, 26.7, 25.8, 17.8, 16.4; MS (EI) *m/e* 631 (5, M^+), 562 (25), 350 (31), 306 (49), 214 (63), 57 (100); HRMS (EI) *m/e* (M^+) calcd (for $C_{36}H_{61}N_3O_6$) 631.4560, found 631.4583.

***N*¹,*N*²,*N*³-Tris(*tert*-butoxylcarbonyl)-4,6-dihydro-5-methylenepyrimidine (10).** To a biphasic solution of CH_2Cl_2/H_2O (1:1) (3 mL) were 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 **8** (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 × 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; 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 (for $C_{20}H_{34}N_3O_6$) 412.2448, found 412.2459.

N^1-Benzyl-N^1,N^2,N^3-tris(*tert*-butoxycarbonyl)-N^2-(3-methylbut-2-ene) (12). To a biphasic solution of CH_2Cl_2 (1.5 mL) and H_2O (1.5 mL) was added the tri-Boc-guanidine **8** (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 × 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 **8**.

The tri-Boc-prenylguanidine **11** was stirred in a biphasic mixture of CH_2Cl_2 (1.5 mL) and H_2O (1.5 mL). To this mixture were 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 × 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 (for $C_{28}H_{43}N_3O_6$) 517.3152, found 517.3168.

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Supporting Information Available: Spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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